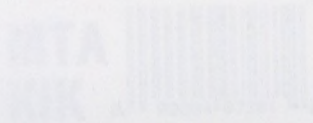


Atlas of Fetal Diagnosis



Atlas of Fetal Diagnosis

Edited by

Zoltán Papp, MD, PhD, DSc

Professor and Director of the 1st Department of Obstetrics and Gynaecology,
Semmelweis University Medical School of Budapest, Budapest, Hungary
(Formerly: Professor of the Department of Obstetrics and Gynaecology, University
Medical School of Debrecen, Debrecen, Hungary)

Foreword by

John M Opitz, MD, DSc

Chairman, Department of Medical Genetics, Shodair Hospital, Helena, Montana, USA

Contributors

Károly Csécsei, MD, PhD

Senior Lecturer, Department of Obstetrics and Gynaecology, University Medical
School of Debrecen, Debrecen, Hungary

Richard H Lindenbaum, MD

Consultant, Department of Medical Genetics, Churchill Hospital, Oxford, UK

György T Szeifert, MD

Senior Registrar, National Institute of Neurosurgery, Budapest, Hungary
(Formerly: Senior Lecturer of the Department of Pathology, University Medical
School of Debrecen, Debrecen, Hungary)

Zoltán Tóth, MD, PhD

Senior Lecturer, Department of Obstetrics and Gynaecology, University Medical
School of Debrecen, Debrecen, Hungary

Valéria Váradi, MD, PhD

Consultant, Division of Neonatology, Department of Obstetrics and Gynaecology,
St. Margaret Hospital, Budapest, Hungary
(Formerly: Senior Lecturer of the Department of Paediatrics, University Medical
School of Debrecen, Debrecen, Hungary)

Akadémiai Kiadó * Budapest 1992

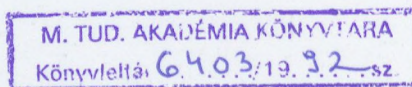
MTA
KIK



687378

MAGYAR
TUDOMÁNYOS AKADÉMIA
KÖNYVTÁRA

ISBN 963 05 6094 1



© Z. PAPP 1992

All rights reserved. No part of this book may be reproduced by any means, or transmitted or translated into machine language without the written permission of the copyright owner.

Printed in Hungary by Alföldi Nyomda, Debrecen

Foreword

We live not only in an era of hope, but also in one of stupefying scientific advances. Nowhere are these advances as conspicuous as in genetics where the methods of molecular biology have allowed an unprecedented insight into the ways all living forms are related and organized with respect to transmission from one generation to the next.

However, many biologists have voiced disappointment that our understanding of development has not progressed to a similar degree. And of course, they are largely correct. Even knowing "The Code" as well as we do, we are still far from understanding the relationship between genetic and cytogenetic variability and the "reason" for the truly extraordinary conservatism of morphogenetic themes that characterizes vertebrate development. While it is true that we have made much greater progress in understanding phylogeny than ontogeny, recent insights into cellular adhesion molecules, peptide regulatory (growth) factors, homeoboxes and the role of retinoic acid and its receptors in brain and limb differentiation give great hope of further advances in the understanding of ontogeny.

Clinicians can be proud of the role they have played in advancing such understanding through the study of "developmental pathology". It was Meckel and Etienne Geoffroy St. Hilaire who first studied the evolutionary implications of malformations in humans and other vertebrates, particularly as they relate to normal stages of development in different species. It was the latter's son Isidore Geoffroy St. Hilaire who

introduced the term *Tératologie* to designate the systematic study of dysmorphogenesis at the beginning of a century of investigation which saw the emergence of genetics as a causal attempt to understand development, experimental embryology and teratology (*Roux's Entwicklungsmechanik*) as an attempt to analyse mechanisms of development and developmental genetics to resolve the thorny problem of recapitulation (i.e. the relationship between phylogeny and ontogeny). For a while it looked as if developmental pathology would also suffer the same recent fate as the rest of morphology – namely virtual extinction; however, this supremely important field of biology is experiencing a very gratifying resurgence.

The reason for this is easy to identify and is well documented in the present "Atlas of Fetal Diagnosis" edited by Zoltán Papp. With an ever increasing care in planning reproduction and concern about its outcome, there is an ever growing need for the expertise of clinical genetics, fetal pathology, anatomy, embryology and teratology to provide accurate causal and pathogenetic answers to the "why" and "how" of human maldevelopment asked by every parent and professional. This beautifully produced and illustrated book will provide many of these answers in one of the best ways morphology can be studied – namely by use of hundreds of good pictures correlating clinical, anatomical and ultrasonographic data and images. The illustrations are surely the most instructive part of this book in portraying conditions sometimes diffi-

cult or impossible to describe in words; however, the text accompanying each section will amply repay even a cursory study and the well-chosen references will provide access to additional and related material.

Thus, from a clinical perspective this book is a beautiful illustration of the truth of von Baer's statement: *Die Entwicklungsgeschichte ist der wahre Lichtträger für Untersuchungen über organische Körper* (Über Entwicklungsgeschichte der Thiere, 1828), and amply justifies our enthusiasm in continuing our study of developmental abnormalities in humans before birth!

December 1991 John M. Opitz

Introduction

About 20 to 25% of perinatal deaths result from fetal anomalies. Techniques and practice of genetic counselling and prenatal diagnosis can obviously reduce this rate. Parents now expect accurate counselling after the birth of a severely malformed child, and this can only be provided when a precise diagnosis is known. The assessment of such material requires a combination of skills and knowledge spanning the fields of clinical genetics, embryology, pathology, teratology, obstetrics and paediatrics.

The information obtained from careful study of aborted or malformed conceptuses is crucial in providing accurate information to parents and physicians. There is a genuine need for an easy-to-use text with colour pictures that offers a systematic approach to the evaluation and study of maldevelopment in the embryo and fetus diagnosed prenatally (*embryopathology, fetopathology*). Termination may follow prenatal diagnosis in pregnancies after the birth of a child with a rare syndrome. In these cases, it is essential for the examiner to have access to the relevant literature before detailed examination of the termination specimen.

This book should be regarded as a supplement to my previous book entitled *Obstetric Genetics*, published by Akadémiai Kiadó (Budapest 1990). Subsequently, the text is mainly based on the *Obstetric Genetics*. This atlas is intended as a working manual for obstetricians, paediatricians, clinical geneticists and pathologists faced with specific diagnostic problems.

The illustrations for the book have been selected from the rich collection of material provided by our own cases. For the preparation of the photographs and pictures I am indebted to my Contributors who were my students and colleagues (and still are my best friends!) (Drs Csécssei, Szeifert, Tóth), and my wife (Dr. Váradi). Conversations with Dr Lindenbaum have enabled me to clarify many difficult problems in clinical genetics and dysmorphology. I wish to thank Emese Nagy, Dr. Csaba Papp and Dr. Ernő Tóth-Pál for their unstinting help with the typing of the manuscript into the computer. Some figures were kindly provided by my colleagues (Drs István Mórocz, László Csabay and István Szabó). I am indebted to the Publisher for agreeing to publish the book, to István Benkő and Viktor Szabó, general managers of Alföldi Nyomda, for providing professional copies of the photographs and supervising the demanding work of printing.

March 1992

Zoltán Papp

Contents

Foreword	5
Introduction	7
Chapter 1 Prenatal Human Development	11
Chapter 2 Oligohydramnios Sequence	45
Chapter 3 Amniotic Band Sequence (ADAM Complex)	55
Chapter 4 Pathology of Multiple Pregnancy	69
Chapter 5 Prenatal Cerebral Abnormalities	87
Chapter 6 Neural Tube Defects	117
Chapter 7 Cervical, Thoracic and Abdominal Malformations	139
Chapter 8 Renal and Urinary Tract Abnormalities	169
Chapter 9 Skeletal Dysplasias and Limb Defects	195
Chapter 10 Hydropic Anomalies	215
Chapter 11 Chromosome Aberrations	227
Chapter 12 Perinatal Brain Damage	243
Subject Index	254

Prenatal Human Development

Human development is a continuous process that begins when an *ovum* from a female is fertilized by a sperm from a male. Growth and differentiation transform the *zygote*, a single cell formed by the union of the ovum and the sperm, into a multicellular adult human being. Most developmental changes occur during the embryonic and the fetal periods, but development does not stop at birth; important developmental changes, in addition to growth, occur after birth. The most striking advances in development occur during the first eight weeks, in which the *embryonic period* is included. The first three weeks are called the *pre-embryonic period*. By the end of the eighth week the rudiments of all major structures are present. During the *fetal period* (from the ninth week), many organs develop further. Though developmental changes are not as dramatic as those occurring during the embryonic period, they are very important. The rate of body growth is remarkable, especially during the third and fourth months, and weight gain is phenomenal during the later months.

Pre-embryonic and Embryonic Period

Human development begins at *fertilization*. It is complete when the maternal and paternal chromosomes intermingle during the metaphase of the first meiotic division of the zygote. As it passes along the uterine tube, the zygote undergoes *cleavage* (a series of mitotic divisions) into a

number of small cells called *blastomeres*. About three days after fertilization, a ball of 12 to 16 blastomeres, called the *morula*, enters the uterus. A cavity soon forms in the morula, converting it into a *blastocyst* consisting of (1) an inner cell mass, or *embryoblast*, which gives rise to the embryo, (2) a blastocyst cavity, or *blastocoele*, and (3) an outer layer of cells, the *trophoblast*, which encloses the inner cell mass and blastocyst cavity. The pellucid zone disappears by enzymatic lysis (days 4 to 5) and the blastocyst attaches to the endometrial epithelium (days 5 to 6). The trophoblastic cells then invade the epithelium and the underlying endometrial stroma. By the end of the first week, the blastocyst is superficially implanted in the endometrium. At least 15-20 per cent of zygotes are lost during the first week of development, commonly as the result of chromosomal abnormalities.

Implantation of the blastocyst begins at the end of the first week and ends during the second week. The trophoblast begins to differentiate into two layers. The inner cellular layer is the *cytotrophoblast*, the outer syncytium is the *syncytiotrophoblast*. Lacunae develop in the syncytiotrophoblast and soon fuse to form *lacunar networks*. The syncytiotrophoblast erodes the endometrial tissues (maternal sinusoids and endometrial glands), and the blastocyst starts to embed in the endometrium (day 8) and sinks beneath the surface of the endometrial epithelium (days 9 to 10). A primitive *uteroplacental circulation* is established as maternal blood seeps

into the lacunar networks. Primary *chorionic villi* form on the external surface of the *chorionic sac*, and implantation is completed as the conceptus is wholly embedded within the endometrium. The defect in the, and around the conceptus a marked *decidual reaction* occurs (days 13 to 14).

During implantation the *primary yolk sac* forms and *extraembryonic mesoderm* arises from the cytotrophoblast. The *extraembryonic coelom* forms from spaces that develop in the extraembryonic mesoderm. The primary yolk sac becomes smaller and gradually disappears as the *secondary yolk sac* develops. As these changes occur the *amniotic cavity* appears as a slit-like space between the cytotrophoblast and the embryoblast, and the embryoblast differentiates into a *bilaminar embryonic disc* consisting of *epiblast* related to the amniotic cavity and *hypoblast* adjacent to the blastocyst cavity. The epiblast gives rise to all three germ layers of the embryo (ectoderm, mesoderm and endoderm), the hypoblast represents the primitive embryonic endoderm.

The third week is characterized by the development of three germ layers, from which all tissues and organs of the embryo derive, and by the formation of three important structures (the *primitive streak*, the *notochord* and the *neural tube*). The process by which the bilaminar embryonic disc is converted into a trilaminar embryonic disc is called *gastrulation*.

Blood vessels first appear on the yolk sac, around the allantois. They develop within the embryo shortly

thereafter. At the end of the third week, the *primitive heart* is represented by paired *endocardial heart tubes* that are joined to blood vessels in the embryo and in the extraembryonic membranes. The primitive blood cells are derived mainly from the endothelial cells of blood vessels in the yolk sac and the allantois.

Primary chorionic villi become *secondary chorionic villi* as they acquire mesenchymal cores. Before the end of the third week, capillaries develop in the villi, transforming them into *tertiary chorionic villi*. The rapid development of chorionic villi during the third week greatly increases the surface area of the chorion for the exchange of nutrients and other substances between the maternal and embryonic circulations.

The third week is a period of rapid development of the conceptus, coinciding with the *first missing menstrual period*. Bleeding at the expected time of menstruation does not rule out pregnancy because there may be haemorrhage from the implantation site. This *implantation bleeding* results from leakage of blood into the uterine lumen from disrupted blood vessels around the implantation site. Early confirmation of pregnancy is possible by tests depending on the presence of *human chorionic gonadotropin (hCG)* in the mother's urine or by *ultrasound techniques*.

In the embryonic period (fourth to eighth weeks) the three germ layers differentiate into various tissues and organs, so that by the end of the embryonic period, the beginnings of all the main organ systems have been established, however, with minimal function of most organs. As the organs develop, the shape of the embryo changes: longitudinal and transverse folding converts the flat trilaminar embryonic disc into a C-shaped cylindrical embryo. The dorsal part of the *yolk sac* is incorporated into the embryo during folding and gives rise to the *primitive gut*. The primitive gut becomes

pinched off from the yolk sac but remains attached to it by a narrow *yolk stalk*. As the amnion expands, it forms an epithelial covering for the *umbilical cord*.

The head fold results in the heart eventually lying ventrally and the brain becoming the most cranial part of the embryo. The tail fold causes the connecting stalk (primordium of the umbilical cord) and the allantois to move to the ventral surface of the embryo.

By nine weeks, the *yolk sac* has shrunk to a pear-shaped remnant, about 5 mm in diameter, which is connected to the midgut by the narrow yolk stalk. At week 10, the small yolk sac lies in the chorionic cavity between the amnion and the chorionic sac. The yolk sac shrinks as pregnancy advances, eventually becoming very small and rather solid. By 20 weeks, the yolk sac is very small; thereafter, it is usually not visible. Extremely rarely it is recognizable on the fetal surface of the placenta beneath the amnion near the attachment of the umbilical cord even at term. In about 2% of adults, the proximal intra-abdominal part of the yolk stalk persists as a diverticulum of the ileum known as Meckel's diverticulum.

By the end of the eighth week, the regions of the limbs are apparent, the fingers have lengthened, the toes are distinct, and all evidence of the tail disappears. The head is more rounded and erect, but is still disproportionately large, constituting almost half of the embryo. The neck region has become established, and the eyelids are more obvious. The abdomen is less protuberant, and the umbilical cord is relatively reduced in size. The intestines are still within the proximal portion of the cord. During the eighth week, the eyes are usually open, but toward the end of the week, the eyelids may begin to meet and become united by epithelial fusion. The auricles of the external ears begin to assume their final shape, but they are still low-set. Although sex differences exist in

the appearance of the external genitalia, they are not distinct enough to permit accurate sexual identification to be made by lay persons.

Because the beginnings of all essential external and internal structures are formed during the embryonic period, the fourth to eighth weeks constitute the most critical period of development. Developmental disturbances during this period may give rise to *major fetal anomalies (embryopathies)*.

At the fourth week (six weeks after the last menstrual period, LMP), the embryo, the amnion and the yolk sac compose an over 5 mm long structure (the *gestational sac*) that is detectable with scanning. After the fifth week (seventh gestational week), discrete embryonic structures can be visualized, and "crown-rump" measurements are predictive of embryonic age. Furthermore, after the sixth week (eighth gestational week), dimensions of the head and trunk can be obtained and used for assessment of embryonic size. The diameter of the gestational sac can be measured, but this provides only an unreliable estimate of gestational age. Later the *biparietal diameter (BPD)* and the femur length provide the best parameters for estimating the age of the fetus. Even at this stage the size and appearance of the sac provide useful information about possible maldevelopment of the embryo. The healthy sac is rounded and thick-walled, but an abnormal gestational sac may be C-shaped, with a thin, ragged wall. There is a ring of intense echoes around the normal embryo, which disappears by the 11th to 13th week; this disappearance can be explained by the fusion of the parietal and capsular decidua and the resorption of part of the embryonic trophoblast.

The embryonic heart can be seen beating from the end of the sixth week, providing proof that the embryo is alive. Heartbeat frequency is variable, from 120 to 170/min; at this time the atria of the

heart are actively developing and differentiating. One must be aware of these variations because echoes can also arise from maternal vessels, and these may be confused with the fetal heartbeat if the mother has a tachycardia.

From the eighth week fetal movements can be seen, a further and immediate proof of viability.

Fetal Period

The transition from embryo to fetus is not abrupt, but the name change is meaningful because it signifies that the embryo has developed from a single cell, the zygote, into a recognizable human being. Development during the *fetal period* (after the ninth week) consists primarily in body growth and differentiation of tissues and organs having started to develop during the embryonic period. The rate of body growth during the fetal period is very rapid, especially between the ninth and twentieth weeks. An obvious change is the relative slowing of head growth compared with that of the rest of the body. Lanugo and hair appear, and the skin is coated with vernix caseosa by the beginning of the twentieth week. The eyelids are closed during most of the fetal period but begin to reopen at about 26 weeks.

The external genitalia of males and females appear somewhat similar until the end of the ninth week. Their mature fetal form is not established until the twelfth week. By week 16, the ovaries are differentiated and have many primordial follicles containing oogonia. By the 18th week, the uterus of a female fetus is completely formed, and canalization of the vagina has begun.

Intestinal coils are clearly visible within the proximal end of the umbilical cord up to the middle of the tenth week, when the intestines return to the abdomen. Urine starts to form between the ninth and twelfth weeks and is excreted into the am-

niotic fluid. Ossification of the skeleton has progressed rapidly by the beginning of the 16th week.

Until about 30 weeks, the fetus appears reddish and wizened because of the thinness of the skin and the relative absence of subcutaneous fat. Fat usually develops rapidly during the last six to eight weeks, giving the fetus a smooth and plump appearance. Changes occurring during the fetal period are not as dramatic as those appearing in the embryonic period, but they are very important. The fetus is less vulnerable to the teratogenic effects of drugs, viruses and radiation, but these agents may interfere with normal functional development and may cause fetal diseases (*fetopathies*).

Various techniques are available for assessing the status of the fetus and for diagnosing certain diseases and developmental abnormalities before birth.

From the sixth gestational week ultrasound provides an increasing amount of information on the embryo/fetus; the characteristic embryonal/fetal anatomy can be examined with the grey-scale apparatus.

The fetal tissues and organs can be divided into three groups on the basis of their acoustic properties. Ultrasound waves are reflected by high-density structures (like the bones), and these organs give echodense images, with acoustic shadows behind them. On the other hand fluid-filled organs show echo-free images; the acoustic waves pass freely through and give no inner echo. The amniotic fluid, the cardiovascular system, the stomach, the gallbladder, the urinary bladder, the cerebrospinal fluid, ascitic fluid, etc. are all echo-free. A further group of tissues/organs give medium-gray echoes; some of the ultrasound is reflected, some passes through, in a deflected/modified direction. The parenchymal organs (brain, lungs, liver, spleen, kidneys, muscles, intestines, etc.) belong to this intermediary group.

The Placenta and the Fetal Membranes

The placenta has two components: (1) a fetal portion developed from the chorion, and (2) a maternal portion formed by the endometrium. The term *decidua* (deciduus = a falling off) is applied to the functional layer of the pregnant endometrium, indicating that it is shed at parturition. Three regions of the decidua are identified according to their relation to the implantation site: (1) The part underlying the conceptus and forming the maternal component of the placenta is the *basal decidua*; (2) the superficial portion overlying the conceptus is the *capsular decidua*; and (3) all the remaining uterine mucosa is the *parietal decidua*. As the conceptus enlarges, the decidua capsularis bulges into the uterine cavity and soon becomes greatly attenuated. Eventually, the capsular decidua fuses with the parietal decidua, thereby obliterating the uterine cavity. By about 22 weeks, reduced blood supply causes the capsular decidua to degenerate and disappear.

The *chorion*, the *amnion*, the *yolk sac*, and the *allantois* constitute the embryonic or *fetal membranes*. These membranes develop from the zygote, but do not form part of the embryo, with the exception of portions of the yolk sac and allantois. The dorsal part of the yolk sac is incorporated into the embryo as the primordium of the *primitive gut*. The allantois is represented in the adult as a fibrous cord, the *median umbilical ligament*, which extends from the apex of the urinary bladder to the navel.

Up to about the eighth week, *villi* cover the entire surface of the chorionic sac. As the sac grows, the villi associated with the capsular decidua become compressed, and their blood supply reduced; subsequently, these villi begin to degenerate, producing a relatively avascular, bare area known as the *smooth chorion*, or *chorion laeve*. As this occurs, the

villi associated with the basal decidua rapidly increase in number, branch profusely and enlarge. This portion of the chorionic sac is known as the *villous chorion*, or *chorion frondosum*.

The *amnion* is a membranous sac that surrounds the embryo, and later, the fetus. Normally the embryo, the umbilical cord and the amniotic fluid are contained within the amniotic sac. The amnion forms the inner layer of the fetal membranes (the fetal aspect). Externally the chorion, which is of mesodermal origin, strongly adheres to the amnion, and separates it from the maternal decidua and the uterine wall. The amnion is a protective membrane essential for the physiological development of the embryo/fetus. Because the amnion is attached to the margins of the embryonic disc, its junction with the embryo is located on the ventral surface after folding of the embryo. As the amnion enlarges, it gradually obliterates the chorionic cavity and sheathes the umbilical cord, forming its epithelial covering. The epithelial cells of the amnion possess microvilli that probably play a role in fluid transfer, e.g., the exchange of water and dissolved substances via vessels in the parietal decidua.

The amnion is first visible in the dorsal part of the germinal layer on the 7th–8th day after conception. By the 10th–12th weeks of pregnancy the fluid-filled amniotic cavity occupies the whole extraembryonic coelom, and then begins to spread around the adherent pedicle and the regressing yolk sac. Considering an early amniocentesis it is important to understand the development of the amnion. If this is performed before the 10th–12th weeks of gestation, the needle can easily penetrate the jelly-like extraembryonic coelom.

Initially some fluid may be secreted by the amniotic cells, but most amniotic fluid is undoubtedly derived from the maternal blood by transport across the amnion. The fetus also makes a contribution by excreting urine into the amniotic

fluid; by late pregnancy, about 500 ml of urine is added daily. Fetal swallowing of amniotic fluid is a normal occurrence. Most of the fluid passes into the gastrointestinal tract, but some of it also passes into the lungs. In either case, the fluid is absorbed into the fetal circulation and then passes into the maternal circulation via the placental membrane. In the final stages of pregnancy, the fetus swallows up to 400 ml of amniotic fluid per day.

When genetic amniocentesis is performed, at 16–18 gestational weeks, the amniotic fluid volume is usually between 170 and 300 ml. Of this, 5–20 ml are withdrawn. This amount is made up in a few hours; the development of the fetus is not disturbed by amniocentesis.

The external part of the fetal membranes consists of the *chorion laeve*; this, together with the amnion, is pierced by the needle at amniocentesis. In anencephaly the macrophage-containing layers of the fetal membranes are thickened, and well visible in PAS-stained preparations; the macrophages contain conspicuous amounts of fat and haemosiderin, which are derived from material reaching the amniotic fluid through the fetal lesion.

The fetal component of the placenta consists of the chorionic plate and the chorionic villi that arise from it and project into the intervillous spaces containing maternal blood. The maternal component of the placenta is formed by the basal decidua. As the villi invade the basal decidua, they leave several wedge-shaped areas of decidual tissue called *placental septa*. The placental septa divide the fetal part of the placenta into ten to 38 irregular convex areas, composed of lobes and lobules, called *cotyledons*. Each cotyledon consists of two or more main stem villi and their many branches. The shape of the placenta is determined by the form of the persistent area of chorionic villi; usually this is circular, giving the placenta a discoid shape.

The welfare of the embryo and fetus depends more on the adequate bathing of the chorionic villi by maternal blood than on any other factor. Acute reductions of uteroplacental circulation result in fetal *hypoxia*, or fetal death. Chronic reductions of uteroplacental circulation result in disturbances of growth and development that constitute a syndrome known as *intrauterine growth retardation*.

Between the two circulations there is a “barrier” called *placental membrane*. It consists of the fetal tissues separating the maternal and fetal blood. Until about 20 weeks, it consists of four layers: (1) syncytiotrophoblast, (2) cytotrophoblast, (3) the connective tissue core of the villus, and (4) the endothelium of the fetal capillaries. The placental membrane acts as a true barrier only when the molecule has a certain size, configuration and charge. Most drugs or other chemicals present in the maternal plasma will also be found in the fetal plasma. Most infectious organisms also penetrate the placental membrane and enter the fetal blood, often causing death and/or anomaly of the embryo/fetus.

The *umbilical cord* attaches to the fetal surface, and its amniotic covering is continuous with the amnion adherent to this surface of the placenta. The vessels radiating from the umbilical cord are clearly visible through the smooth transparent amnion. The *umbilical cord vessels* subdivide on the fetal surface to form the chorionic vessels, which supply the chorionic villi. The attachment of the umbilical cord is usually near the centre of the placenta, but it may be found at any point (e.g., at the edge producing a *battledore placenta*, or to the membranes forming a *velamentous insertion*). The umbilical cord usually contains two arteries and one vein surrounded by mucoid connective tissue, often called *Wharton's jelly*.

Because the umbilical vessels are

longer than the cord, twisting and bending of the vessels is common. The vessels frequently form loops, producing so-called *false knots* that are of no importance. *True knots* in the cord may cause fetal hypoxia and death. Because the knots are usually loose, they have no clinical importance. If a true knot forms early in pregnancy and tightens owing to fetal movements, the knot may interfere with the fetal circulation and cause death and abortion of the fetus. Simple looping of the cord around the fetus occasionally occurs, sometimes without increased fetal risk. In some malformed fetuses, only one umbilical artery is present (*single umbilical artery*). The single umbilical artery results from either agenesis or obliteration of the other artery early in development.

When, twenty years ago, it was found that amniotic fluid cells could be used for cytogenetic analysis, it was shown that chorionic villus cells (trophoblasts) provided an even

faster karyotype. The method with trophoblast is time-saving, for this is a continuously dividing tissue, whereas the cells exfoliated into the amniotic fluid must be cultured *in vitro* to provide dividing cells in sufficient number. However, there had earlier been no well-developed method for sampling trophoblast, and *amniocentesis*, an easier procedure to perform, became more popular.

In the development of *chorionic villus sampling (CVS)*, the introduction of ultrasound technique deserves emphasis. As ultrasound diagnosis was improved, the CVS technique developed further. It has now been shown that not only the whole chromosome set of the embryo, but its DNA constitution, and even certain enzyme activities, can be examined in chorionic villus material. Some authors aspirate the sample, others use a biopsy device; some prefer the transabdominal route to the transcervical. Samples obtained may weigh 10 to 30 mg. [The preferred minimum weight for

DNA studies has been 30 mg, for chromosome analysis 10 to 20 mg, and for enzyme tests 1 to 2 mg; but DNA work can now be done on very small samples (< 1 mg), using *polymerase chain reaction (PCR)*.] The sample is examined immediately under the stereomicroscope to confirm that it consists of chorionic tissue and not decidua.

Second-trimester (transabdominal) CVS can be performed at any time between eight gestational weeks and term. When this technique is used in the second or third trimester it is often called *placental biopsy*.

In general CVS is the better method for DNA analysis, amniocentesis might be required for certain enzyme tests, and the two methods are equally effective for chromosome analysis.

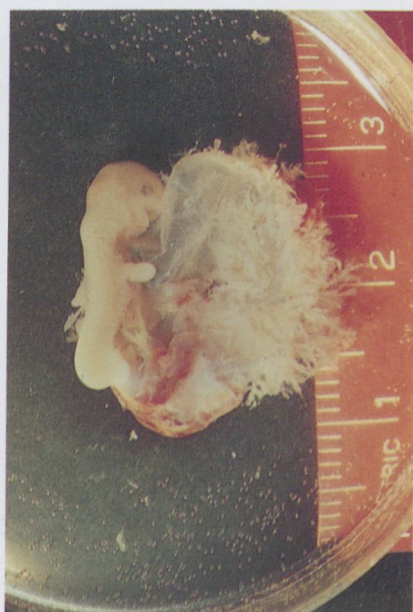
In the third trimester placental biopsy may be used for chromosome analysis, indications including intrauterine growth retardation and abnormal ultrasound finding (malformation?).



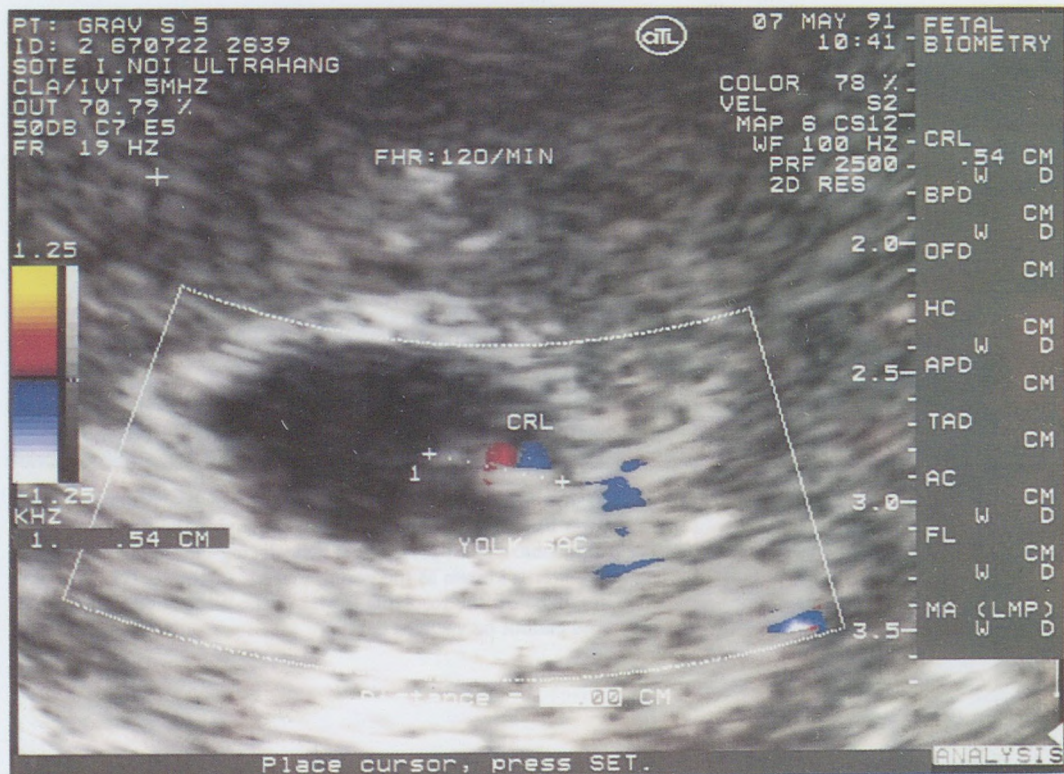
Figure 1-1. A normal five-week-old embryo showing anterior and posterior limb buds and normal vascularization of the yolk sac. The relatively large brownish-coloured liver can be seen in the abdomen.



Figure 1-2. Longitudinal scan obtained by transvaginal probe after five weeks of amenorrhoea, displaying the earliest ultrasonic sign of pregnancy: a small ring-like structure inside the uterus known as the gestational sac (arrows). The fetal pole is still below the resolving power of the ultrasound unit and cannot be visualized.



Figures 1-3a and 3b. A completely expelled egg-shaped five-week gestational sac partly covered with chorionic villi. Inside, the outlines of the yellow-coloured embryo are clearly visible (1-3a). Figure 1-3b shows the opened sac with the embryo.



1-4a



1-4b

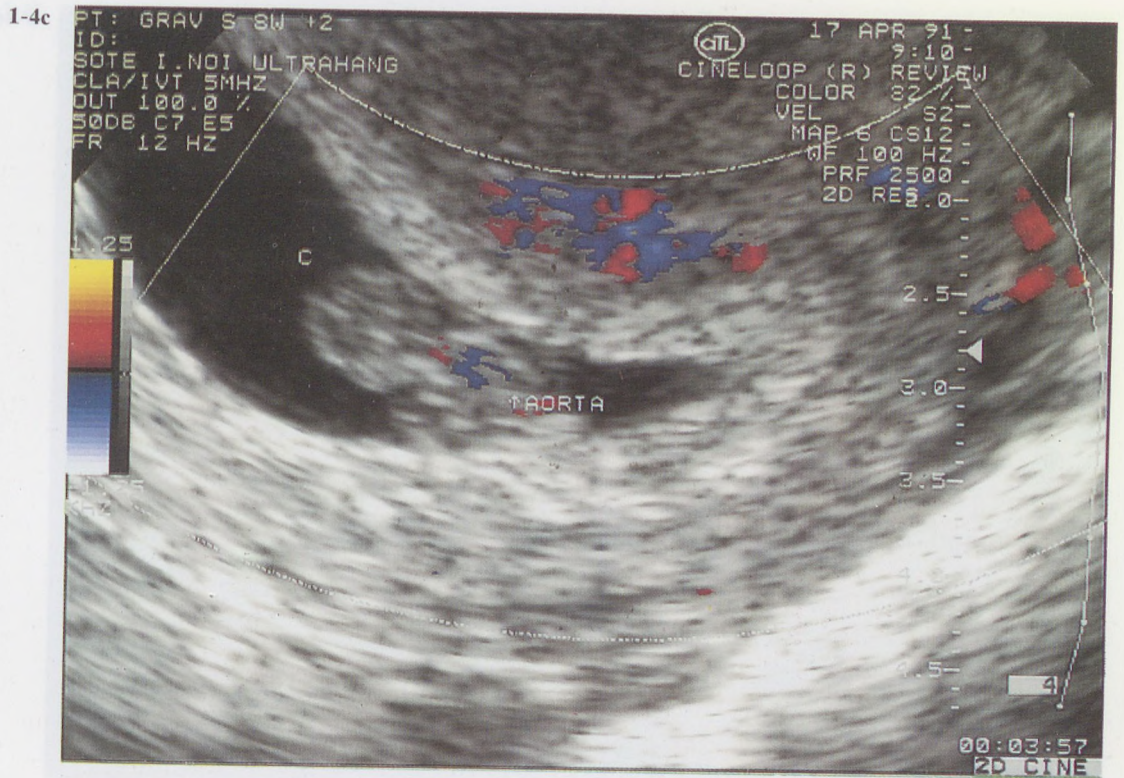
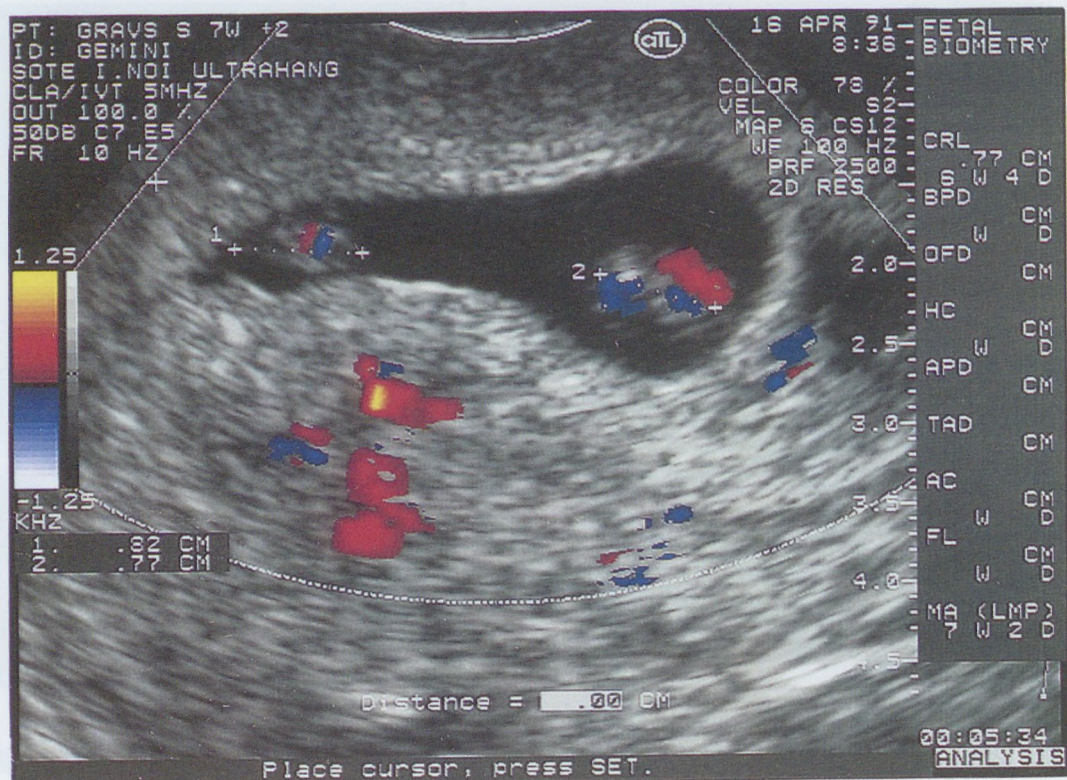


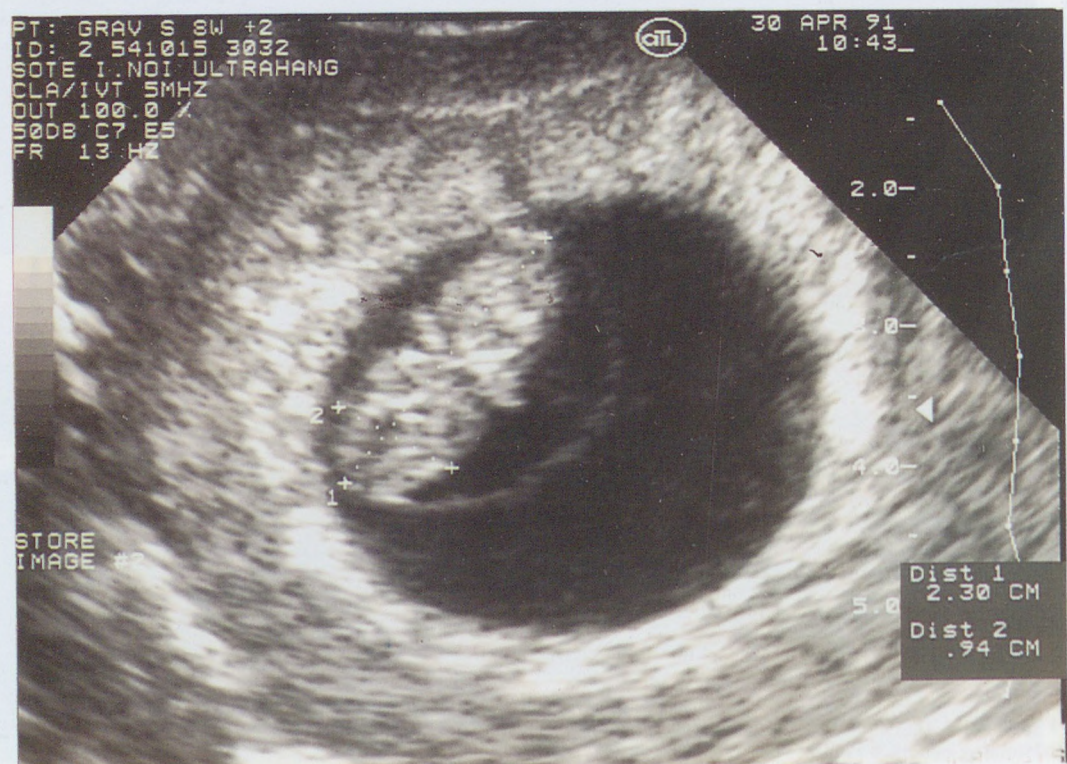
Figure 1-4a. A normal five-gestational-week-old embryo in the gestational sac (CRL = 0.54 cm). Yolk sac, primitive heart (red) and implantation bleeding (blue) are also seen (transvaginal colour Doppler imaging). (Transvaginal scanning causes no inconvenience for the patient and the examinations are not dependent on a filled bladder. The short distance to the organs of interest makes it possible to use a high resolution transducer giving well differentiated image information.)

Figure 1-4b. Longitudinal scan obtained by transvaginal colour Doppler probe after seven weeks of amenorrhoea, displaying embryo and yolk sac in the gestational sac. The placenta starts to develop as an echogenic area at the lower pole of the uterus.

Figure 1-4c. In a normal eight-gestational-week-old embryo the aorta can be seen. The intervillous spaces are containing maternal blood.



1-4d



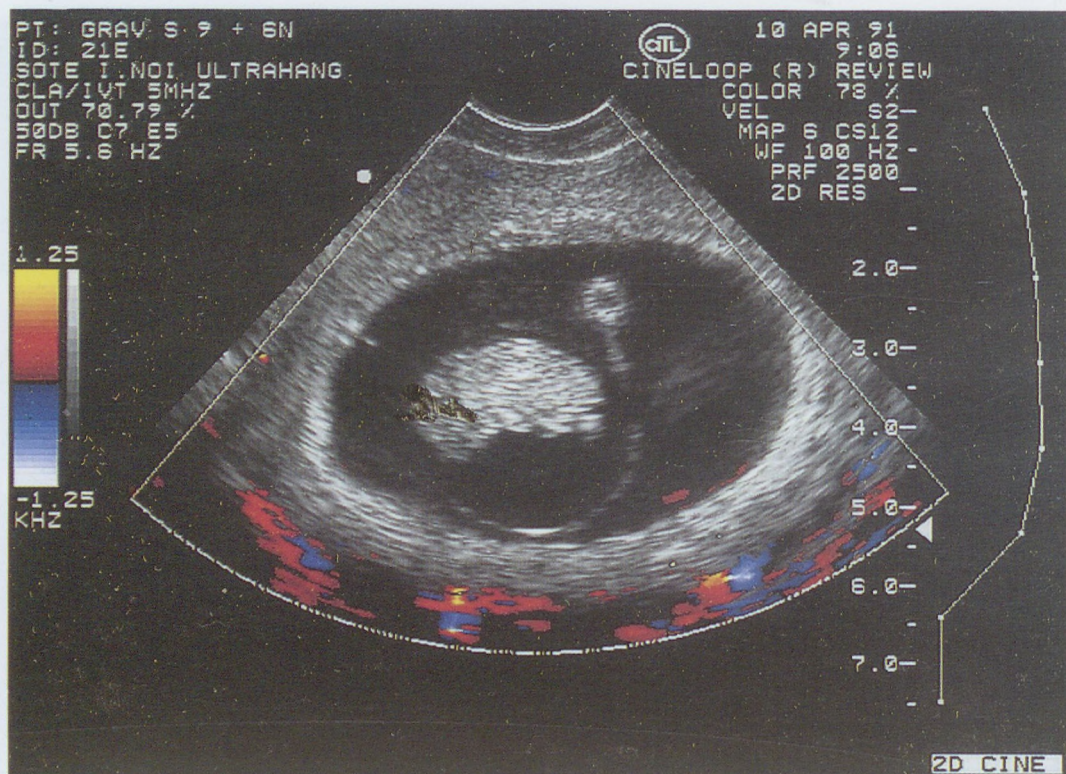
1-4e



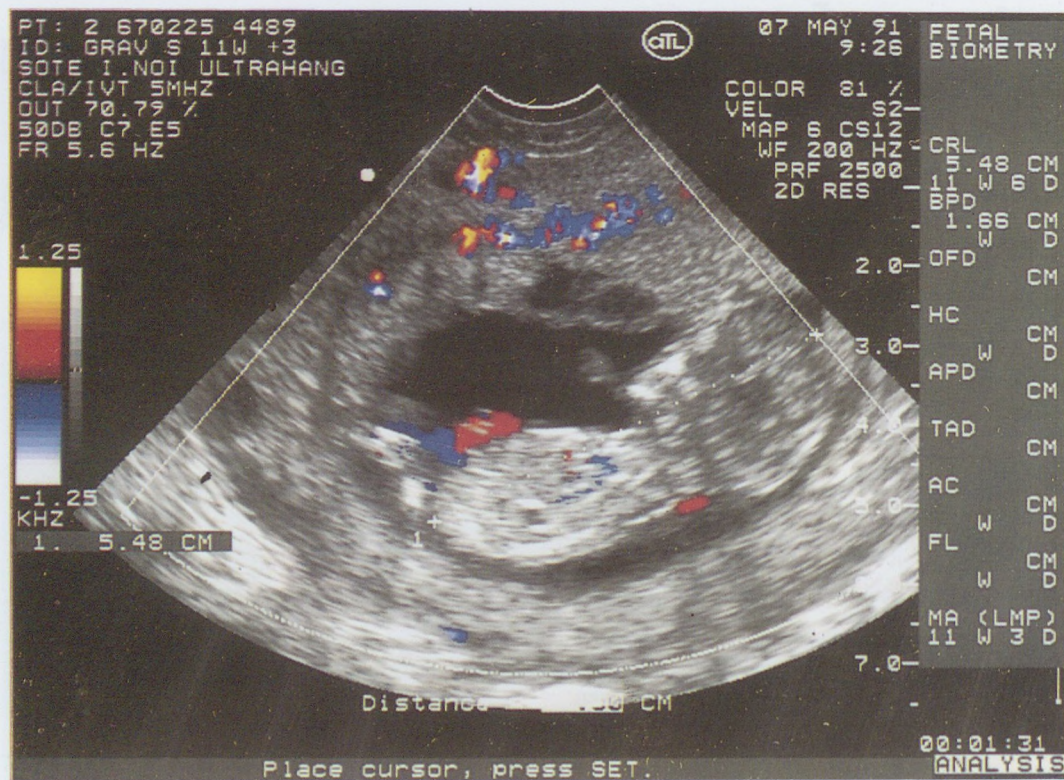
Figure 1-4d. First-trimester diagnosis of a twin conception (eighth gestational week, transvaginal colour Doppler imaging).

Figure 1-4e. Ultrasound scan obtained by transvaginal probe after eight weeks of amenorrhoea. The embryo, the amnion and the extraembryonic coelom are seen.

Figure 1-4f. In an eight-gestational-week-old gestational sac the yolk sac is attached to the embryo by a narrow yolk stalk.



1-4g



1-4h

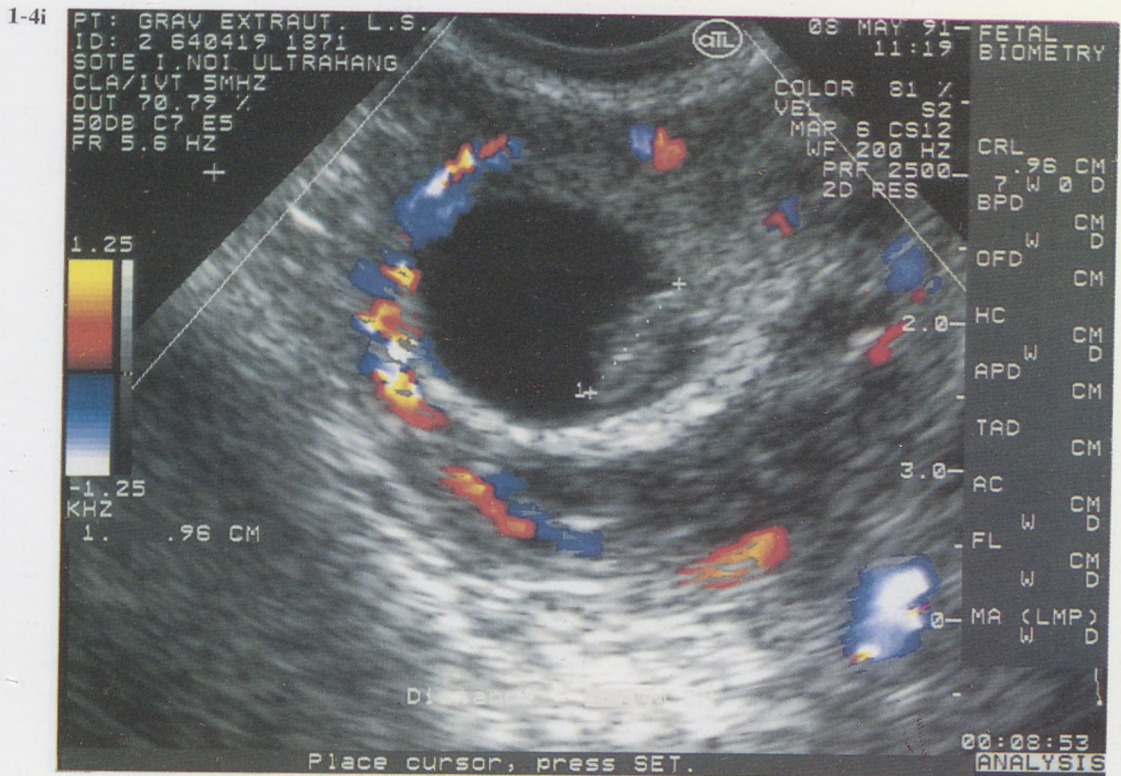
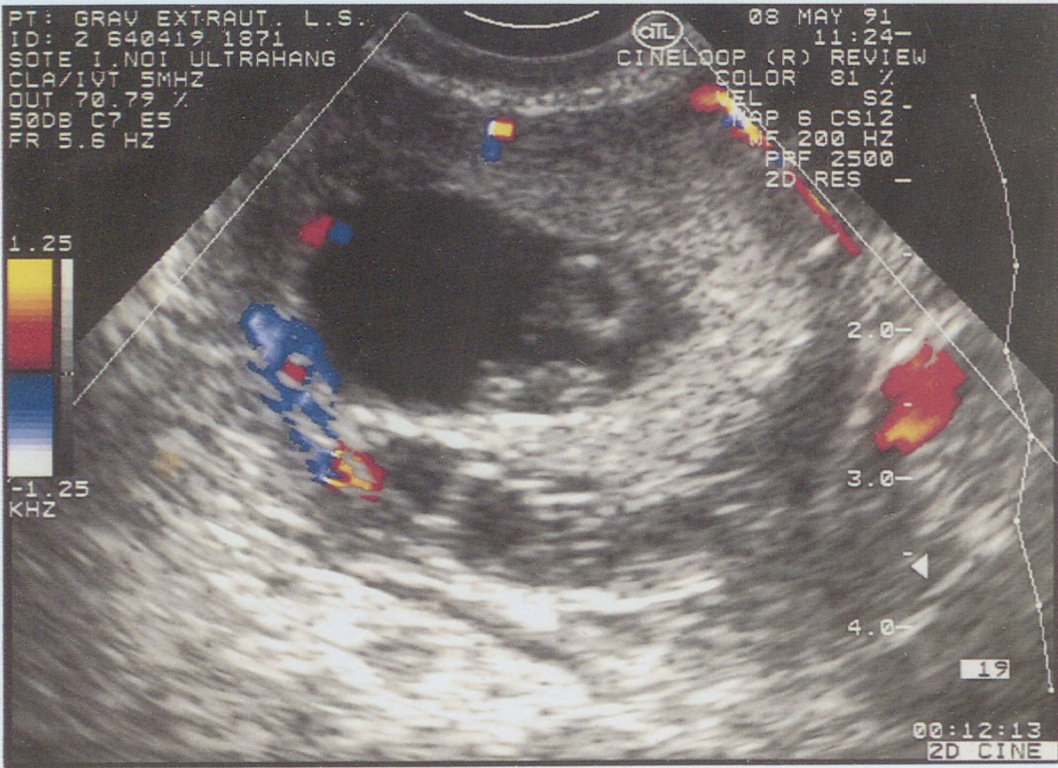


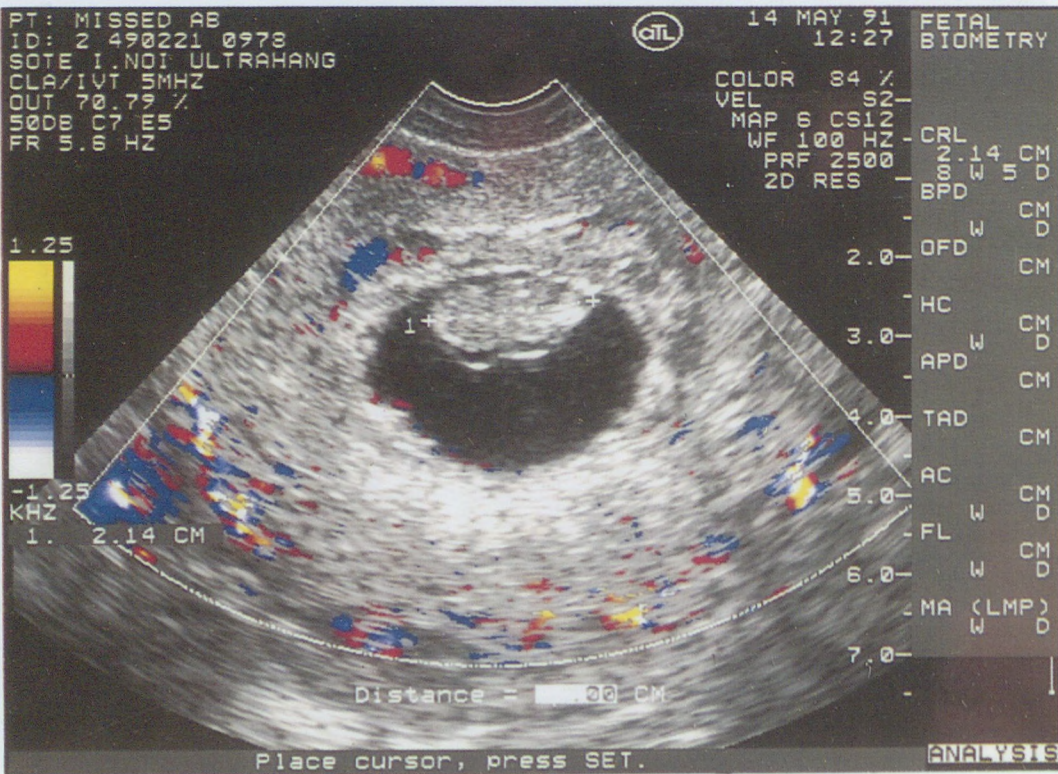
Figure 1-4g. Transvaginal colour Doppler scan of a normal nine-week-old embryo, yolk sac and yolk stalk. The colours at the low pole of the gestational sac sign the circulation of the maternal blood in the intervillous spaces.

Figure 1-4h. Normal ultrasound anatomy of an eleven-week-old embryo. Circulation in the umbilical cord and in the heart is also seen (transvaginal colour Doppler imaging).

Figure 1-4i. Intact ectopic pregnancy of seven weeks. The embryo can be seen in the gestational sac surrounded by maternal vessels (transvaginal colour Doppler imaging).



1-4j



1-4k

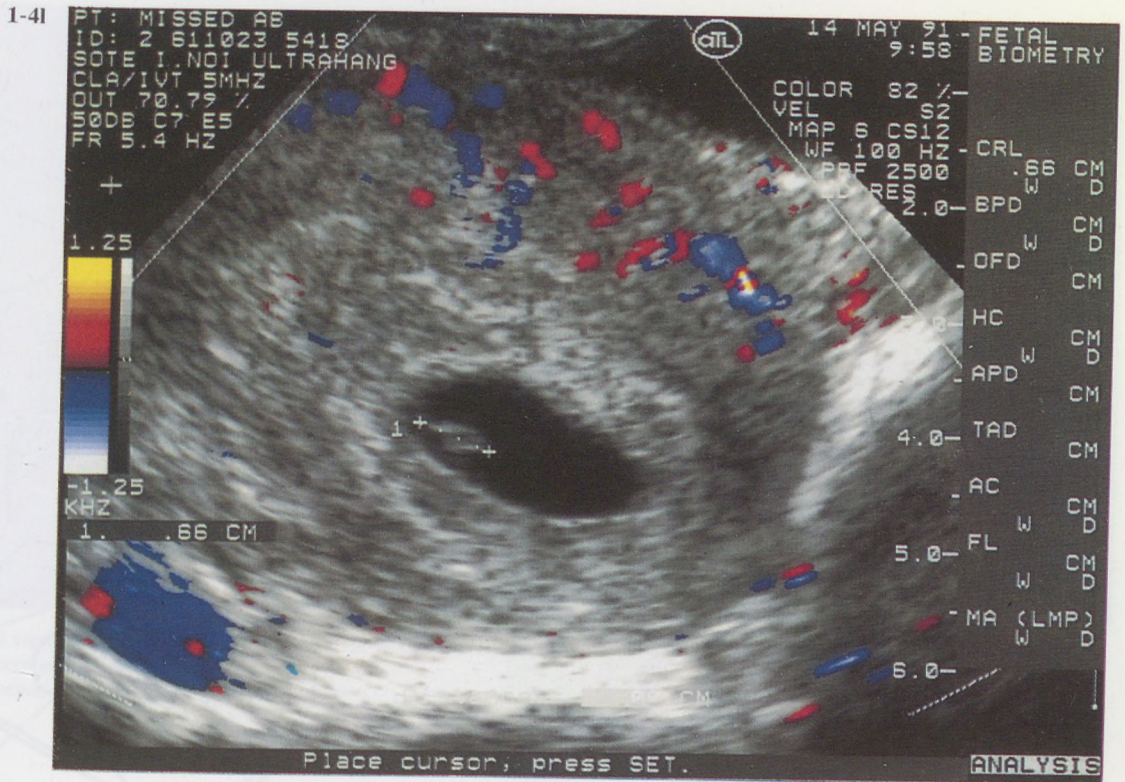


Figure 1-4j. In an intact ectopic pregnancy not only the embryo but the yolk sac is also seen.

Figure 1-4k. Missed abortion: in the deformed gestational sac colour flow in the embryonic mass cannot be detected. No cardiac activity. (Transvaginal colour Doppler imaging).

Figure 1-4l. Ultrasound scan of a very small-for-date embryo in a gestational sac in missed abortion. Colour flow showing a highly vascularized area close to the gestational sac in the intervillous space vessels.

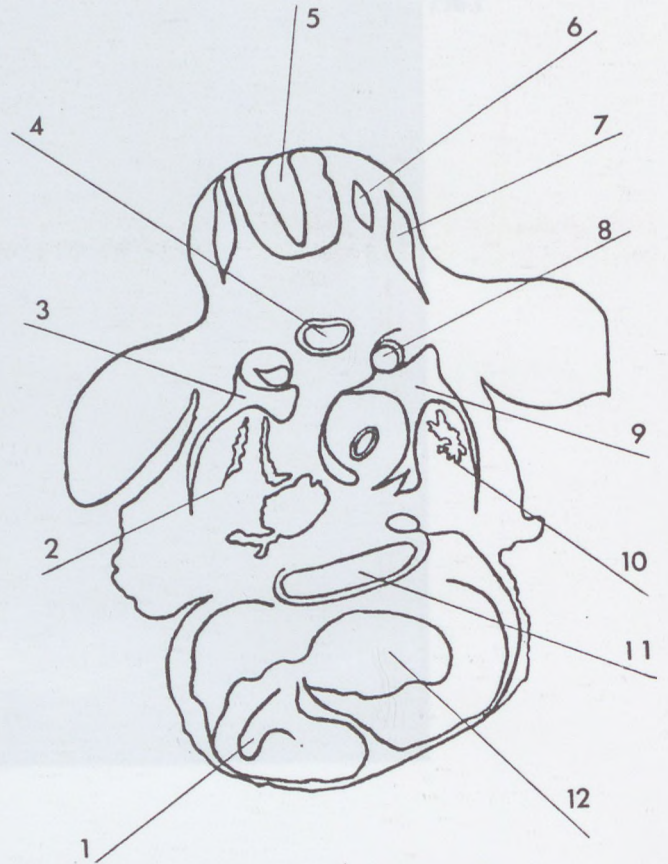


Figure 1-5. A mid-segment transverse section of a five-week-old embryo (1 = right ventricle, 2 = right lung bud, 3 = pleural cavity, 4 = dorsal aorta, 5 = cavity of spinal cord, 6 = posterior root ganglion, 7 = myotome, 8 = left posterior cardinal vein, 9 = left pleuro-peritoneal cavity, 10 = left lung bud, 11 = vena cava inferior, 12 = left ventricle).



Figure 1-7. The transverse transvaginal sonogram of a normal gestation at six weeks shows the embryo lying at the bottom of the sac. The ring-like structure above it represents the primitive yolk sac.

Figure 1-6. A five-week-old embryo.



Figure 1-8. Lateral view of a well-preserved macerated embryo originating from a seven-week spontaneous abortion.



Figure 1-9. A completely expelled seven-week-old embryo with fetal membranes.

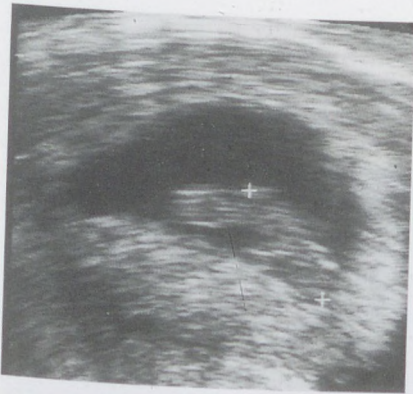


Figure 1-10. Transverse transvaginal sonogram showing an embryo with a crown-rump length of 16 mm consistent with the menstrual age of seven weeks.

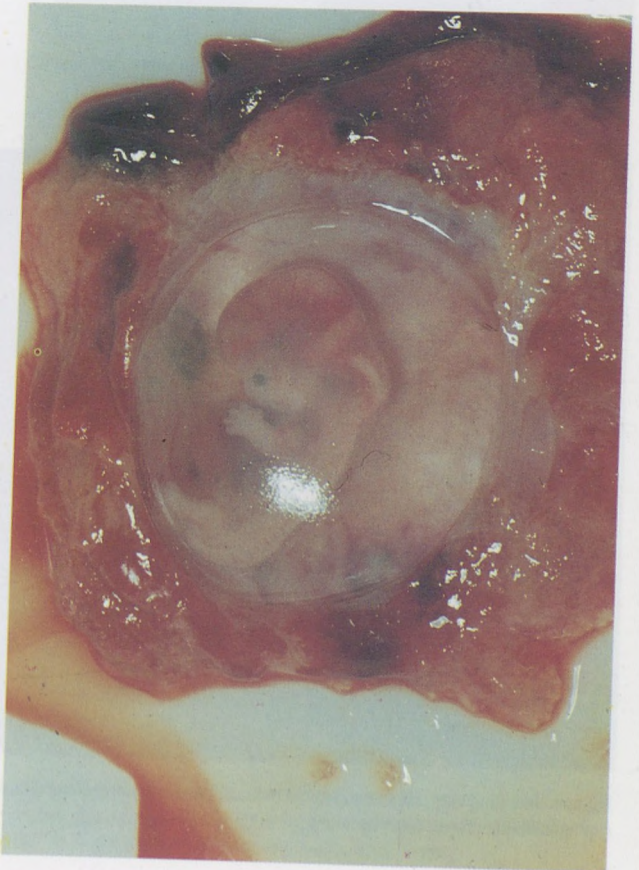


Figure 1-11. Normal seven gestational week-old embryo in the gestational sac surrounded by the placenta.

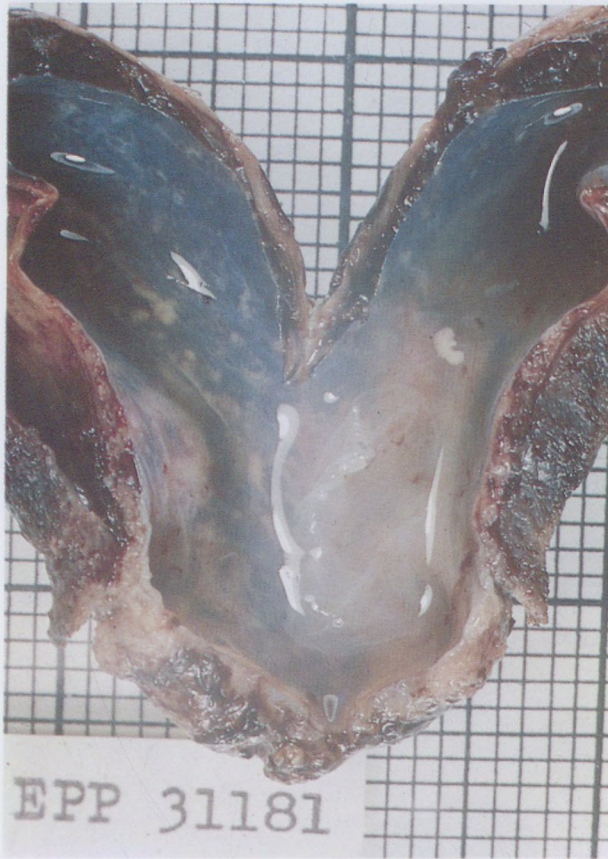


Figure 1-12. A very small growth-retarded embryo in a longitudinally opened gestational sac in a missed abortion. Note the extreme disproportion in size between sac and embryo.

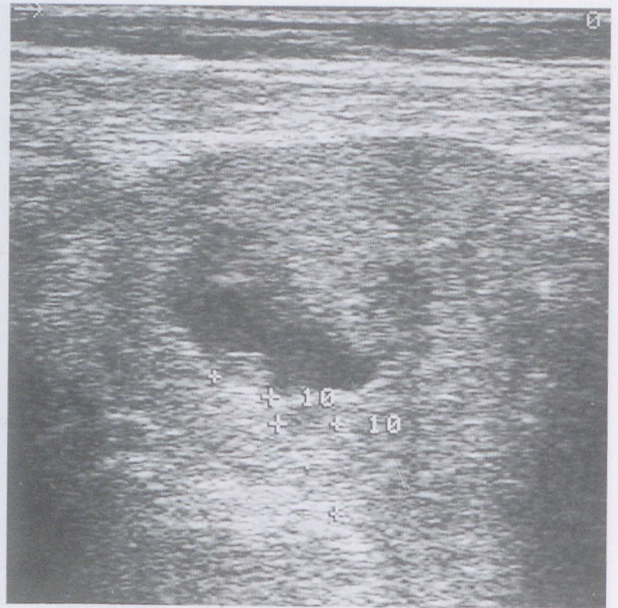


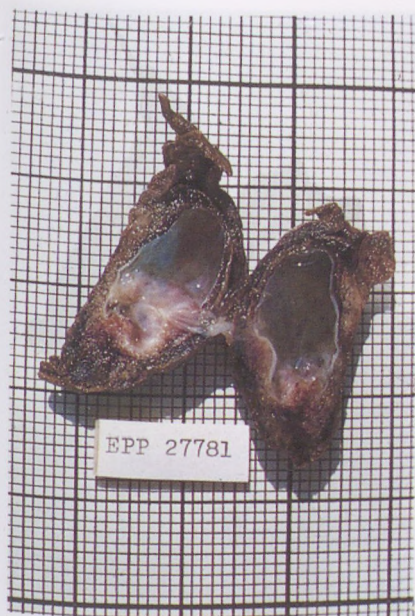
Figure 1-13. Missed abortion at 11 weeks. The uterine cavity is filled with a mass of echogenic tissue. [Note the small growth-retarded fetus (10 mm) and the haemorrhagic decidual tissue.] There was no cardiac activity.



Figure 1-14. Occipital neural tube defect in a seven-week-old macerated embryo (spontaneous abortion material).



Figure 1-15. Lumbosacral spina bifida in a seven-week-old macerated embryo (missed abortion material).



1-16



Figures 1-16 and 17. Blighted ova (longitudinally sectioned empty gestational sacs).

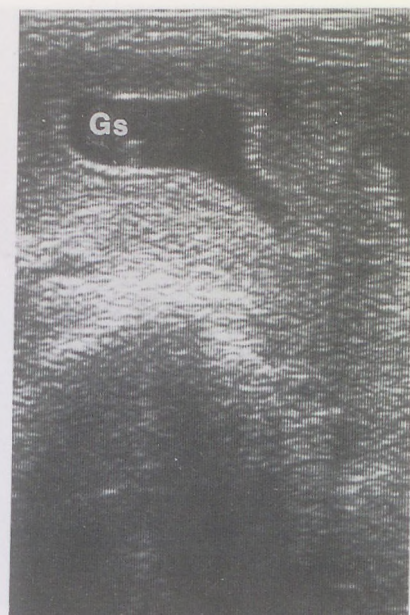


Figure 1-18. Longitudinal scan through a pregnant uterus at nine-weeks gestation showing a blighted ovum with some solid echoes within the sac.

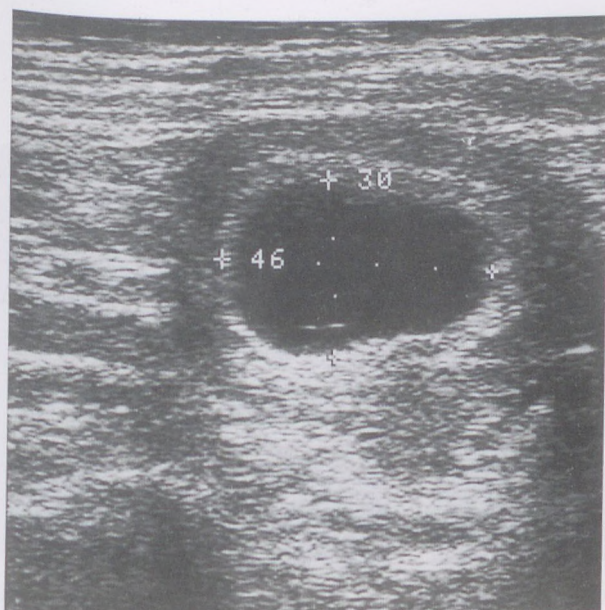


Figure 1-19. The uterine sonogram at 11 weeks of menstrual age shows a blighted ovum with a round sac.



Figure 1-20. An abnormally shaped cylindrical embryo within a completely expelled gestational sac in missed abortion. Around the sac is haemorrhagic decidual tissue.



Figure 1-21. Growth-retarded embryo with anterior and posterior limb buds and tail. The gestational sac is opened longitudinally. The embryonic head has an abnormal contour, the umbilical cord cannot be identified. There are scattered haemorrhagic and fibrinoid necrotic changes in the chorionic plate.



Figure 1-22. Transverse sonogram showing a nine-week irregular gestational sac (Gs) with a dead embryo (E). The irregular hypoechoic area represents blood in the uterine cavity. The amniotic and chorionic membranes are greatly elevated.



Figure 1-23. An eight-week-old disorganized embryo with median cleft lip and large exomphalos (spontaneous abortion).



Figure 1-24. Normal nine-gestational-weeks-old fetus and placenta.



Figure 1-25. The developing embryonal organs are well seen in sagittal section (nine weeks gestation).

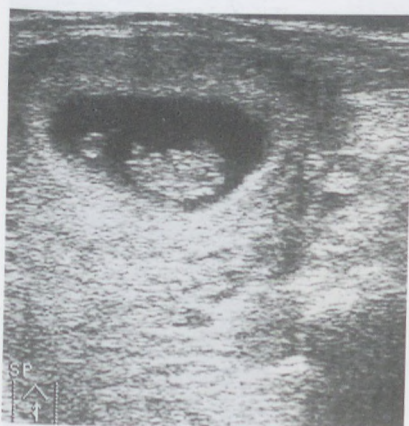


Figure 1-26. Transverse sonogram showing a 25 mm fetus corresponding to a nine-week-old embryo. The yolk sac can be discerned in the extraembryonic coelom.



Figure 1-27. Longitudinal sonogram showing a 51 mm, 12-week-old fetus lying on its back. The head, body and arm can be discerned. The amniotic membrane can be delineated.



Figure 1-28. A 14-week-old fetus with clearly visible fetal head, body and limbs.



Figure 1-29. Normal 14-gestational-weeks old fetus in the amniotic cavity. Placenta and both layers of the membranes (amnion and chorion laeve) are well seen.

Figure 1-30. Unfused membranes at 11 weeks. The amnion and chorion can be delineated.

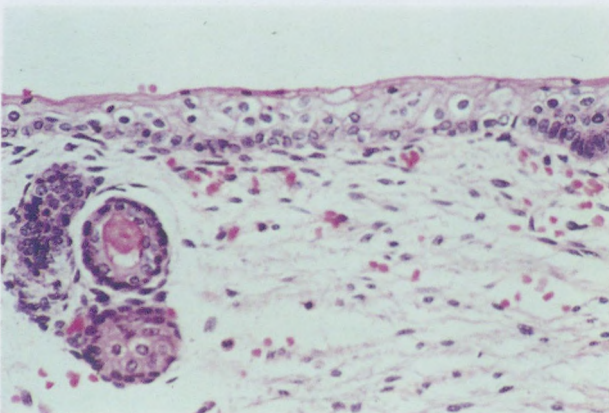
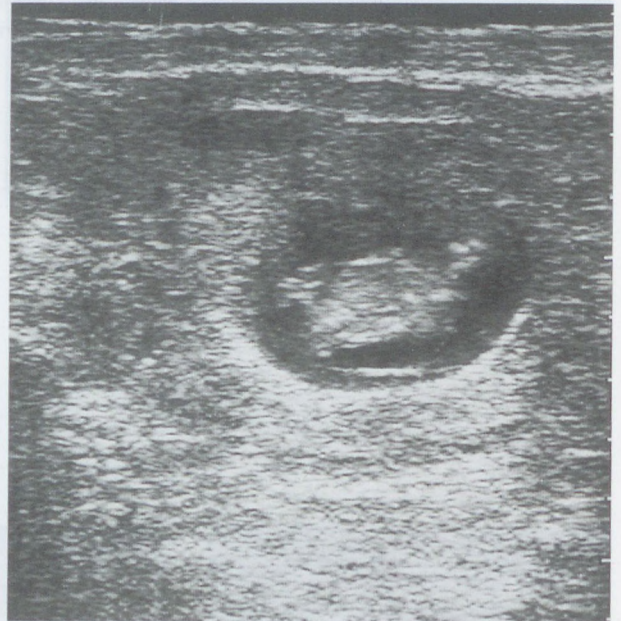


Figure 1-31. The superficial skin layer covering the fetal body consists of a thin keratinizing squamous epithelium [end of the 24th week] (HE, x400).

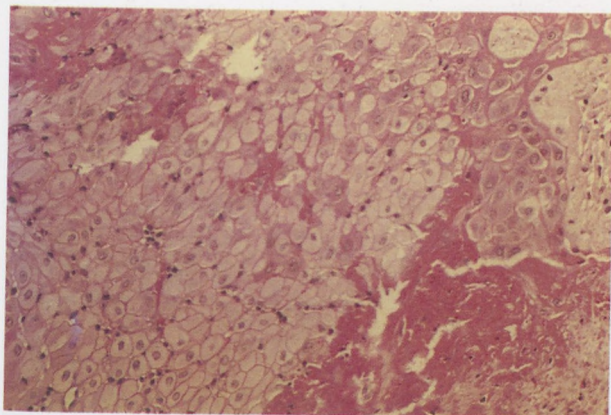


Figure 1-32. Typical swollen groups of decidual cells with a pale or clear cytoplasm, intermingled with necrotic debris: early pregnancy (HE, x160).

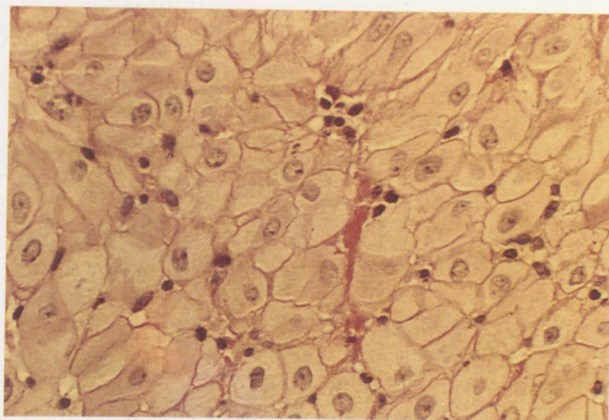


Figure 1-33. Decidual cells at a higher magnification (HE, x400).

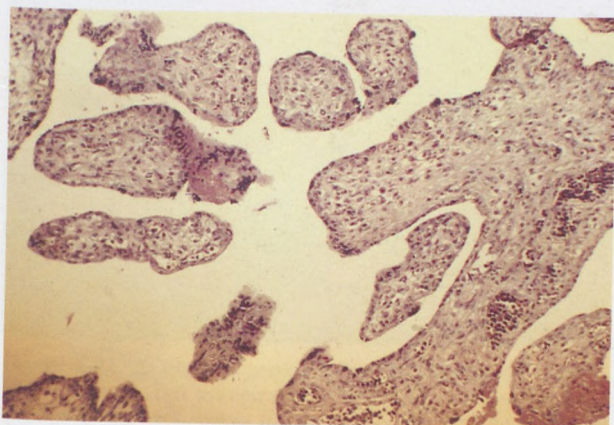


Figure 1-34. Chorionic villi from a ten-week-old placenta (HE, x160).

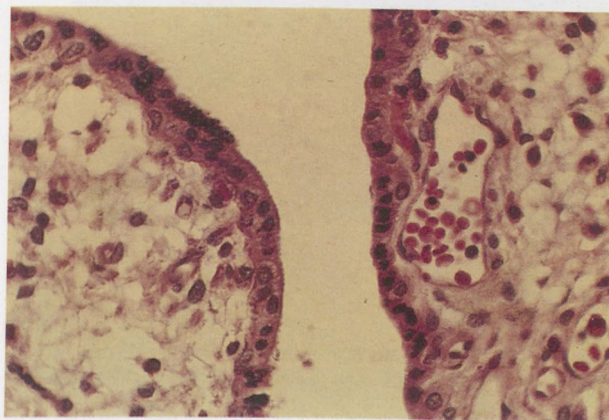


Figure 1-35. Chorionic villi, covered by a layer of syncytiotrophoblast. In the stroma there are thin-walled capillaries (HE, x400).

Figure 1-37. Transcervically performed chorionic villus sampling monitored by ultrasound (A = amniotic fluid, E = embryo, C = cannula).



Figure 1-36. Normal chorionic villi with a regular branching pattern (eight weeks gestation).

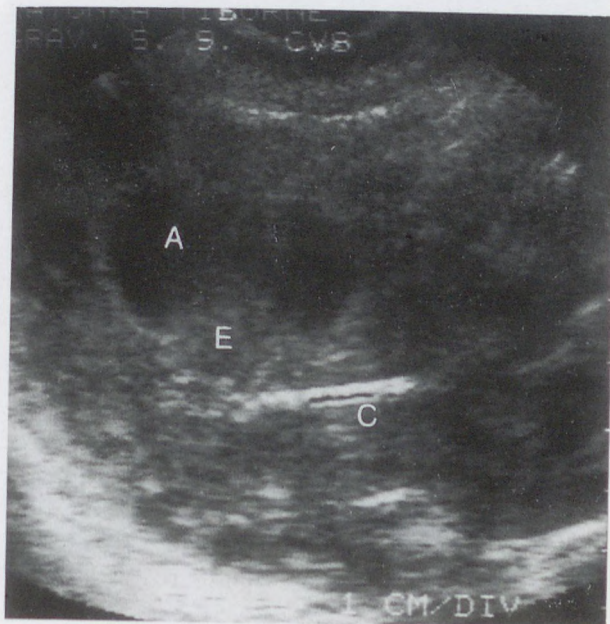




Figure 1-38. Velamentous insertion of the umbilical cord. The fetus has Mayer-Rokitansky-Kuster-Hauser syndrome.

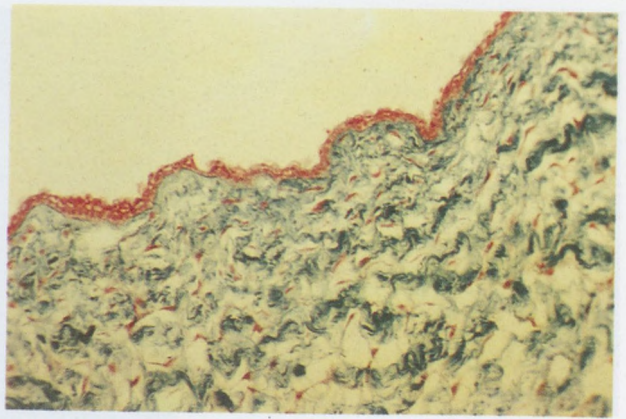


Figure 1-39. Loose connective tissue from the umbilical cord, covered by a layer of amnion (Endes trichrome staining, x160).



Figure 1-40. A medium-sized placental cyst filled with serous fluid. The surface of the cyst is covered by amniotic epithelium. A vascular anomaly is also seen: one vessel runs separately from the placenta (the maternal serum alpha-fetoprotein concentration at the 16th gestational week was elevated, but the fetus had no abnormality).

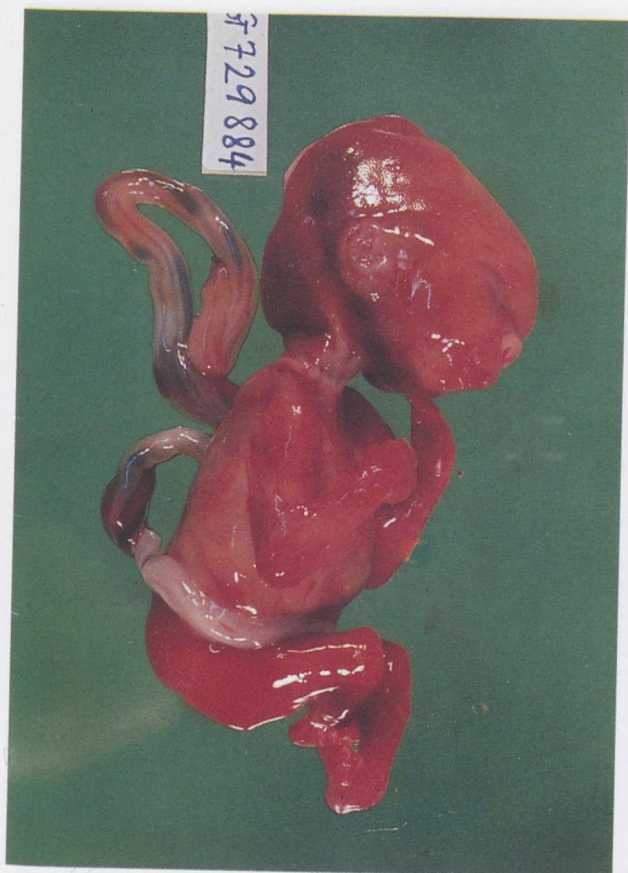


Figure 1-41. At the 11th gestational week; fetus dead from umbilical cord strangulation. There is a groove across the side of the neck, below the ear, and across the edge of the occipital bone.



Figure 1-42. Umbilical cord loops around the fetal legs.

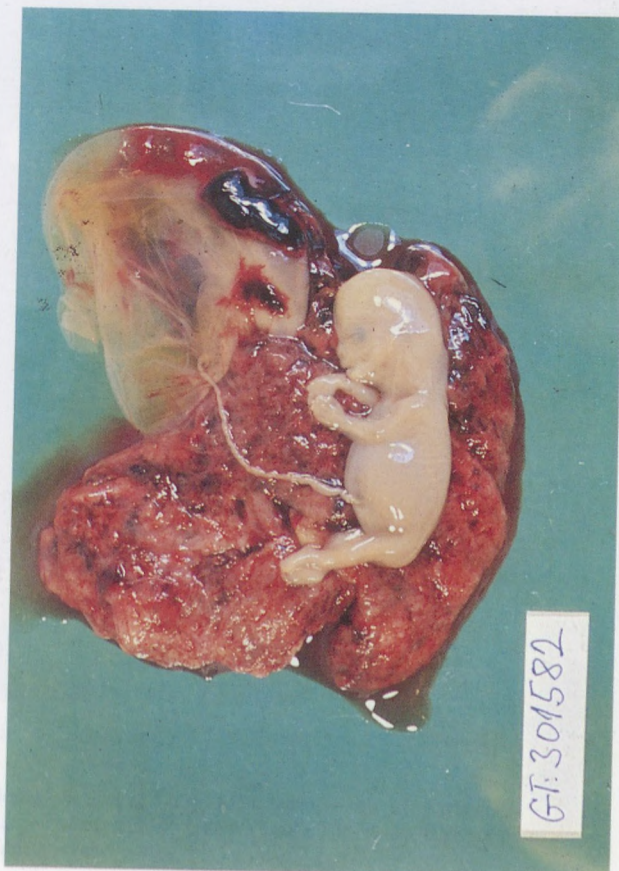


Figure 1-43. Severely macerated fetus and placenta. The umbilical cord is thin, deficient in Wharton's jelly, and twisted many times (termination material after missed abortion diagnosed by ultrasound).

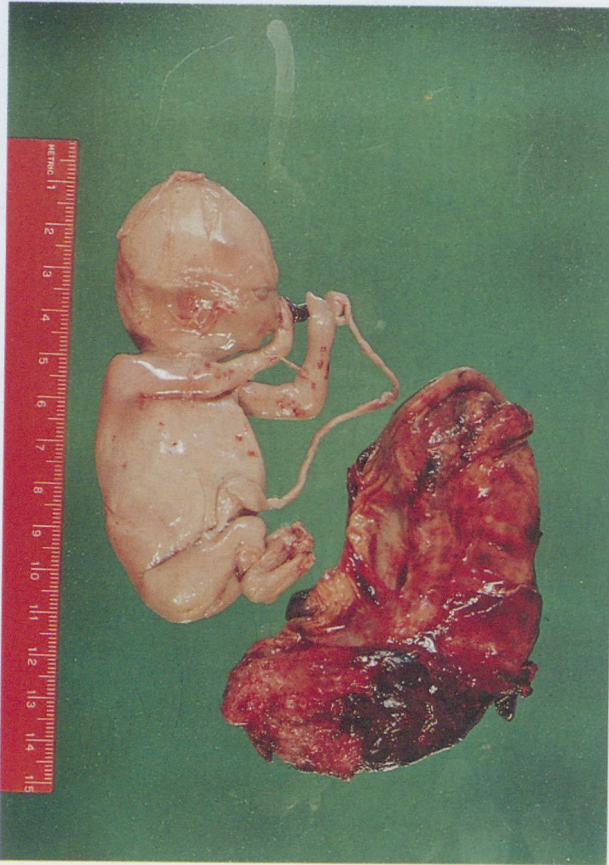


Figure 1-44. An apparently normal, severely autolysed fetus attached to the placenta by a very thin and twisted umbilical cord.

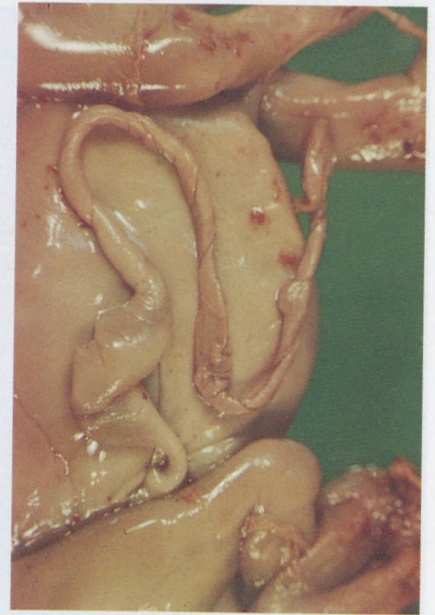


Figure 1-45. Missed abortion material caused by the twisted and macerated umbilical cord.

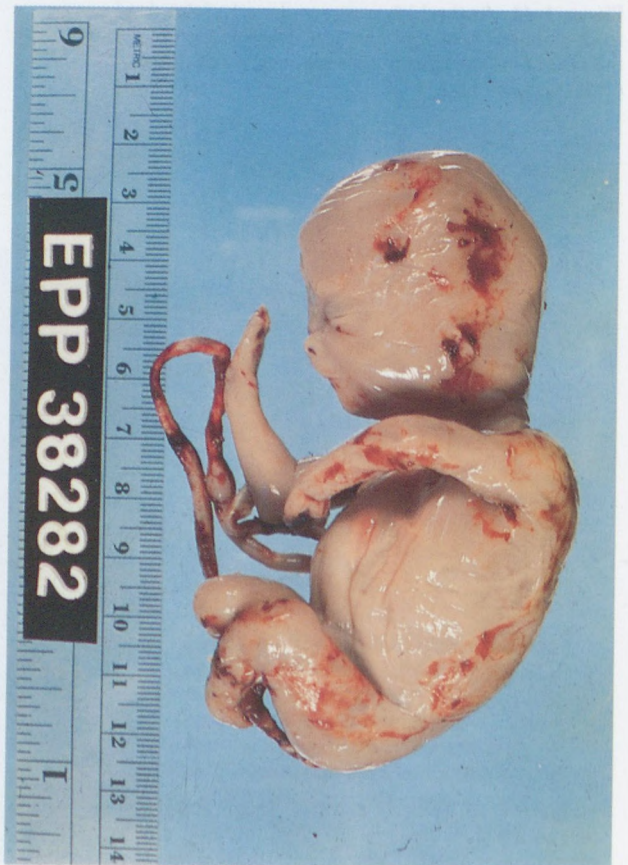


Figure 1-46. An apparently normal but severely autolysed second-trimester fetus with a long twisted umbilical cord emerging from between the legs.

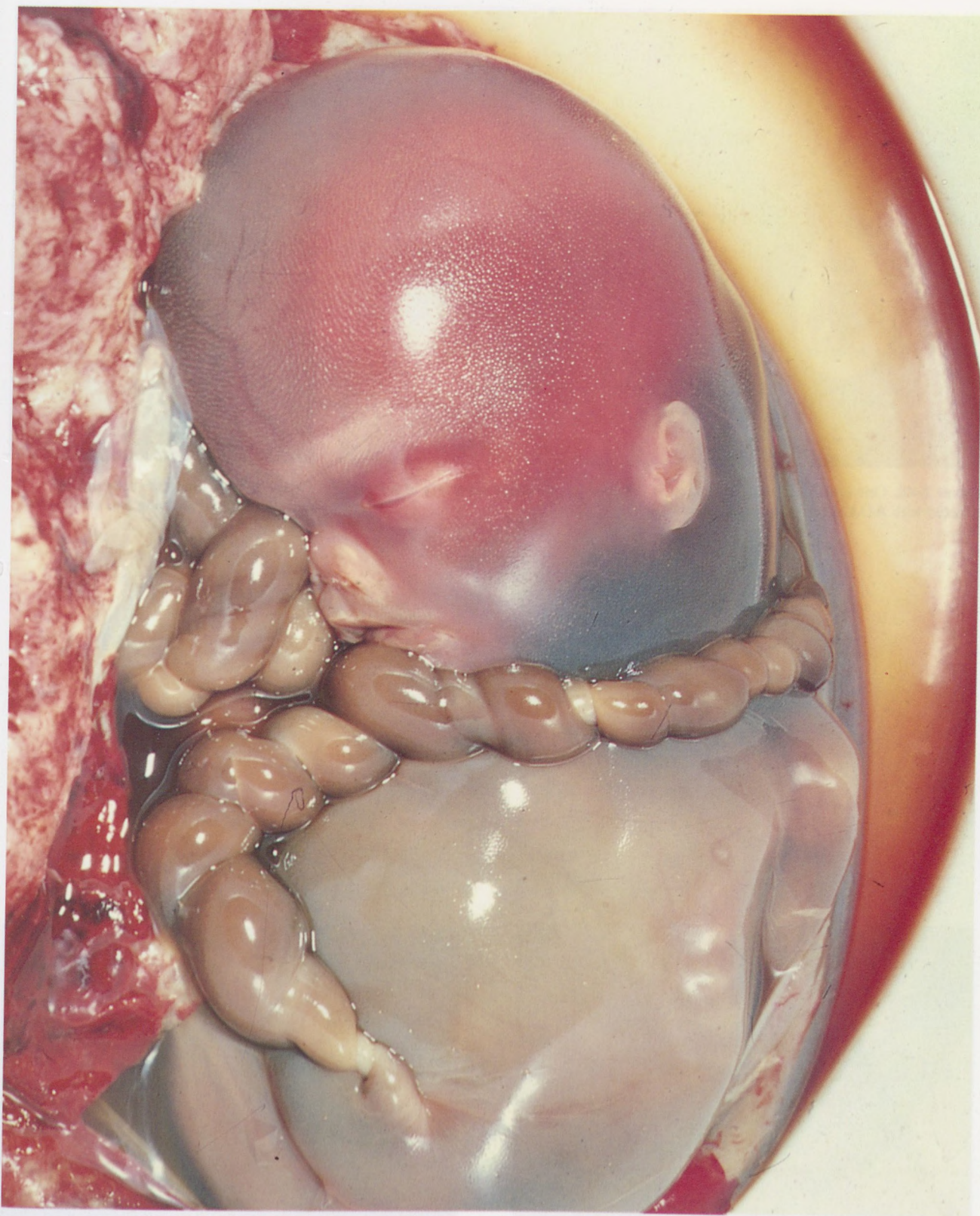


Figure 1-47. Intrauterine death with marked twisting and knotting of the umbilical cord associated with raised maternal serum alpha-fetoprotein.

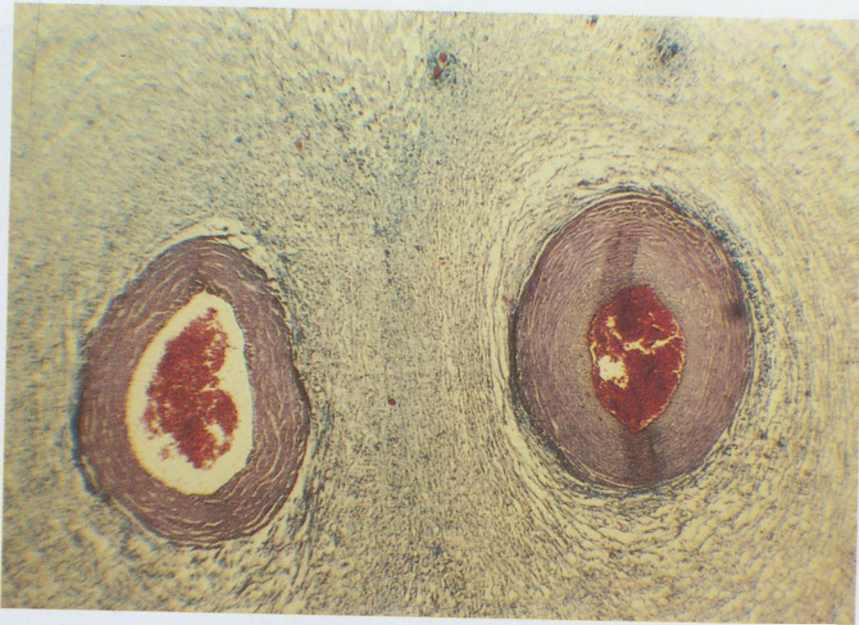


Figure 1-48. One umbilical artery is missing in the cord (single umbilical artery in a fetus affected with ADAM complex, see Chapter 3).

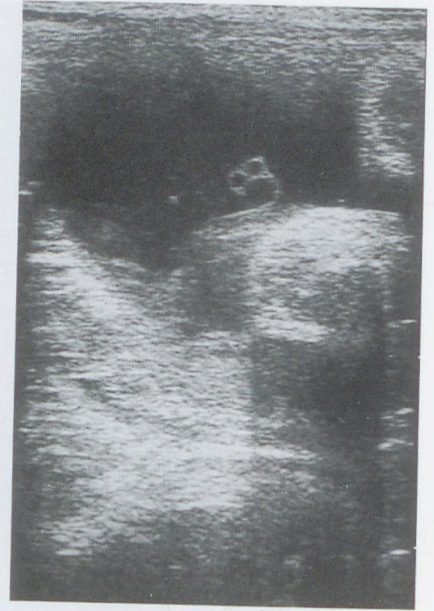


Figure 1-49. Transverse scan of the umbilical cord displaying two arteries and one vein.

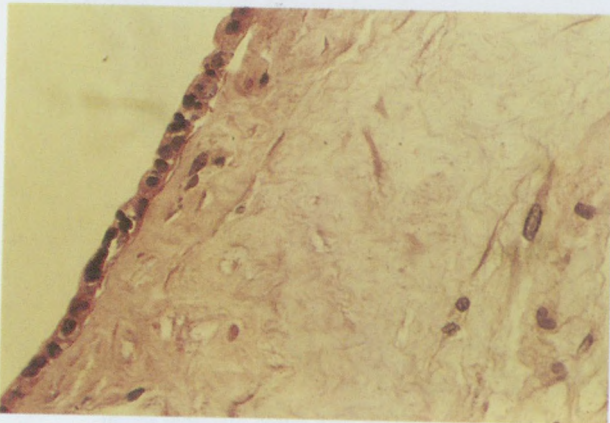


Figure 1-50. Amnion lined with cuboidal epithelium at the 16th gestational week (HE, x400).

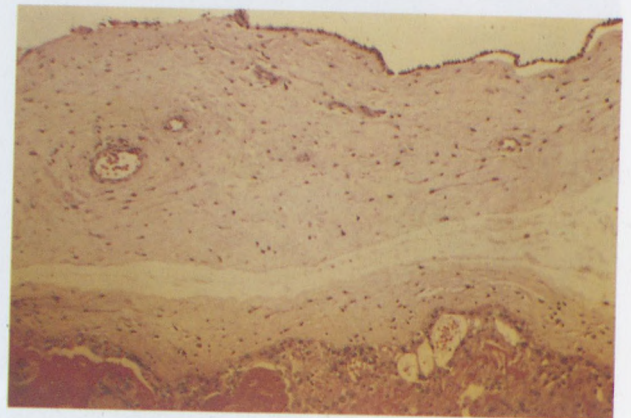


Figure 1-51. Amnion from a third-trimester placenta (HE, x100).

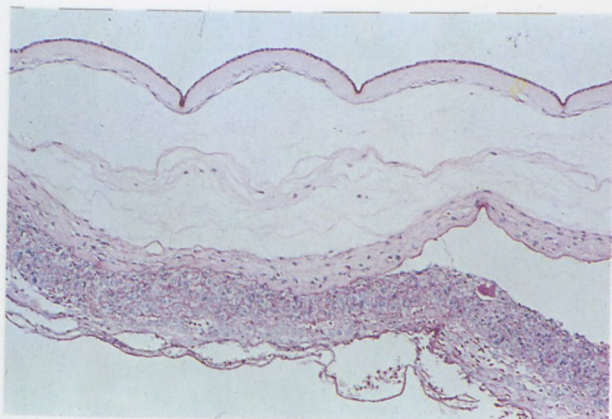


Figure 1-52. A section of fetal membranes from a second-trimester fetus, to show the various cell layers: on the surface the cuboidal epithelium, then the different layers of connective tissue, then the underlying chorion (PAS, x100).

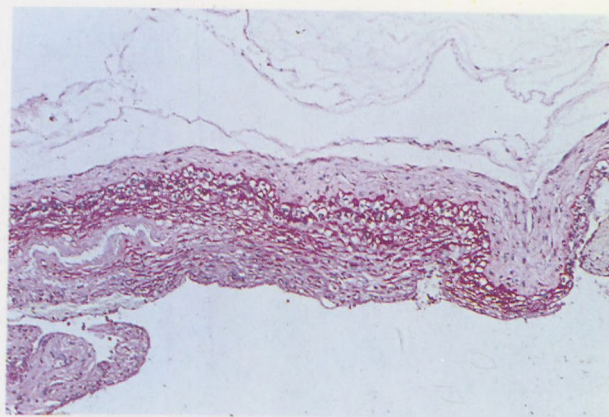


Figure 1-53. The layers rich in macrophages are well visible filled with PAS positive material (16 weeks gestation, anencephaly) (PAS, x100).

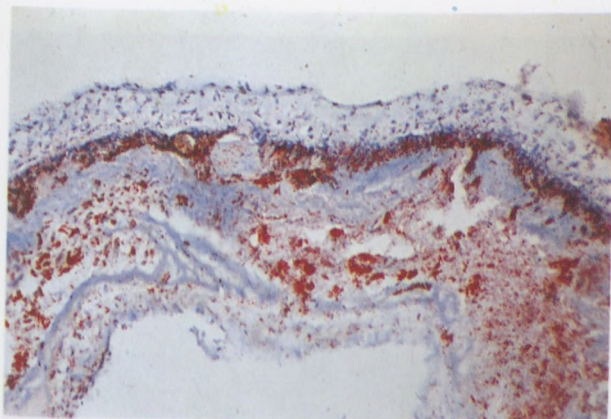


Figure 1-54. Accumulation of fat-droplets is well seen in the macrophage-rich layers of amnion and chorion. This abnormal increase in fat, in a 21-week-old anencephalic fetus, is shown stained with Sudan red (x200).

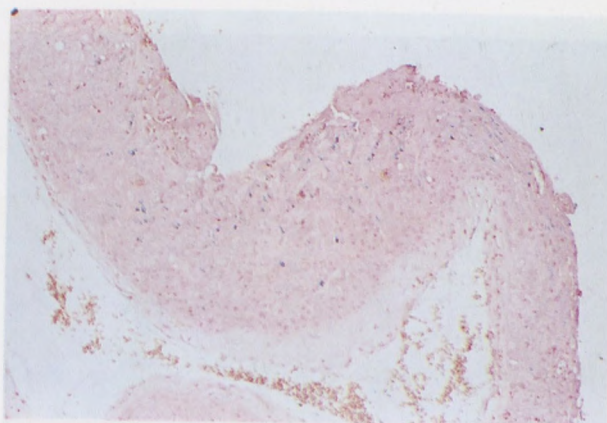


Figure 1-55. Haemosiderin pigmentation (blue-coloured dots) within the fetal membranes (18 weeks gestation, exencephaly) (Prussian blue, x100).

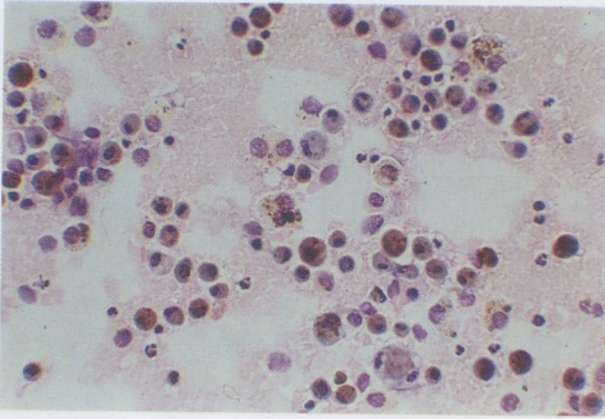


Figure 1-56. Anencephaly: siderophages in a smear of exfoliated amniotic fluid cells (Giemsa, x1000).

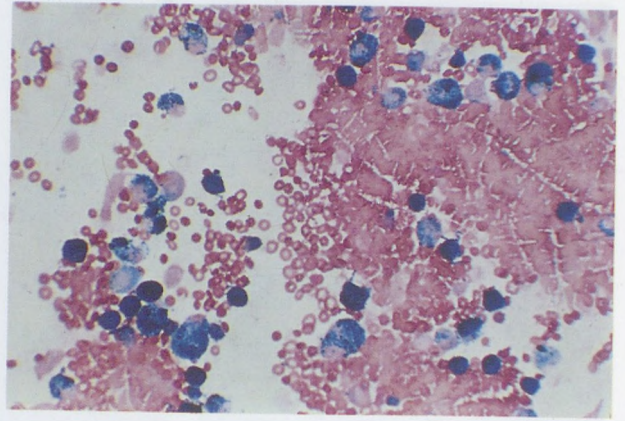


Figure 1-57. Haemosiderin-filled macrophages: smear of exfoliated amniotic fluid cells from a case of spina bifida (18 weeks gestation).

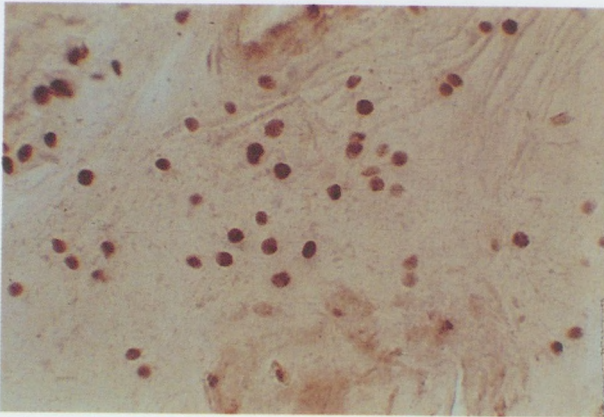


Figure 1-58. Alpha-naphthyl-acetate-esterase (ANAE)-positive macrophages in the amniotic fluid smear (18 weeks' gestation, anencephaly) (ANAE, x400).

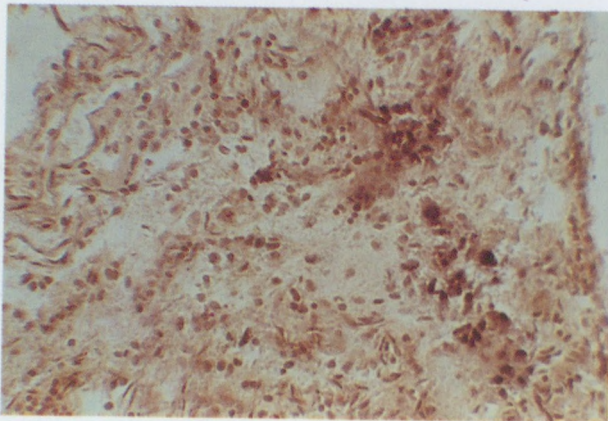


Figure 1-59. ANAE-positive macrophages in the fibrovascular stroma from a case of anencephaly. These cells remove any necrotic brain tissue (ANAE, x400).

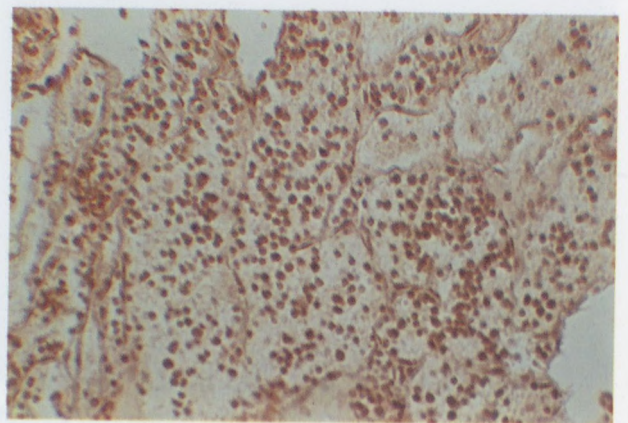


Figure 1-60. Large numbers of ANAE-positive macrophages (ANAE, x400).

Figures 1-61a and 61b. Double immunofluorescent reaction for GFAP (in green) (a) and with Dako-antimacrophage monoclonal antibody (in red) (b) in amniotic fluid pathognomonic for anencephaly (x270).

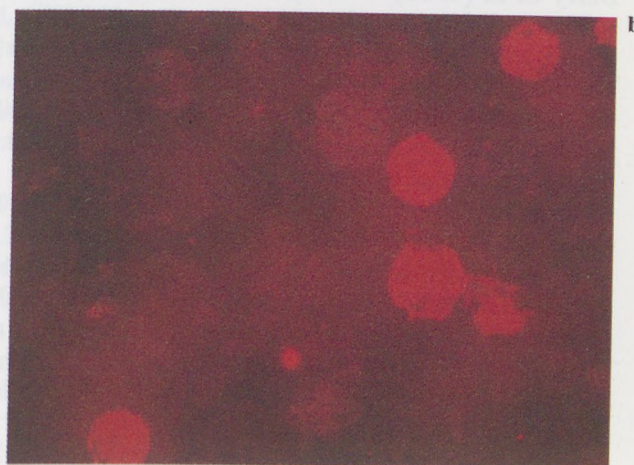
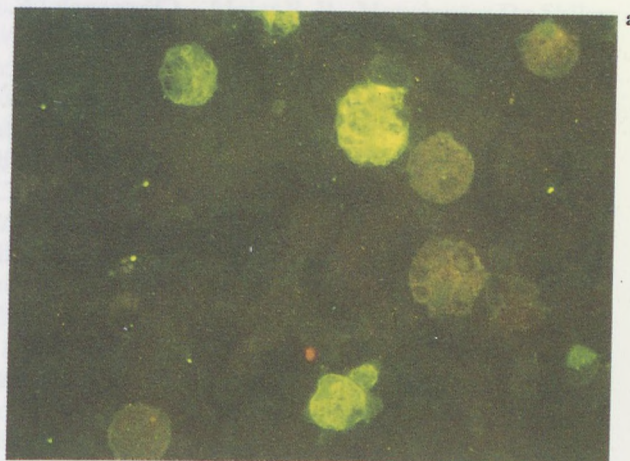


Figure 1-62. Hydatidiform mole.

References

- Benacerraf B. B., Lister J. E., Duponte B. L.** (1988)
1st trimester diagnosis of fetal abnormalities.
J. Reprod. Med. 33, 777-780.
- Berry C. L.** (1980)
The examination of embryonic and fetal material in diagnostic histopathology laboratories.
J. Clin. Pathol. 33, 317-326.
- Boylan P., Parisi V.** (1986)
An overview of hydramnios.
Semin. Perinatol. 10, 136-141.
- Brambati B., Oldrini A., Ferrazzi E., Lanzani A.** (1987)
Chorionic villus sampling: An analysis of the obstetrics experience of 1000 cases.
Prenat. Diagn. 7, 157-169.
- Breart G., Ringa V.** (1990)
Routine or selective ultrasound scanning?
Baill. Clin. Obstet. Gynaec. 4, 45-63.
- Buyse M. L.** (1990)
Birth Defects Encyclopedia. The comprehensive, systematic, illustrated reference source for the diagnosis, delineation, etiology, biodynamics, occurrence, prevention, and treatment of human anomalies of clinical relevance. Center for Birth Defects Information Services, Inc., Dover, MA, USA
- Campbell S., Smith P.** (1990)
Routine screening for congenital abnormalities by ultrasound.
Prenat. Diagn. 10, 325-330.
- Chang H. C., Jones O. W.** (1988)
In vitro characteristic of human fetal cells obtained from chorionic villus sampling and amniocentesis.
Prenat. Diagn. 8, 367-378.
- Chervenak F. A., Isaacson G.** (1986)
Diagnosing congenital malformation in utero. *Ultrasound. Clin. Perinatol.* 13, 593-607.
- Claytons-Smith J., Farndon P. A., McKeown C., Donnai D.** (1990)
Examination of fetuses after induced abortion for fetal abnormality.
Br. Med. J. 300, 295-297.
- Craven C. M., Dempsey S., Carey J. C., Kochenour N. K.** (1990)
Evaluation of a perinatal autopsy protocol. Influence of the prenatal diagnosis conference.
Obstet. Gynecol. 76, 684-688.
- Crooij M. J., Westhuis M., Schoemaker J., Exalto N.** (1982)
Ultrasonographic measurement of the yolk sac.
Br. J. Obstet. Gynaecol. 89, 931-934.
- Cullen M. T., Green J., Whetham J., Salafia C., Gabrielli S., Hobbins J. C.** (1990)
Transvaginal ultrasonographic detection of congenital anomalies in the 1st trimester.
Am. J. Obstet. Gynecol. 163, 466-476.
- Dannevik P., Niemiec E., Lindsay K., Asokan S.** (1982)
The demonstration of the yolk sac in the first trimester of pregnancy using a high-resolution real-time sector scanner.
Med. Ultrasound 6, 57-59.
- Deter R. L., Harrist R. B., Birnholz J. C., Hadlock F. P.** (1986)
Quantitative Obstetrical Ultrasonography.
John Wiley and Sons, New York
- DeVore G. R., Brar H. S., Platt L. D.** (1987)
Doppler ultrasound in the fetus: A review of current applications.
J. Clin. Ultrasound 15, 687-703.
- Dollander A., Fenart R.** (1975)
Éléments d'embryologie. Flammarion Médecine-Sciences, Paris
- Elias S., Simpson J. L., Shulman L. P., Emerson D., Tharapel A. T., Seely L.** (1989)
Transabdominal chorionic villus sampling for 1st trimester prenatal diagnosis.
Am. J. Obstet. Gynecol. 160, 879-886.
- Fairweather D. V. I., Eskes T. K. A. B.** (ed) (1973)
Amniotic Fluid. Research and Clinical Application. Excerpta Medica, Amsterdam
- Furness M. E., Weckert R. C., Parker S. A., Knowles S.** (1989)
Ultrasound in the perinatal necropsy.
J. Med. Genet. 26, 368-372.
- Gebrane-Yuones J., Hoang N. M., Orcel L.** (1986)
Ultrastructure of human umbilical vessels. A possible role in amniotic fluid formation.
Placenta 7, 173-185.
- Gilbert E. F., Opitz J. M.** (1987)
Genetic Aspects of Developmental Pathology. Alan R. Liss, Inc., New York
- Gilbert-Barnes E., Opitz J. M., Barness L. A.** (1989)
The pathologist's perspective of genetic disease.
Pediatr. Clin. North Am. 36, 163-187.
- Goldstein R. B.** (1990)
Endovaginal sonography in very early pregnancy. New observations.
Radiology 176, 7-8.
- Gowland M.** (1988)
Fetal abnormalities diagnosed from early pregnancy.
Clin. Radiol. 39, 106-108.
- Graham D., Sanders R. C.** (1982)
Amniotic fluid.
Semin. Roentgenol. 17, 210-218.
- Grant E. G.** (1991)
Maternal-fetal Doppler sonography. Potential or reality.
Semin. Roentgenol. 26, 75-86.
- Gustavii B., Edvall H., Dahlander K., Jonsson N., Carlén B.** (1986)
Transabdominal chorionic villus sampling.
Lancet 1, 440-441.
- Hahnemann N.** (1974)
Early prenatal diagnosis: A study of biopsy techniques and cell culturing from extraembryonic membranes.
Clin. Genet. 6, 294-306.

- Harris R. D., Simpson W. A., Pet L. R., Marinpadilla M., Crow H. C.** (1990)
Placental hypoechoic-anechoic areas and infarction. Sonographic-pathological correlation. *Radiology* 176, 75-80.
- Hata T., Hata K., Kitao M., Tanaka O.** (1986)
A case of single umbilical artery with various fetal anomalies: Correlations between prenatal ultrasonographic diagnosis and autopsy. *Int. J. Gynaecol. Obstet.* 24, 75-80.
- Heep J., Weidenkopf K. L., Tschahargane C.** (1988)
Polyhydramnios caused by a capillary hemangioma of the umbilical cord. *Geburtshilfe Frauenheilkd.* 48, 819-821.
- Hegge F. N., Franklin R. W., Watson P. T., Calhoun B. C.** (1990)
Fetal malformations commonly detectable on obstetric ultrasound. *J. Reprod. Med.* 35, 391-398.
- Hill M. C., Lande I. M., Larsen J. W.** (1988)
Prenatal diagnosis of fetal anomalies using ultrasound and MRI. *Radiol. Clin. North Am.* 26, 287-307.
- Hogdall C. K., Doran T. A., Shime J., Wilson S., Teshima I.** (1988)
Transabdominal chorionic villus sampling in the second trimester. *Am. J. Obstet. Gynecol.* 158, 345-349.
- Isaacson G., Mintz M. C., Crelin E. S.** (1986)
Atlas of Fetal Sectional Anatomy with Ultrasound and Magnetic Resonance Imaging. Springer-Verlag, New York, Berlin, Heidelberg, Tokyo
- Jauniaux E., Moscoso G., Chitty L., Gibb D., Driver M., Campbell S.** (1990)
An angiomyxoma involving the whole length of the umbilical cord. Prenatal diagnosis by ultrasonography. *J. Ultrasound Med.* 9, 419-422.
- Jauniaux E., Vyas S., Finlayson C., Moscoso G., Driver M., Campbell S.** (1990)
Early sonographic diagnosis of body stalk anomaly. *Prenat. Diagn.* 10, 127-132.
- Jeanty P.** (1989)
Fetal and funicular vascular anomalies. Identification with prenatal ultrasound. *Radiology* 173, 367-370.
- Keeling J. W. (ed.)** (1987)
Fetal and Neonatal Pathology. Springer, London, Berlin
- Kilshaw D.** (1989)
Screening for fetal abnormalities during pregnancy. *Med. Lab. Sci.* 46, 244-249.
- Kuhn W., Rath W., Keith L. G.** (1987)
International colloquy on the management of intrauterine fetal death. *Int. J. Gynaecol. Obstet.* 25, 185-197.
- Kurjak A., Jurkovic D., Alfirovic Z., Zalud I.** (1990)
Transvaginal color Doppler imaging. *J. Clin. Ultrasound* 18, 227-234.
- Kurjak A., Miljan M., Zalud I.** (1990)
Transabdominal and transvaginal color Doppler in the assessment of fetomaternal circulation during all 3 trimesters of pregnancy. *Eur. J. Obstet. Gynecol.* 36, 240-247.
- Lilford R.** (1990)
Prenatal Diagnosis and Prognosis. Butterworths, London
- Lys F., De Wals P., Borlee-Grimee I., Billiet A., Vincotte-Mols M., Levi S.** (1989)
Evaluation of routine ultrasound examination for the prenatal diagnosis of malformation. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 30, 101-109.
- Medina-Gomez P., McBride W. H.** (1986)
Amniotic fluid macrophages from normal and malformed fetuses. *Prenat. Diagn.* 6, 195-205.
- Meier P. R., Manchester D., Shikes R. H., Clewell W. H., Stewart R. N.** (1986)
Perinatal autopsy: Its clinical value. *Obstet. Gynecol.* 67, 349-351.
- Minh H. N., Smajda A., Orcel L.** (1984)
Morphological study of the chorio-allantoic fetal membranes. *Eur. J. Obstet. Gynecol.* 17, 305-314.
- Murken J. D., Stengel-R. S., Schwinger E. (eds)** (1979)
Prenatal Diagnosis. Ferdinand Enke Publishers, Stuttgart
- Niazi M., Coleman D. V., Loeffler F. E.** (1981)
Trophoblast sampling in early pregnancy. Culture of rapidly dividing cells from immature placental villi. *Br. J. Obstet. Gynaecol.* 88, 1081-1085.
- O'Rahilly R., Müller F.** (1984)
Embryonic length and cerebral landmarks in staged human embryos. *Anat. Rec.* 209, 265-271.
- Opitz J. M.** (1987)
Prenatal and perinatal death: The future of developmental pathology. *Pediatr. Pathol.* 7, 363-394.
- Papp Z., Bell J. E.** (1979)
Uncultured cells in amniotic fluid from normal and abnormal foetuses. *Clin. Genet.* 16, 282-290.
- Papp Z., Gardó S., Herpay G., Árvay A.** (1970)
Prenatal sex determination by amniocentesis. *Obstet. Gynecol.* 36, 429-432.
- Papp Z., Polgár K., Tóth Z., Csécséi K.** (1982)
Prenatal diagnosis of neural tube defects by exfoliative cytology of amniotic fluid. *Acta Cytol.* 26, 751-752.
- Polgár K., Ábel Gy., Laczkó J., Sipka S., Papp Z.** (1987)
Immunocytochemical characterization of amniotic fluid macro-

- phages in cases of fetal neural tube defects.
Am. J. Clin. Pathol. 87, 37-42.
- Polgár K., Ábel Gy., Sipka S., Csongor J., Facht J., Papp Z.** (1988)
Immunobiological methods in the prenatal diagnosis and evaluation of fetal neural tube defects.
Acta Physiol. Hung. 71, 551-555.
- Polgár K., Ádány R., Ábel Gy., Kappelmayer J., Muszbek L., Papp Z.** (1989)
Characterization of rapidly adhering amniotic fluid cells by combined immunofluorescence and phagocytosis assays.
Am. J. Hum. Genet. 45, 786-792.
- Polgár K., Sipka S., Ábel Gy., Papp Z.** (1984)
Neutral red uptake by amniotic fluid macrophages in neural tube defects: A rapid test.
N. Engl. J. Med. 310, 1463-1464.
- Powell M. C., Worthington B. S., Buckley J. M., Symonds E. M.** (1988)
Magnetic resonance imaging (MRI) in obstetrics. II. Fetal anatomy.
Br. J. Obstet. Gynaecol. 95, 38-46.
- Reece E. A., Scioscia A. L., Pinter E., Hobbins J. C., Green J., Mahoney M. J., Naftolin F.** (1988)
Prognostic significance of the human yolk-sac assessed by ultrasonography.
Am. J. Obstet. Gynecol. 159, 1191-1194.
- Rehder H., Coerdt W., Eggers R., Klink F., Schwinger E.** (1989)
Is there a correlation between morphological and cytogenetic findings in placental tissue from early missed abortions?
Hum. Genet. 82, 377-385.
- Rhine S. A., Palmer C. G., Thompson J. F.** (1977)
A simple alternative to amniocentesis for first trimester prenatal diagnosis.
Birth Defects Orig. Art. Ser. 13, 231-247.
- Roberts N. S., Dunn L. K., Weiner S., Godmilow L., Miller R.** (1983)
Midtrimester amniocentesis. Indications, technique, risks and potential for prenatal diagnosis.
J. Reprod. Med. 28, 167-188.
- Rodeck C. H., Nicolaides K. H.** (eds) (1984)
Prenatal Diagnosis.
John Wiley and Sons, Chichester-New York
- Rodeck C. H., Nicolini U.** (1988)
Physiology of the mid-trimester fetus.
Br. Med. Bull. 44, 826-849.
- Rottam S., Chervenak F. A.** (1990)
Ultrasound diagnosis of fetal anomalies.
Obstet. Gynecol. Clin. 17, 17-40.
- Saari-Kemppainen A., Karjalainen O., Ylostalo P., Heinonen O. P.** (1990)
Ultrasound screening and perinatal mortality. Controlled trial of systematic one-stage screening in pregnancy.
Lancet 336, 387-391.
- Sanders R. C.** (1990)
Prenatal ultrasonic detection of anomalies with a lethal or disastrous outcome.
Radiol. Clin. North Am. 28, 163-177.
- Sanders R. C., James A. E.** (1985)
The Principles and Practice of Ultrasonography in Obstetrics and Gynecology.
Appleton-Century-Crofts, Norwalk, Connecticut
- Schaffer R. M., Gottesman R., Tortora M., Fox F., Borland M. M., Noyes M. B.** (1983)
The eccentric gestational sac: Sonographic appearance and differential diagnosis.
Med. Ultrasound 7, 157-163.
- Simpson J. L.** (1990)
Incidence and timing of pregnancy losses. Relevance to evaluating safety of early prenatal diagnosis.
Am. J. Med. Genet. 35, 165-173.
- Smith D. W.** (1982)
Recognizable Patterns of Human Malformation.
W. B. Saunders, Philadelphia-London
- Snell R. S.** (1983)
Clinical Embryology for Medical Students.
Little, Brown and Company, Boston-Toronto
- Spirt B. A., Gordon L. P.** (1990)
Sonographic evaluation of the placenta. Importance of pathological correlation.
Radiology 176, 9-10.
- Stabile I., Grudzinskas J. G., Campbell S.** (1990)
Doppler ultrasonographic evaluation of abnormal pregnancies in the 1st trimester.
J. Clin. Ultrasound 18, 497-501.
- Staudach A.** (1986)
Fetale Anatomie im Ultraschall.
Springer, Berlin-Heidelberg-Tokyo
- Szabó J., Herczeg J., Thurzó L., Szemere G.** (1984)
Karyotyping from uncultured human trophoblast in the first trimester of pregnancy.
Obstet. Gynecol. 64, 807-810.
- Wagai T., Fukuda M.** (1988)
Ultrasound in Medicine and Biology.
Excerpta Medica, Amsterdam-New York-Oxford
- Wilt J. C., Brambilla C.** (1966)
Human amnion: Cytology and cell culture.
Can. J. Public Health 57, 158-160.
- Winter R. M.** (1983)
The malformed fetus and stillbirths: Whose patient?
Br. J. Obstet. Gynaecol. 90, 645-649.
- Wong P. C., Arulkumaran S., Ratnam S. S., Pang M.** (1986)
Acute polyhydramnios and cord presentation, complication of chorioangioma of the placenta. A case report.
Int. J. Gynecol. Obstet. 24, 61-64.

Oligohydramnios Sequence

A reduced amniotic fluid volume (*oligohydramnios*) late in pregnancy implies a serious problem for the fetus (placental insufficiency). Recent prenatal diagnostic work has demonstrated that oligohydramnios occurs also in the earlier stages of pregnancy, but then it can only be diagnosed by ultrasound.

One possibility to be always considered is isolated rupture of the amnion. If the chorion remains intact, in spite of amnion rupture, amniotic fluid may be reabsorbed and oligohydramnios develop.

Oligohydramnios of *maternal* origin may develop with certain vaginal and cervical problems, resulting in premature rupture of the membranes and persistent leakage of amniotic fluid.

Among *fetal* factors anomalies of the urogenital apparatus are the most frequent. The earlier the appearance of the oligohydramnios the more serious the prognosis.

The embryo, suspended by the umbilical cord, floats freely in amniotic fluid. This bouillon medium (1) permits symmetrical external growth of the embryo; (2) prevents adherence of the amnion to the embryo; (3) cushions the embryo against injuries by distributing impacts the mother may receive; (4) helps control the embryo's body temperature by maintaining a relatively constant temperature; and (5) enables the fetus to move freely, thus aiding musculoskeletal development.

As oligohydramnios develops the normal intrauterine development of the fetus is disturbed; and a complex anomaly (*multiple deformation sequence*) may result.

Fetuses that have spent a rather long period of intrauterine life in a confined amniotic fluid space are usually born with a flattened nose, ears closely pressed against the scalp, and a typical facial expression (Potter face).

In the absence of normal bronchopulmonary secretion and resorption of amniotic fluid, there is pulmonary hypoplasia. The fetus takes up an abnormal position, which may lead to deformities (hip 'dysplasia', talipes, hypomelia, sirenomelia, ectrodactyly, arthrogryposis, plagiocephaly, etc.), and becomes growth-retarded.

The fetal deformations result from an absence of the mechanical buffering effect of the amniotic fluid.

Potter Sequence

When the above symptoms are due to unilateral or bilateral renal agenesis or, less frequently, severe renal dysplasia, the term "Potter sequence" is used.

This condition is incompatible with postnatal life; death is almost always within a few minutes or hours of birth, not as a result of renal failure, but as that of pulmonary hypoplasia (and very severe atelectasis).

Renal agenesis is usually accompanied by agenesis of the ureters and bladder. Disturbed development of external genitalia may produce a pseudohermaphroditic appearance.

Ultrasonography plays the main role in prenatal diagnosis. The oligohydramnios, the deformed fetal

position and the growth retardation together with poor bladder filling, can be seen on routine ultrasound. The diagnosis of renal agenesis, pulmonary hypoplasia and the various deformities caused by the constrained position require a more thorough ultrasound investigation. Occasionally, the maternal serum AFP may be elevated.

Other urogenital anomalies (urethral agenesis, urethral obstruction, hydronephrosis) can lead to the oligohydramnios deformation sequence. Oligohydramnios as a sign of poor or absent kidney function suggests a hopeless prognosis.

Persistent amniotic fluid leakage, whatever its origin, can also lead to the oligohydramnios deformation sequence. Amniotic fluid in vaginal secretions can be recognized by a simple test (amniotic fluid crystallization test): salts dissolved in the amniotic fluid crystallize from the vaginal secretions, forming a fern-leaf pattern.

As genetic amniocentesis is more and more widely performed, one must watch out for this possibility. Any fluid withdrawn at amniocentesis is soon supplemented. However, if the puncture allows amniotic fluid to slowly leak into the space between amnion and chorion, the fluid loss may lead to oligohydramnios. If the chorion also ruptures, amniotic fluid will ooze into the vagina. In such cases, with a high risk of the deformation sequence and other problems, and also the risk of an ascending intrauterine infection, interruption of pregnancy may be considered.

Leakage of amniotic fluid, lasting

only a few days, may occur after a genetic amniocentesis (3 to 4% of cases). This usually settles with bed rest. The amniotic fluid volume and the fetus should be checked daily by ultrasound.

In less than 1% of amniocenteses amniotic fluid leakage leads to unwanted abortion (including those cases where, following diagnosis of

severe oligohydramnios, pregnancy termination is advised).

In general, oligohydramnios developing before the 20th week of gestation has a poor prognosis, whatever its cause. There is no treatment, and in most cases the condition is irreversible.

A direct relationship has been noted between the objective mea-

surement of amniotic fluid volume and perinatal outcome. Severe oligohydramnios in the second trimester is a particularly poor prognostic sign secondary to development of pulmonary hypoplasia. Oligohydramnios in the post-term patient is also associated with increased perinatal morbidity and mortality.

Figure 2-1. Termination because of severe oligohydramnios (Potter sequence, bilateral renal agenesis): *in toto* expelled fetus and placenta. There is virtually no amniotic fluid present, and the membranes are smoothed tightly around the fetal body, the outline of which is clearly visible, together with the umbilical cord which lies around the fetal neck.

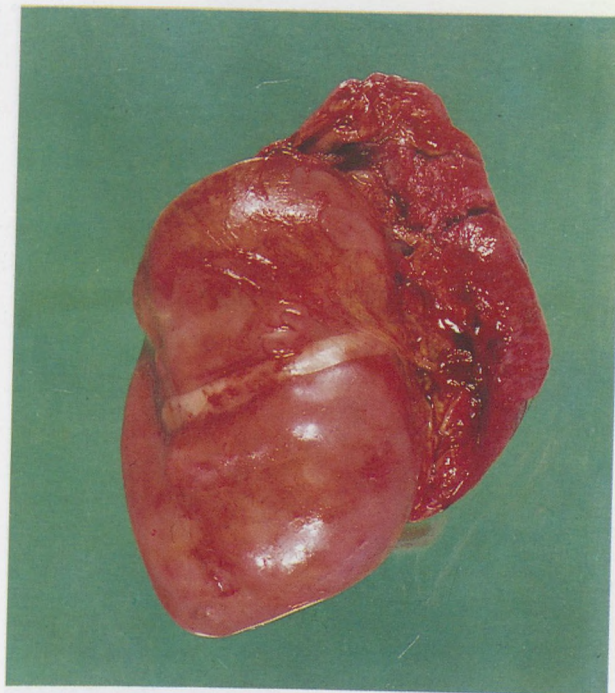


Figure 2-2. Sonographic scan showing typical fetal deformation and compressed position as a consequence of oligohydramnios.

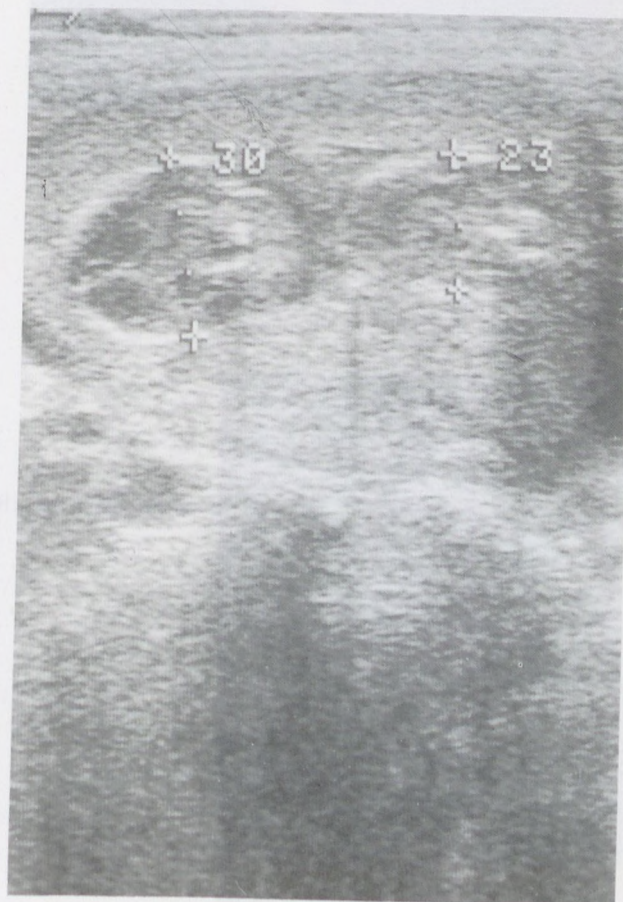


Figure 2-3. Fetal structures difficult to discern; a case of oligohydramnios. The head (30 mm) and trunk (23 mm) can be seen. No kidneys visualized on high-resolution ultrasound.



Figure 2-4. Typical Potter face and bell-shaped thorax with lung hypoplasia resulting from an absence of the mechanical buffering effect of the amniotic fluid.

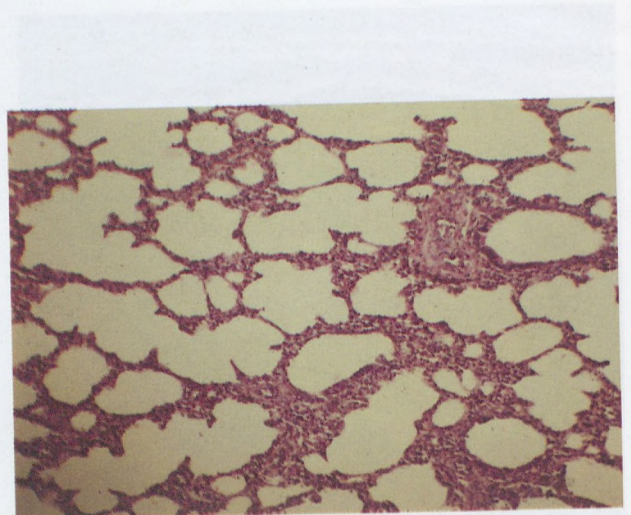


Figure 2-5. Term newborn: normal lung (HE, x100).

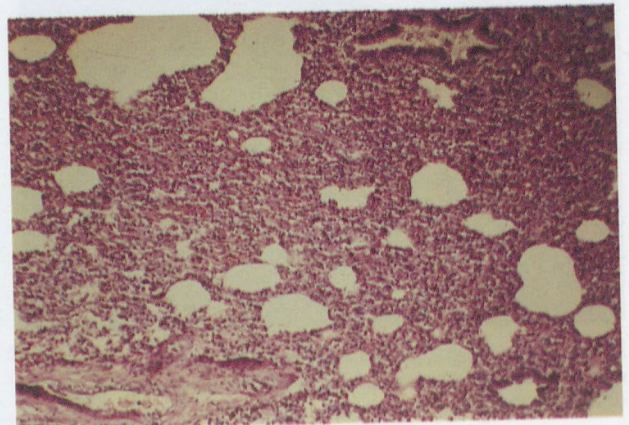


Figure 2-6. Atelectasis in a hypoplastic lung: most of the alveoli are unexpanded (HE, x100).



Figure 2-7. A typical Potter face: lateral view. It is characteristically part of the oligohydramnios malformation sequence.



Figure 2-8. Potter face in a case of bilateral renal agenesis.

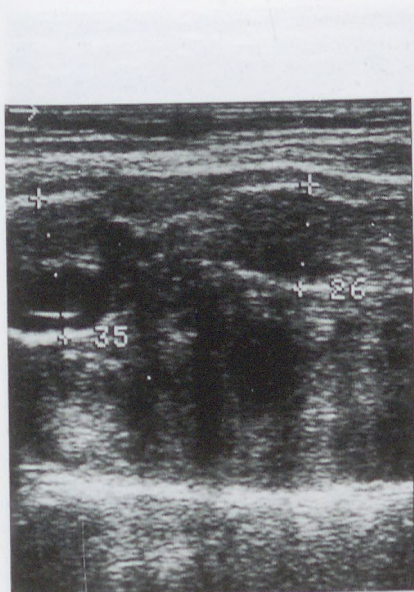


Figure 2-9. Oligohydramnios, deformed fetal position and growth retardation can be seen in the first half of pregnancy.



Figure 2-10. Longitudinal scan of a fetus showing severe oligohydramnios. Note the lack of kidneys and bladder (bilateral renal agenesis).

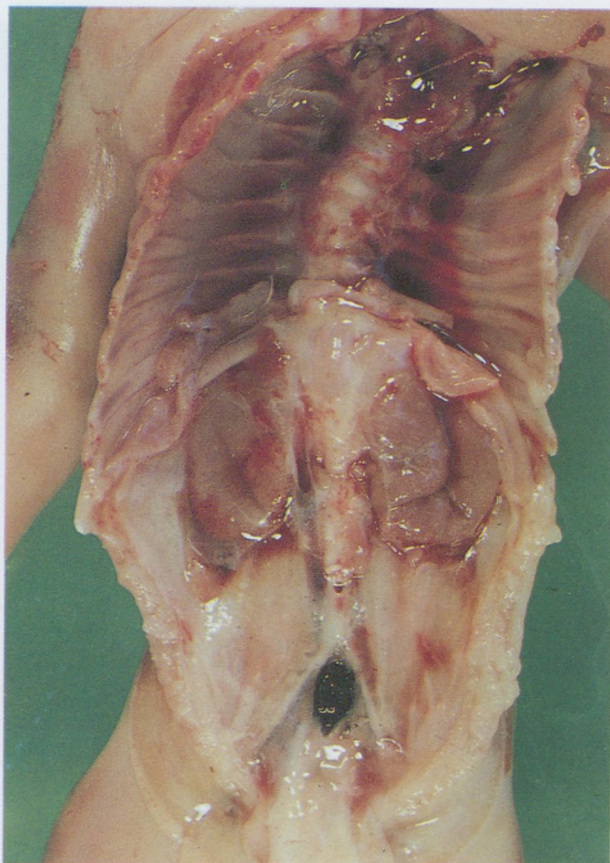


Figure 2-11. Retroperitoneum of a 19-week-old fetus affected with bilateral renal agenesis.



Figure 2-12. Renal agenesis in a 17-week-old fetus.

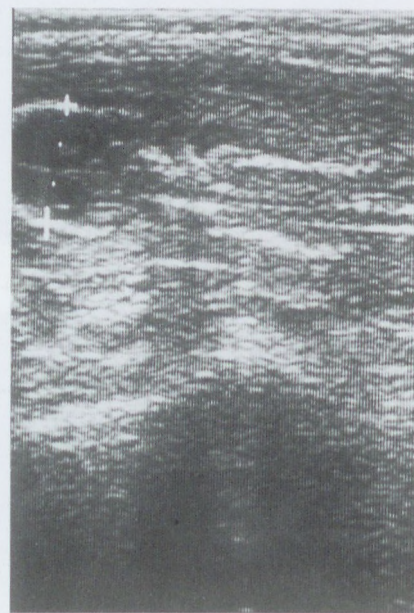


Figure 2-13. Renal agenesis. Note the oligohydramnios, the narrow fetal trunk and the head-trunk disproportion.



Figure 2-14. Caudal regression syndrome (sirenomelia sequence) with bilateral renal agenesis. In addition to fusion of the lower limbs, there is anal atresia and agenesis of the rectum and part of the sigmoid, agenesis of the internal genitalia and genital ambiguity externally.



Figure 2-15. Fusion of the lower limbs: characteristic deformity sequence (sirenomelia).



Figure 2-16. Potter sequence. There is oligohydramnios, and the head and trunk can be seen, but the limbs are difficult to discern.

Figure 2-17. Longitudinal scan through the fetal limb. There is a severe oligohydramnios and the legs are not distinguishable.





Figure 2-18. Potter sequence: characteristic deformity sequence (sirenomelia).



Figure 2-19. Potter sequence: fusion of the lower limbs.

References

- Bastide A., Manning F., Harman C., Lange I., Morrison I.** (1986) Ultrasound evaluation of amniotic fluid. Outcome of pregnancies with severe oligohydramnios. *Am. J. Obstet. Gynecol.* 154, 895-900.
- Benacerraf B. B.** (1990) Examination of the 2nd-trimester fetus with severe oligohydramnios using transvaginal scanning. *Obstet. Gynecol.* 75, 491-493.
- Cardwell M. S.** (1988) Bilateral renal agenesis. Clinical implications. *South. Med. J.* 81, 327-328.
- Chenoweth C. K., Kellogg S. J., Abu-Yousef M. M.** (1991) Antenatal sonographic diagnosis of sirenomelia. *J. Clin. Ultrasound* 19, 167-171.
- Crane J. P., Rohland B. M.** (1986) Clinical significance of persistent amniotic fluid leakage after genetic amniocentesis. *Prenat. Diagn.* 6, 25-31.
- Cruikshank D. P., Varner M. W., Cruikshank J. E., Grant S. S., Donnelly E.** (1983) Midtrimester amniocentesis. An analysis of 923 cases with neonatal follow-up. *Am. J. Obstet. Gynecol.* 146, 204-211.
- Davies B. R., Lomeli R. M.** (1983) Pressure malformations from a chronic leakage of amniotic fluid: Possible iatrogenic origin of extra-membranous pregnancy and the extrachorial placenta. *Am. J. Obstet. Gynecol.* 147, 838-839.
- DeCleyne K., DeGryse H., Slangen T., DeVree M. T., Buytaert P., DeSchepp. A.** (1989) MRI in the prenatal diagnosis of bilateral renal agenesis. *Fortschr. Geb. Röntgenstr. Nuklearmed. Ergänzungsband* 150, 104-105.
- Dyer S. N., Burton B. K., Nelson L. H.** (1987) Elevated maternal serum α -feto-protein levels and oligohydramnios: Poor prognosis for pregnancy outcome. *Am. J. Obstet. Gynecol.* 157, 336-339.
- Fitzmorris-Glass R., Mattrey R. F., Cantrell C. J.** (1989) Magnetic resonance imaging as an adjunct to ultrasound in oligohydramnios. Detection of sirenomelia. *J. Ultrasound Med.* 8, 159-162.
- Freling E. N., Kawada C. Y., Blake G.** (1983) Elevated maternal serum α -feto-protein associated with Potter's syndrome. *Am. J. Obstet. Gynecol.* 146, 218-219.
- Gilbert W. M., Brace R. A.** (1989) The missing link in amniotic fluid volume regulation. Intramembranous absorption. *Obstet. Gynecol.* 74, 748-754.
- Gold R. B., Goyert G. L., Schwartz D. B., Evans M. I., Seabolt L. A.** (1989) Conservative management of second trimester post-amniocentesis fluid linkage. *Obstet. Gynecol.* 74, 745-747.
- Greenberg C. R., Trevenen C. L., Evans J. A.** (1988) The BOR syndrome and renal agenesis. Prenatal diagnosis and further clinical delineation. *Prenat. Diagn.* 8, 103-108.
- Grunnet M. L., Bale J. F.** (1981) Brain abnormalities in infants with Potter syndrome (oligohydramnios tetrad). *Neurology* 31, 1571-1574.
- Hill L. M., Breckle R., Wolgram K. R., Obrien P. C.** (1983) Oligohydramnios. Ultrasonically detected incidence and subsequent fetal outcome. *Am. J. Obstet. Gynecol.* 147, 407-410.
- Hogge W. A., Vick D. J., Schnatterly P. A., MacMillan R. H.** (1989) Bilateral renal agenesis and Müllerian anomalies in a 47,XXX fetus. *Am. J. Med. Genet.* 33, 242-243.
- Honda N., Shimokawa H., Yashiyuki Y., Satoh S., Nakano H.** (1988) Antenatal diagnosis of sirenomelia (sympus apus). *J. Clin. Ultrasound* 16, 675-677.
- Kelly R. B., Nyberg D. A., Mack L. A., Fitzsimmons J., Uhrich S.** (1989) Sonography of placental abnormalities and oligohydramnios in women with elevated alpha feto-protein levels. Comparison with control subjects. *A. J. R.* 153, 815-819.
- Kovács T., Csései K., Tóth Z., Papp Z.** (1991) Familial occurrence of bilateral renal agenesis. *Acta Paediatr. Hung.* 31, 13-21.
- Leonidas J. C., Bhan I., Beatty E. C.** (1982) Radiographic chest contour and pulmonary air leaks in oligohydramnios-related pulmonary hypoplasia. *Invest. Radiol.* 17, 6-10.
- Leschot N. J., Verjaal M., Treffers P. E.** (1985) Risks of midtrimester amniocentesis. Assessment in 3000 pregnancies. *Br. J. Obstet. Gynaecol.* 92, 804-807.
- Mercer L. J., Brown L. G.** (1986) Fetal outcome with oligohydramnios in the 2nd trimester. *Obstet. Gynecol.* 67, 840-842.

- Moessinger A. C., Bassi G. A., Ballantyne G., Collins M. H., James L. S., Blanc W. A. (1983)**
Experimental production of pulmonary hypoplasia following amniocentesis and oligohydramnios. *Early Hum. Dev.* 8, 343-350.
- Moessinger A. C., Collins M. H., Blanc W. A., Rey H. R., James L. S. (1986)**
Oligohydramnios-induced lung hypoplasia. The influence of timing and duration in gestation. *Pediatr. Res.* 20, 951-954.
- Moore P. T., Mencini A., Spitz B. (1984)**
Sonographic diagnosis of hydramnios and oligohydramnios. *Semin. Ultrasound* 5, 157-169.
- Morse R. P., Rawnsley E., Crowe H. C., Marinpadilla M., Graham J. M. (1987)**
Bilateral renal agenesis in three consecutive siblings. *Prenat. Diagn.* 7, 573-579.
- Nakayama D. K., Glick P. L., Harrison M. R., Villa R. L., Noall R. (1983)**
Experimental pulmonary hypoplasia due to oligohydramnios and its reversal by relieving thoracic compression. *J. Pediatr. Surg.* 18, 347-353.
- Nicolini U., Fisk N. M., Rodeck C. H., Talbert D. G., Wigglesworth J. S. (1989)**
Low amniotic pressure in oligohydramnios. Is this the cause of pulmonary hypoplasia? *Am. J. Obstet. Gynecol.* 161, 1098-1101.
- Nimrod C., Varela-Gittings F., Machin G., Campbell D., Wesenberg R. (1984)**
The effect of very prolonged membrane rupture on fetal development. *Am. J. Obstet. Gynecol.* 148, 540-543.
- Rabe D., Leucht W., Hendrik H. J., Boos R., Schmidt W. (1986)**
Sonographic assessment of the quantity of amniotic fluid 2. Oligohydramnios. Its importance in pregnancy and parturition. *Geburtshilfe Frauenheilkd.* 46, 422-426.
- Reuss A., Wladimiroff J. W., Van der Wijngaar J. A., Pijpers L., Stewart P. A. (1987)**
Fetal renal anomalies, a diagnostic dilemma in the presence of intrauterine growth retardation and oligohydramnios. *Ultrasound Med. Biol.* 13, 619-624.
- Richards D. S., Seeds J. W., Katz V. L., Lingley L. H., Albright S. G., Cefalo R. C. (1988)**
Elevated maternal serum alpha-fetoprotein with oligohydramnios. Ultrasound evaluation and outcome. *Obstet. Gynecol.* 72, 337-341.
- Schmidt W., Schroeder K. M., Buchinger G., Kubli F. (1982)**
Genetics, pathoanatomy and prenatal diagnosis of Potter syndrome and other urogenital tract disease. *Clin. Genet.* 22, 105-127.
- Sherer D. M., Thompson H. O., Armstrong B., Woods J. R. (1990)**
Prenatal sonographic diagnosis of unilateral fetal renal agenesis. *J. Clin. Ultrasound* 18, 648-652.
- Sirtori M., Ghidini A., Romero R., Hobbins J. C. (1989)**
Prenatal diagnosis of sirenomelia. *J. Ultrasound Med.* 8, 83-88.
- Sivit C. J., Hill M. C., Larsen J. W., Kent S. G., Lande I. M. (1986)**
The sonographic evaluation of fetal anomalies in oligohydramnios between 16 and 30 weeks gestation. *A. J. R.* 146, 1277-1281.
- Stiller R. J., Pinto M., Heller C., Hobbins J. C. (1988)**
Oligohydramnios associated with bilateral multicystic dysplastic kidneys. Prenatal diagnosis at 15 weeks gestation. *J. Clin. Ultrasound* 16, 436-439.
- Stirrat G. M., Gough J. D., Bullock S., Wald N. J., Cuckle H. S. (1981)**
Raised maternal serum AFP, oligohydramnios and poor fetal outcome. *Br. J. Obstet. Gynaecol.* 88, 231-235.
- Tibboel D., Gaillard J. L., Spritzer R., Wallenburg H. C. S. (1990)**
Pulmonary hypoplasia secondary to oligohydramnios with very premature rupture of fetal membranes. *Eur. J. Pediatr.* 149, 496-499.
- Trigaux J. P., Van Beers B., Delchambre F. (1991)**
Male genital tract malformations associated with ipsilateral renal agenesis. Sonographic findings. *J. Clin. Ultrasound* 19, 3-10.
- Varma T. R., Bateman S., Patel R. H., Chamberlain G. V., Pillai U. (1988)**
Ultrasound evaluation of amniotic fluid. Outcome of pregnancies with severe oligohydramnios. *Int. J. Gynecol. Obstet.* 27, 185-192.
- Voigt H. J., Grünsteidel W., Faschinger Ch. (1989)**
Prenatal diagnosis and prognosis of oligohydramnios. *Geburtshilfe Frauenheilkd.* 49, 350-356.
- Yates J. R. W., Mortimer G., Connor J. M., Duke J. E. (1984)**
Concordant monozygotic twins with bilateral renal agenesis. *J. Med. Genet.* 21, 66-67.

Amniotic Band Sequence (ADAM Complex)

The "amniotic band sequence" is a typical example of a multiple disruption sequence. Bands, forming during intrauterine development, may destroy limbs or larger body regions of an otherwise normally developing embryo, and lead to disruption. The dysmorphic picture depends on the pregnancy stage at which the bands arise. Early adhesions can lead to intrauterine death and spontaneous abortion; bands that appear after organogenesis can cause a wide range of disruptions, from mild finger constrictions to whole limb amputations.

There is no generally accepted nomenclature for this disruption sequence. The fantasy name "ADAM complex" (amniotic, deformity, adhesion, mutilation) seems to be the most expressive.

The main sequence patterns are as follows: craniofacial disruption, eventration leading to absence of the thoracic and/or abdominal wall, and limb constrictions and amputations. Adhesions may affect the head and face of the fetus; or upper limbs, thoracic and abdominal wall; or abdominal wall, perineum and lower limbs. The disruptions are always asymmetric, frequently multiple, and invariably there is evidence of undue fetal constraint (facial deformity, scoliosis, talipes, etc.)

The most acceptable explanation involves a primary amniotic rupture, not involving the chorion. The amniotic fluid then oozes between the two membranes and partially separates them. As the uterus grows, the embryo will be surrounded by amnion-free chorion over an ever-in-

creasing area, so that the remnants of amnion may often be reduced to a small sac at the placental insertion of the umbilical cord. Here and there the amnion remains attached to the chorion, and appears as a bundle of bands running between the surface of the chorion and the insertion of the cord. In addition, the exposed mesodermal surface of the amnion, and the chorion, tend to attach to the fetal skin and form bands and/or deformations.

Amniotic fluid is reabsorbed through the bare chorion deprived of amnion, oligohydramnios develops, and fetal deformation results; deformations become more extensive and the likelihood of adhesion increases. Adhesions are also facilitated by the short umbilical cord usually found in the ADAM complex. It is also possible that, as the uterus grows, the chorion transforms into a smooth endothelium-like layer able to retain amniotic fluid.

A single umbilical artery is an almost obligatory concomitant of the ADAM complex, though the causal mechanism of this association is unknown. The embryo and amnion may be damaged as early as the 4th or 5th week of gestation, when the body stalk develops, and bands form at a later stage.

Amniotic band formation has been demonstrated after amniocentesis, but this complication might be preventable by improved technique. Nevertheless, some evidence supports the view that the risk of amniotic band formation is increased by any spontaneous or artificial reduction of the amniotic

fluid volume, or by injury to the fetus.

Ultrasound plays the leading role in the prenatal diagnosis of amniotic bands and their complications. Almost all cases can now be recognized at routine fetal malformation screening.

Care should be exercised in management of those cases in which amniotic bands appear early, in the presence of a morphologically and functionally normal fetus. They require continuous monitoring, and if disruption cannot be demonstrated (*innocent amniotic bands*), the pregnancy should not be terminated.

Figure 3-1a. Chorioamniototal adhesion (craniofacial type). The fetal head severely destroyed by the placenta. The adhesion caused asymmetrical craniofacial defects.

The brain tissue remained uncovered, there is only a wide cutaneoplacental band above it.



Figure 3-1b. Ultrasound scan of the choriofetal adhesion (Fh = fetal head; arrows show the band).

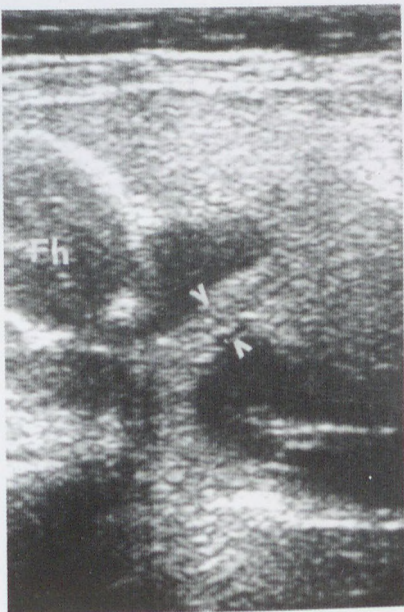
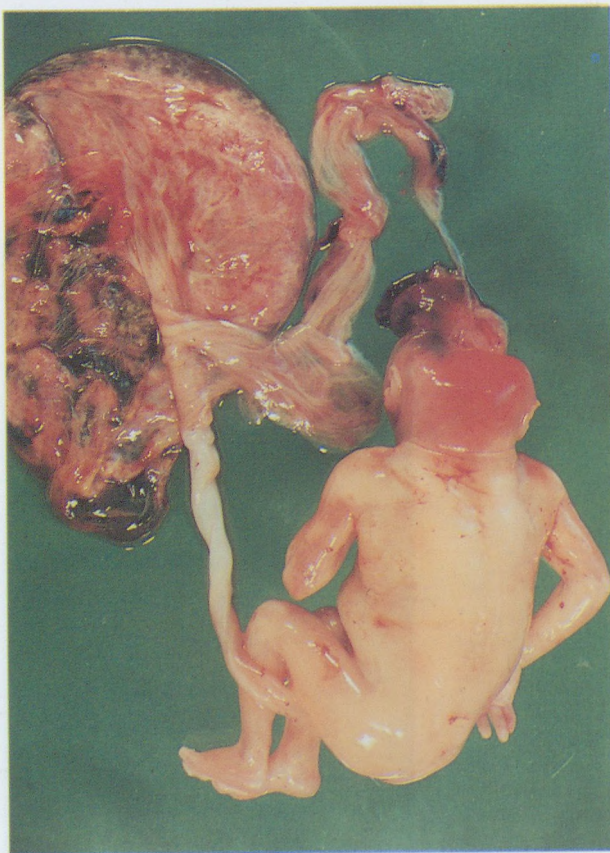
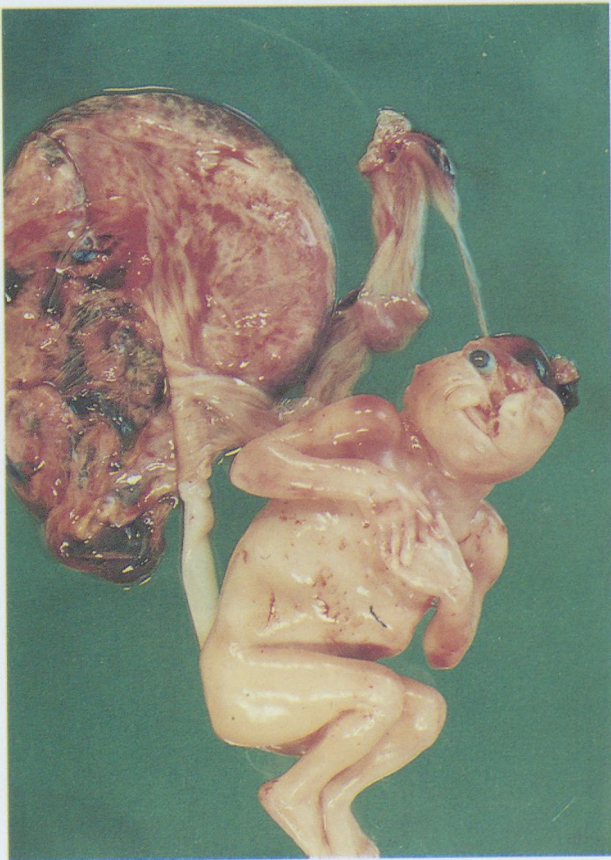


Figure 3-2. Mid-trimester fetus with severe facial deformity caused by amniototal adhesion. There is also a left hand deformity associated with an amniotic band. The facial clefts and limb defects are secondary to amniotic bands. A strand can be seen still adherent to the left hand.



Figures 3-3a, b and c. Amniotic bands, ADAM complex: asymmetrical mid-face defects and extensive malformation of the head.



Figure 3-5b. Macroscopic view of a frontal section of the fetal head, membranes and placenta. The chorioamniotic adhesion destroyed the calvarium. The placental amnion adheres tightly to the remnants of the cranial fibrovascular membrane.



Figure 3-4. Severe craniofacial defect and phocomelia. The cranial bones and brain tissue are also largely destroyed. Associated with early rupture of amnion and choriofetal adhesion.



Figure 3-5a. Chorioamniotic adhesion. The fetal head is deformed by the placenta resulting in severe craniofacial deformation. There is also a large omphalocele and short umbilical cord. Between the cord and placenta is a fine, filamentous amniotic band. Note the short cord which suggests early amnion rupture.



Figure 3-6a. Mid-trimester fetus with omphalocele, short umbilical cord and early rupture of amniotic membrane.



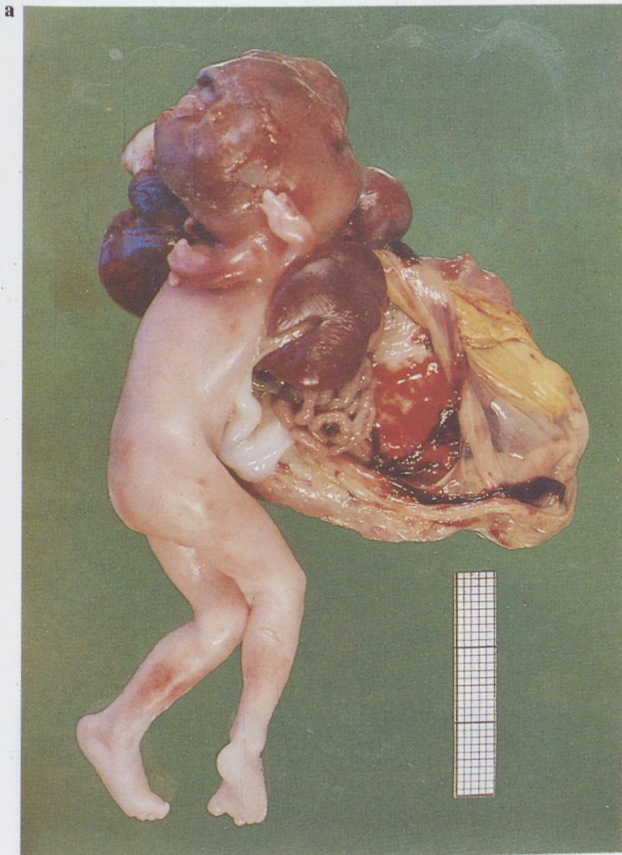
Figure 3-7a. Extensive abdominal midline defect with eventration of abdominal organs. There is severe scoliosis and rotation of the legs to face posteriorly. A ribbon of amnion is attached to the lower pole of the abdominal defect. The genitalia are ambiguous.



Figure 3-6b. Ultrasound picture showing typical oligohydramnios associated with an abnormal position of the fetus. A small omphalocele is also seen.



Figure 3-7b. Ultrasound scan showing exposed internal organs (A = amniotic fluid; Sm = solid mass of the exposed organs).



Figures 3-8a and b. Severe disruption sequence with fetoplacental adhesion, disruption of thorax and abdomen with eventration of internal organs, short umbilical cord and bilateral phocomelia (**a**). After the removal of adherent placenta (**b**) the abdominal organs are lying outside the body, and some remnants of placenta are attached to the deformed head.



Figure 3-9. Amniotomal bands attached to the back of a fetus after serious oligohydramnios.



Figure 3-10. Severe midline defect of abdominal wall with eventration, and ambiguous appearance of the external genitalia.



Figure 3-11a. Severe abdominal wall defect with eventration of the abdominal organs due to amniotofetal adhesion. The amniotic membrane adheres widely to the right side of the abdominal wall. There is a short umbilical cord.



Figure 3-11b. Ultrasound scan showing the exposed mass in the amniotic fluid.

Figure 3-12. Amniotic disruption sequence: extensive abdominal defect of the body wall. Most of the abdominal organs are outside of the body.



Figure 3-13a. Intrauterine device embedded in a spontaneously aborted gestation sac; the embryo is macerated, and partial disruption of the amnion is associated with tight bands and finer filaments anchoring it to the chorion.

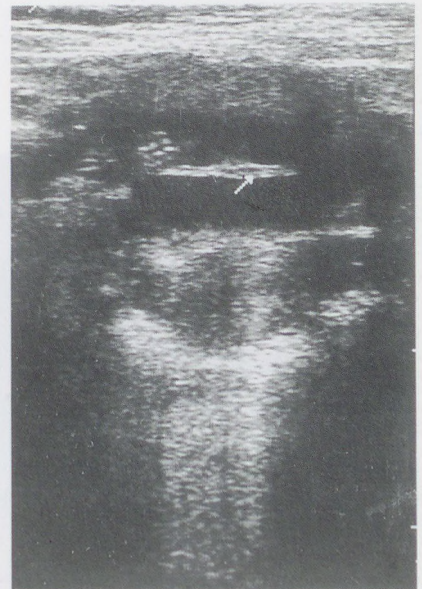


Figure 3-13b. Ultrasound scan showing amniotic band.

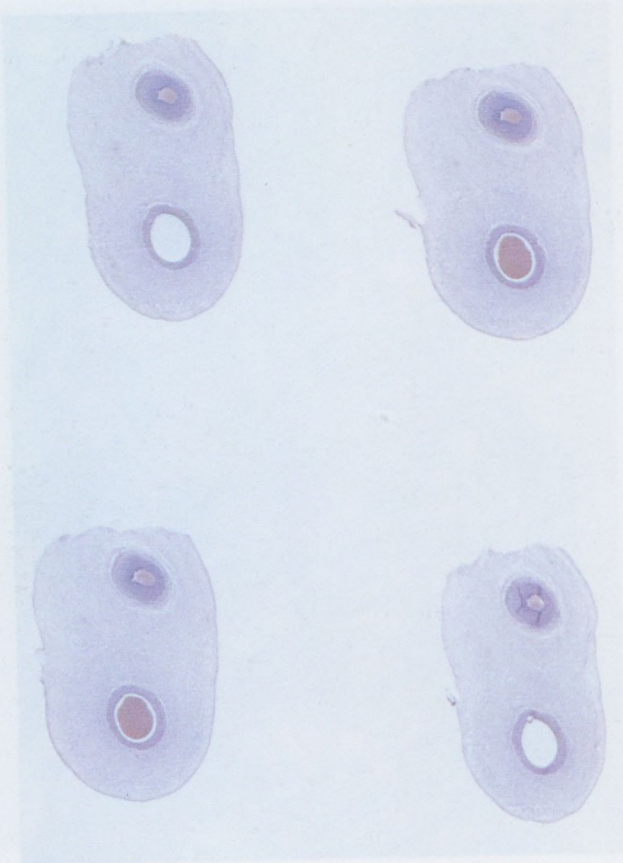


Figure 3-14a. Single umbilical artery. In the transverse sections of the umbilical cord there are only two lumina (HE stain, x8).

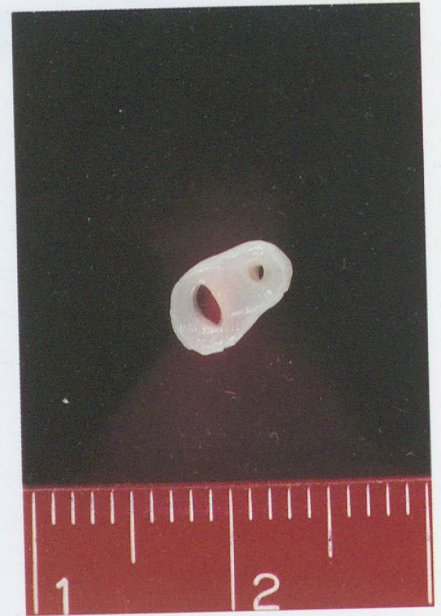


Figure 3-14b. Section of umbilical cord with two vessels only. A smaller artery and a larger vein embedded in the Wharton's jelly. Single umbilical artery is often associated with ADAM complex.

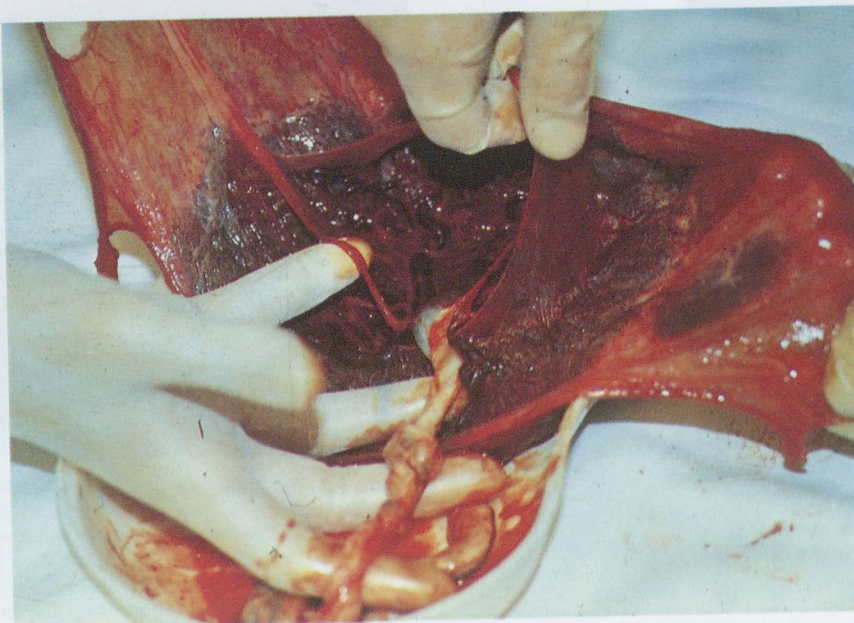
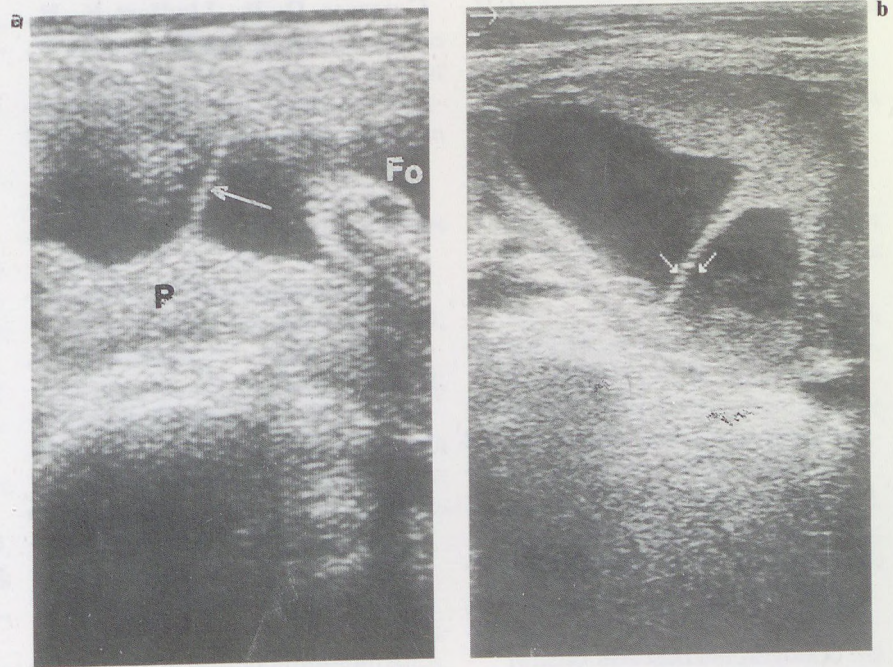


Figure 3-15. Fetal surface of the placenta after a normal delivery. Near to the umbilical cord an innocent amniotic band bridges a gap of a few centimetres between two points on the inner surface of the chorion, causing no fetal abnormality.



Figures 3-16a and b. Harmless amniotic bands, easily documented on ultrasound (P = placenta; Fo = fetal foot).

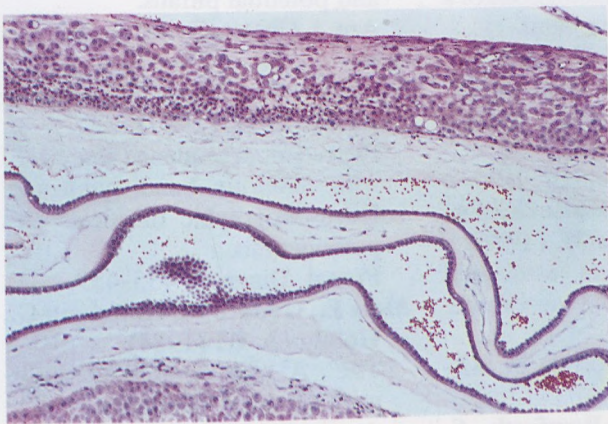


Figure 3-17. Photomicrograph of amniotic bands. In the surrounding chorion there is an inflammatory cell reaction (HE, x100).

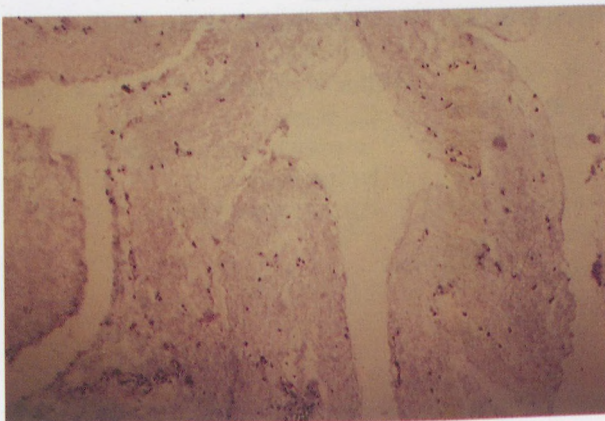


Figure 3-18. Amniotic bands, with inflammatory cell reaction (HE, x200).

References

- Aitken D. A., May H. M., Ferguson-Smith M. A.** (1984)
Amniotic band disruption syndrome associated with elevated amniotic AFP and normal acetylcholinesterase gel test. *Prenat. Diagn.* 4, 443-446.
- Brown D. L., Felker R. E., Emerson D. S.** (1989)
Intrauterine shelves in pregnancy. Sonographic observations. *A. J. R.* 153, 821-824.
- Burton D. J., Filly R. A.** (1991)
Sonographic diagnosis of the amniotic band syndrome. *A. J. R.* 156, 555-558.
- Chen H., Gonzalez E.** (1987)
Amniotic band sequence and its neurocutaneous manifestations. *Am. J. Med. Genet.* 28, 661-673.
- Christiaens G. C., Van Baarlen J., Huber J., Leschot N. J.** (1989)
Fetal limb constriction. A possible complication of CVS. *Prenat. Diagn.* 9, 67-71.
- Csécsei K., Szeifert G. T., Papp Z.** (1987)
Amniotic bands associated with early rupture of amnion due to an intrauterine device. *Zentralbl. Gynäkol.* 109, 738-741.
- Donnai D., Winter R. M.** (1989)
Disorganization. A model for early amnion rupture. *J. Med. Genet.* 26, 421-425.
- Donnenfeld A. E., Dunn L. K., Rose N. C.** (1985)
Discordant amniotic band sequence in monozygotic twins. *Am. J. Med. Genet.* 20, 685-694.
- Gorczyca D. P., Lindfors K. K., McGahan J. P., Hanson F. W.** (1990)
Limb body wall complex. Another cause for elevated maternal serum alpha fetoprotein. *J. Clin. Ultrasound* 18, 198-201.
- Grillo M., Wisner D., Semm K.** (1989)
Sonographic diagnosis of the amniotic band syndrome. *Geburtshilfe Frauenheilkd.* 49, 1093-1095.
- Hartwig N. G., Vermeijker C., DeVries H. E., Kagie M., Kragt H.** (1989)
Limb body wall malformation complex. An embryologic etiology. *Hum. Pathol.* 20, 1071-1077.
- Herva R., Karkinen-J. M.** (1984)
Amniotic adhesion malformation syndrome: Fetal and placental pathology. *Teratology* 29, 11-19.
- Hill L. M., Kislak S., Jones N.** (1988)
Prenatal ultrasound diagnosis of a forearm constriction band. *J. Ultrasound Med.* 7, 293-295.
- Hughes R. M., Benzie R. J.** (1984)
Amniotic band syndrome causing fetal head deformity. *Prenat. Diagn.* 4, 447-450.
- Ito M., Onitsuka Y., Matsui K., Fujisaki S., Maeyama M.** (1986)
Craniofacial defects associated with amniotic band syndrome. A case report. *Int. J. Gynecol. Obstet.* 24, 43-45.
- Kalousek D. K., Bamforth S.** (1988)
Amnion rupture sequence in pre-viable fetuses. *Am. J. Med. Genet.* 31, 63-73.
- Kaplan L. C., Matsuoka R., Gilbert E. F., Opitz J. M., Kurnit D. M.** (1985)
Ectopia cordis and cleft sternum. Evidence for mechanical teratogenesis following rupture of the chorion or yolk-sac. *Am. J. Med. Genet.* 21, 187-199.
- Kohn G.** (1987)
The amniotic band syndrome. A possible complication of amniocentesis. *Prenat. Diagn.* 7, 303-305.
- Lage J. M., Van Marter L., Bieber F. R.** (1988)
Questionable role of amniocentesis in the etiology of amniotic band formation. A case report. *J. Reprod. Med.* 33, 71-73.
- Lockwood C., Ghidini A., Romero R.** (1988)
Amniotic band syndrome in monozygotic twins. Prenatal diagnosis and pathogenesis. *Obstet. Gynecol.* 71, 1012-1016.
- Lockwood C., Ghidini A., Romero R., Hobbins J. C.** (1989)
Amniotic band syndrome. Re-evaluation of its pathogenesis. *Am. J. Obstet. Gynecol.* 160, 1030-1033.
- Mahony B. S., Filly R. A., Callen P. W., Golbus M. S.** (1985)
The amniotic band syndrome. Antenatal sonographic diagnosis and potential pitfalls. *Am. J. Obstet. Gynecol.* 152, 63-68.
- Malinger G., Rosen N., Achiron R., Zakut H.** (1987)
Pierre Robin sequence associated with amniotic band syndrome. Ultrasonographic diagnosis and pathogenesis. *Prenat. Diagn.* 7, 455-459.
- Merz E., Gerlach R., Hoffmann G., Goldhofer W.** (1984)
The ADAM (amniotic-deformity-adhesion-mutilation) syndrome (amniotic bands) in ultrasound. *Geburtshilfe Frauenheilkd.* 44, 576-578.
- Miller M. T., Deutsch T. A., Cronin C., Keys C. L.** (1987)
Amniotic bands as a cause of ocular anomalies. *Am. J. Ophthalmol.* 104, 270-279.

- Moessinger A. C., Blanc W. A., Byrne J., Andrews D., Warburton D., Bloom A. (1981)**
Amniotic band syndrome associated with amniocentesis. *Am. J. Obstet. Gynecol.* 141, 588-591.
- Opitz J. M. (1985)**
Ectopia cordis and cleft sternum. Evidence for mechanical teratogenesis following rupture of the chorion or yolk-sac. *Am. J. Med. Genet.* 21, 201-202.
- Papp Z., Tóth Z., Csései K., Lindenbaum R. H. (1986)**
Are there „innocent” amniotic bands? *Am. J. Med. Genet.* 24, 207-209.
- Patten R. M., Vanallen M., Mack L. A., Wilson D., Nyberg D., Hirsch J., Viamont T. (1986)**
Limb-body wall complex. In utero sonographic diagnosis of a complicated fetal malformation. *A. J. R.* 146, 1019-1024.
- Rowell A. R. (1988)**
The amniotic band disruption complex. The pathogenesis of congenital limb ring-constrictions. An experimental study in the fetal rat. *Br. J. Plast. Surg.* 41, 45-51.
- Seeds J. W., Cefalo R. C., Herbert W. N. P. (1982)**
Amniotic band syndrome. *Am. J. Obstet. Gynecol.* 144, 243-248.
- Tanaka O., Koh T., Otani H. (1986)**
Amniogenic band anomalies in a fifth-month fetus and in a newborn from maternal oophorectomy during early pregnancy. *Teratology* 33, 187-193.
- Torpin R. (1965)**
Amniochorionic mesoblastic fibrous strings and amniotic bands. *Am. J. Obstet. Gynecol.* 91, 65-75.
- Urich H., Herrick M. K. (1985)**
The amniotic band syndrome as a cause of anencephaly. *Acta Neuropathol.* 67, 190-194.
- Vanallen M. I., Myhre S., Shiota K., Chen W. J. (1984)**
Ectopia cordis thoracalis with craniofacial defects resulting from early amnion rupture. *Clin. Res.* 32, 115-115.
- Yang S. S. (1990)**
ADAM sequence and innocent amniotic band. Manifestations and early amnion rupture. *Am. J. Med. Genet.* 37, 562-568.
- Yang S. S., Levine A. J., Sanborn J. R., Delp R. A. (1984)**
Amniotic rupture, extra-amniotic pregnancy, and vernix granulomata. *Am. J. Surg. Pathol.* 8, 117-122.
- Zosmer A., Shoham Z., Dgani R., Ashkenazi M., Levin J., Lancet M. (1989)**
Solitary thick intrauterine membranes not associated with the amniotic band syndrome. Three case reports. *Eur. J. Obstet. Gynecol.* 32, 173-178.

Pathology of Multiple Pregnancy

Multiple pregnancy may result from the development of a single fertilized ovum: *monozygotic* (MZ) twins, triplets, quadruplets, etc. It can also result from two or more independently fertilized ova; twins, triplets, etc. arising in this manner are DZ, *dizygotic*. MZ twins are genetically identical; DZ twins are genetically no more alike than brothers or sisters born from separate pregnancies.

If the twinning process starts early, in the first 5-7 days postconceptionally, then two separate blastocysts develop, and subsequently two placentas, two chorions and two amnions. This is *diplacental, dichorionic, diamniotic* (DDD) *placentation*. If the developing embryos are embedded in close proximity then the two placentas will fuse into a single mass. This is *monoplacental, dichorionic, diamniotic* (MDD) *placentation*.

If separation of the two embryos begins after development of the chorion, then two amnions will develop within a single chorion [*monoplacental, monochorionic, diamniotic* (MMD) *placentation*]; if separation occurs after development of the amnion, then only a single amnion will be present [*monoplacental, monochorionic, monoamniotic* (MMM) *placentation*]. Separation commencing at 14-17 days postconceptionally, or later, will always be incomplete; conjoined twins result.

The placentation of DZ twins may be DDD or MDD only; MMD and MMM types do not occur.

The obstetric importance of twin pregnancy lies in the fact that the

intrauterine environment may not be very favourable for the development of two or more fetuses. The frequency of multiple pregnancy is two to three times as high in spontaneous abortions as in live births; premature delivery often occurs, and perinatal mortality is two to three times as high for twins as for singletons.

There should be no difficulty in diagnosing fetal malformations in multiple pregnancy on ultrasound. Fetal disease or disorder diagnosed in a twin pregnancy may be concordant or discordant. Repeated ultrasound examination will help in timing the induction of labour, and the manner of delivery. Unfortunately, opportunities for prenatal therapy are limited.

There are special abnormalities associated with multiple pregnancy.

Acardia (*chorioangiopagus parasiticus*) represents a monstrous "inside out" malformation/deformity sitting on an umbilical cord with a single artery and vein. It is maintained entirely by the heart of the normal "twin".

Teratoma represents a tumorous transformation of the fetus's own gonad or of the gonad of a twin. Several forms of teratoma are known, and all are associated with polyhydramnios. It occurs most frequently in a sacrococcygeal location.

In the prenatal diagnosis of pathological twin pregnancies ultrasound, and sometimes AFP assay, provide valuable help. The recurrence risk for these conditions is not higher than the general population risk.

If in a monoamniotic (MMM) twin pregnancy there is a vascular

anastomosis not only in the placenta but also between corresponding parts of the two embryos we talk of *conjoined twins*. Supposedly, conjoined twins come about through late and incomplete separation of the primitive streak and embryonic disc. Thus the twins are not conjoined, but represent a disturbance of separation: nonetheless, the term "conjoined" is still used. Females are more frequently affected. As regards location of the "join", thoracopagus occurs the most frequently. Conjoined twins can easily be demonstrated on ultrasound. Their postnatal separation is only rarely successful.

Absorption of One Fetus. Fetus Papyraceus

According to Hellin's well-known formula, if the frequency of twin deliveries in a population is $1/N$, then that of triplets is $1/N^2$, quadruplets $1/N^3$, etc. This classical rule is still more or less valid, if one excludes induced multiple ovulations.

However, in recent years it has become clear that the frequency of multiple conceptions is considerably higher than that of multiple births. The difference is due partly to the high spontaneous abortion rate for twin conceptions, partly to selective death of one of the twin embryos. Thus, an originally multiple pregnancy may continue as a single one ("vanishing twin"). The changes can be followed by ultrasound, and the absorption process be studied pathologically.

Death in a singleton pregnancy is followed by autolysis and maceration. If the autolysis is of mild degree, the fetus is bright red in colour, its organs softened, and the body flaccid: this appearance would suggest that the fetus died one to two days before examination. If the autolysis is severe, the dehydrated fetus appears as a yellowish-white deformed and greasy mass: autolysis of this degree requires several weeks to develop. (The friable, liquefied material is unsuitable for histology; sometimes bony or cartilaginous tissue, less frequently striated muscle, may be recognizable in it.)

A fetus from a multiple pregnancy, dying in first or mid-trimester, may undergo severe autolysis and mummification; this is a *fetus papyraceus*. The membranes of the surviving fetus press the dead fetus against the uterine wall, thus, the latter becomes paper-like (*papyraceus*) in appearance. In singleton pregnancies a fetus papyraceus does not form; there is no uneven compression, and singleton dead fetuses are usually aborted.

Fetus papyraceus has earlier been observed as an incidental finding at birth. It has gained in practical importance with the widespread use of ultrasound and prenatal diagnosis. Ultrasonography can confirm that in

some pregnancies diagnosed as multiple in the first trimester and ending with the birth of a single fetus, there was no "diagnostic error": the other fetus had died *in utero* and was partially or completely absorbed. Recent studies suggest that the frequency of multiple conceptions is three to four times that predicted by Hellin's formula for live births.

If a twin embryo dies before the tenth week it may be completely absorbed, or at most there is some vaginal haemorrhage. Fetal reabsorption can be monitored by serial ultrasound.

In later pregnancy ultrasound may show no trace of the dead embryo, yet embryonic fragments are histologically detectable at term; to the naked eye these may appear as a greasy formation on the fetal surface of the placenta, beneath the amnion. After delivery of the placenta retained embryonic remnants may occasionally cause puerperal complications.

Death and absorption of one of twins sometimes affects the survivor. It is assumed that a "disruption sequence" following late prenatal death of a twin leads to disseminated intravascular coagulation in the survivor due to toxic decay products from the dead twin such as cadave-

rine, etc. This may kill the survivor or be associated with problems including haemolysis, anaemia, jaundice, renal shut-down and, above all, multiple central nervous system infarction with ultimate production of a "Swiss cheese" brain, mental retardation, cerebral palsy, seizures, microcephaly and, sometimes, cortical blindness. It is not known whether the occasional appearance of cleft lip, aplasia cutis congenita, gastroschisis or intestinal atresia in the survivor is related to the presence of a fetus papyraceus.

Although further studies are needed, there is no doubt that when a fetus papyraceus is identified the surviving fetus needs thorough examination and follow-up with ultrasound and any other relevant techniques.

Finally, it is important in clinical practice to regard first-trimester ultrasound diagnosis of two gestational sacs as evidence of *twin conception*, but not *twin pregnancy*. The designations "twin pregnancy" or "multiple pregnancy" should not be used before the 12th gestational week.

Multiple pregnancy should be considered a high-risk condition; mothers carrying twins require regular follow-up, both clinically and by serial ultrasound.

Figure 4-1. Dizygotic twin fetuses, mid-trimester: one with anencephaly, the other with cranial ventriculomegaly.



Figure 4-2. Twin fetuses concordant for neural tube defect: one with spina bifida, the other with anencephaly.



Figure 4-3. Acardiac fetus sitting on an umbilical cord with a single umbilical artery.

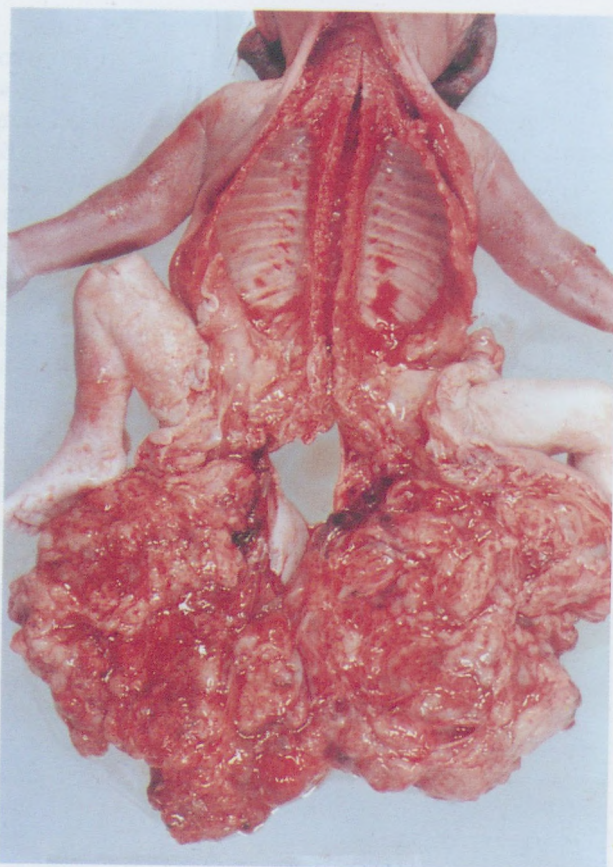


Figure 4-4. Sagittal section of a sacrococcygeal teratoma: much of the tumour appears to consist of disorganized brain tissue.

invasion, and subsequent death of the foetus are usually shared.

Fetus papyraceus has earlier been described as an incidental finding at birth. It has proved to be practically asymptomatic with the wider spread use of ultrasound and previous diagnosis of multiple pregnancy during pregnancy.

Death and resorption of one of the foetuses can happen in the uterus. It is assumed that a "disturbance in decance" following late prenatal death of a foetus leads to disseminated intravascular coagulation in the uterus due to toxic decay products from the dead foetus such as endo-

thelial thromboses. However, recent data suggest that the cause of the multiple central nervous system involvement with subsequent production of a "Swiss cheese" brain, similar to teratoma, cerebral palsy, autism, microcephaly and schizophrenia, is not known.

Although further studies are needed, there was doubt that when a fetus papyraceus is identified the surviving foetus needs thorough examination and follow-up with ultrasound and any other relevant techniques.

Finally, it is important in clinical practice to prevent first-trimester ultrasound diagnosis of two gestations and to avoid a false low-risk report, but not over-pregnancy. The designation "twin pregnancy" or "multiple pregnancy" should not be used before the 13th gestational week.

Multiple pregnancy should be considered a high-risk condition, implying delivery in a tertiary centre and the need for a multidisciplinary approach.

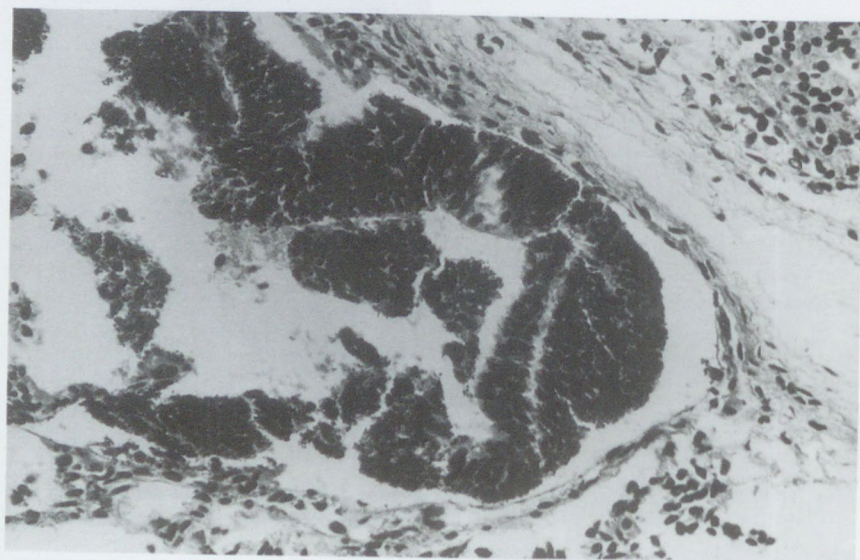


Figure 4-5. All three germinal layers can be found in the teratoma. This section shows retinal tissue rich in melanin (HE, x400).



Figure 4-6. The large sacrococcygeal teratoma distorts the anatomy of the anal opening and the external genitalia.

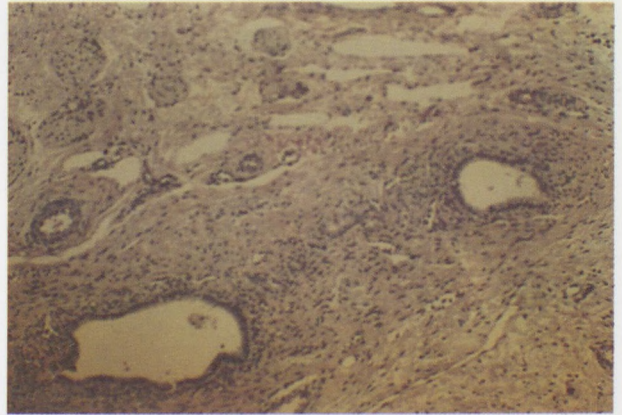


Figure 4-7. Sacral teratoma: primitive ducts lined by columnar epithelium (HE, x200).

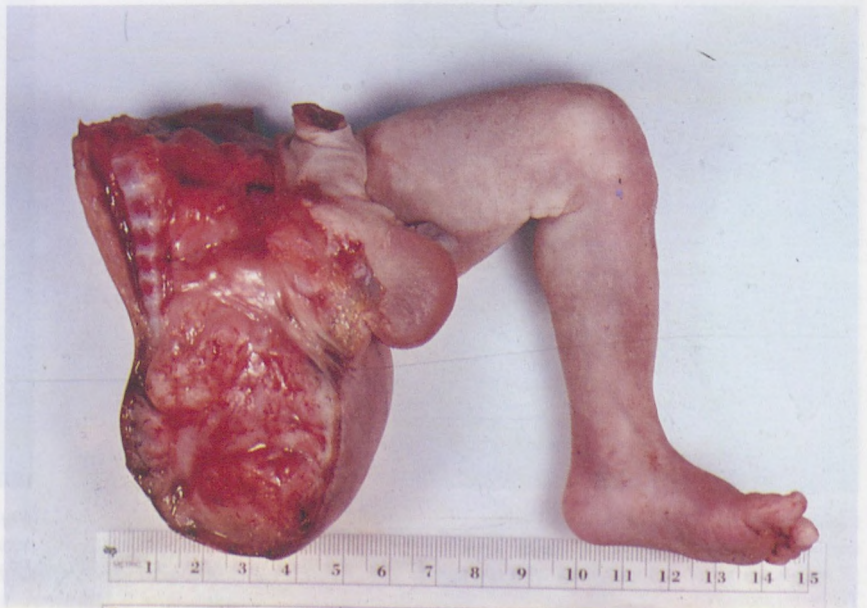


Figure 4-8. Sagittal section of a sacrococcygeal teratoma showing the solid mass elevating the pelvic floor and pelvic organs. The spine is well developed.

Figure 4-9. Extremely large ruptured sacrococcygeal teratoma.

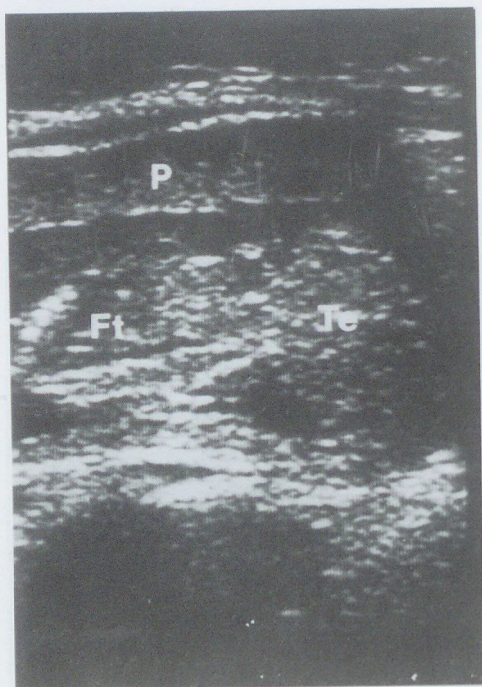


Figure 4-10. Ultrasound view of a large sacrococcygeal teratoma at 16 weeks (P = placenta; Ft = fetal trunk with the spine; Te = teratoma).

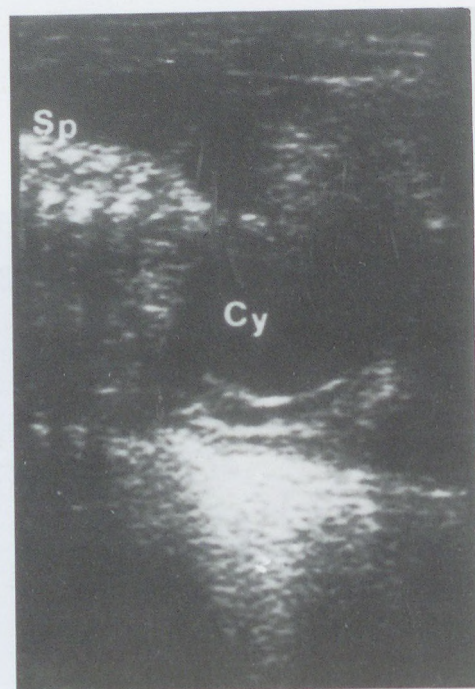


Figure 4-11. Cystic form of sacrococcygeal teratoma (ultrasound at 20 gestational weeks) (Sp = spine, Cy = cystic area).

Figure 4-12. Teratoma arising from the sacrum (17-week-old fetus).

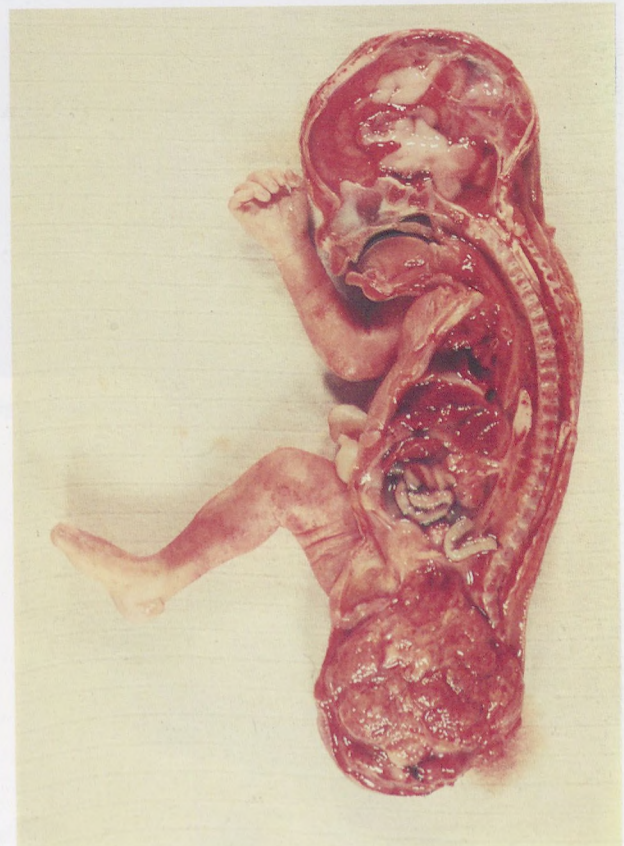


Figure 4-13. Median longitudinal section of the previous fetus with sacrococcygeal teratoma.

a



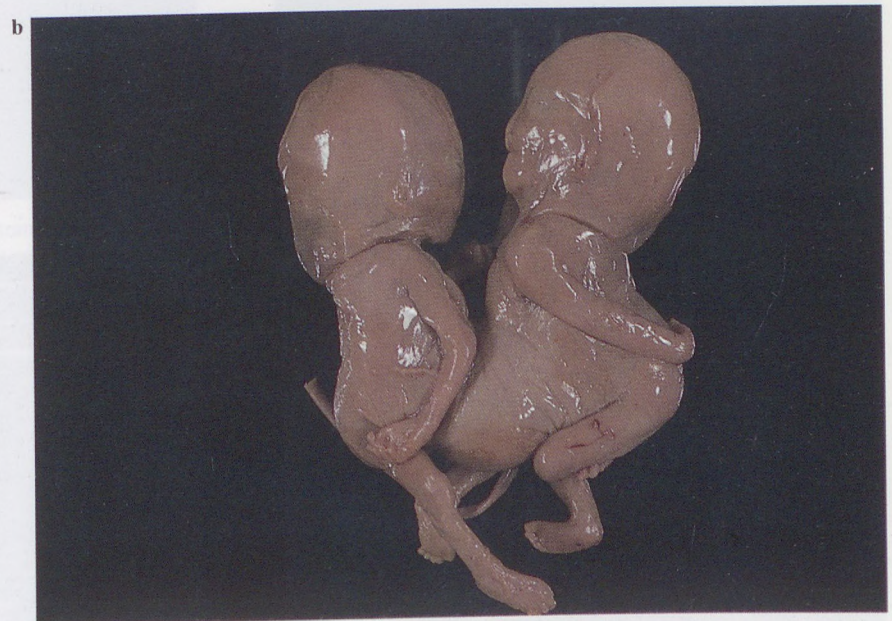
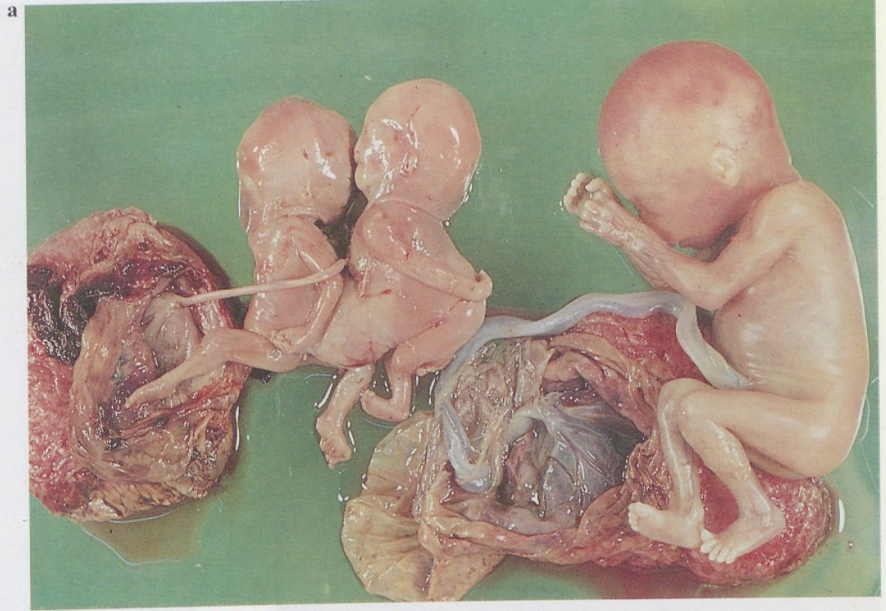
b



Figures 4-14a and b. Conjoined twins: anterior and posterior view.



Figure 4-15. Conjoined twins: X-rays of a thoracopagus.



Figures 4-16a and b. Triplet pregnancy: two of them with an abdominopagus abnormality.



Figure 4-17. Double-faced monster with partial absence of the brain.

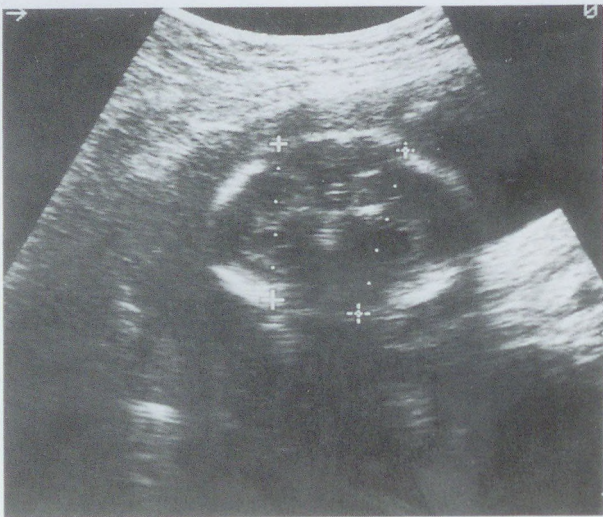


Figure 4-18a. Ultrasound view of two fused fetal heads (conjoined twins).

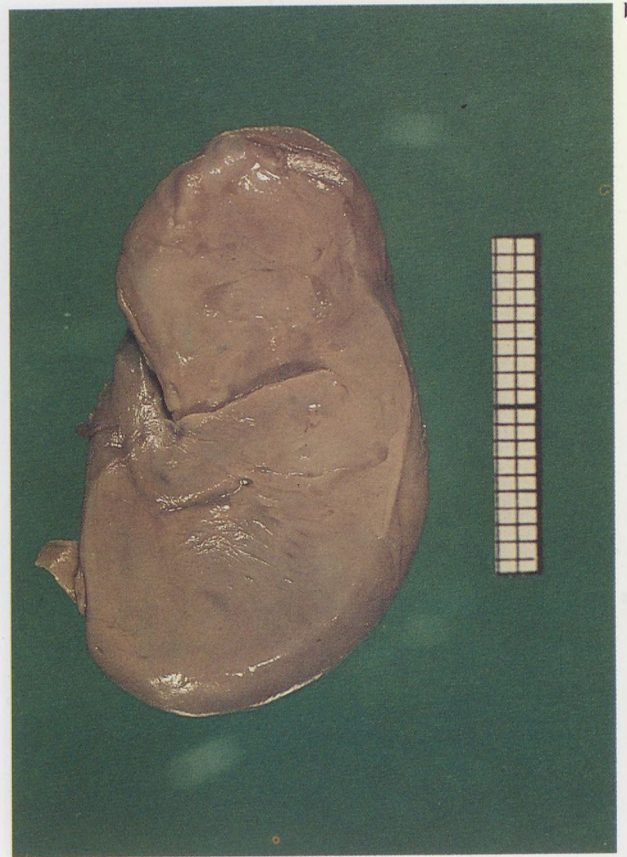


Figure 4-18b. Dilated bladder can be seen in the fused abdomen of conjoined twins at 15 gestational weeks.

a



b



Figures 4-19a and b. Fetus papyraceus: intrauterine death in the second trimester, with subsequent compression by the surviving co-twin.

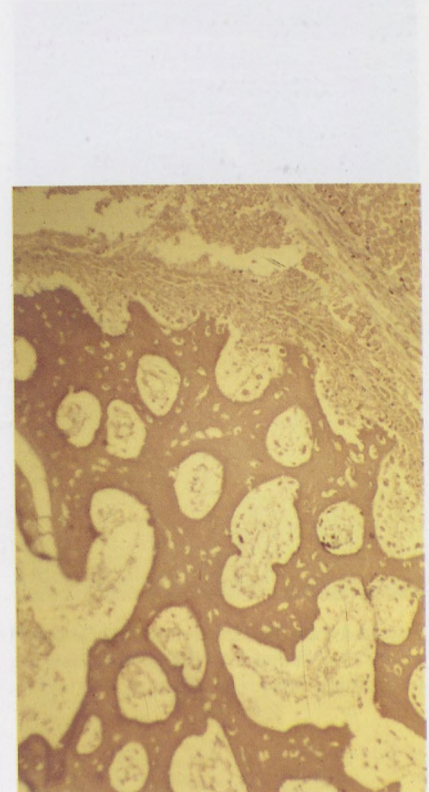
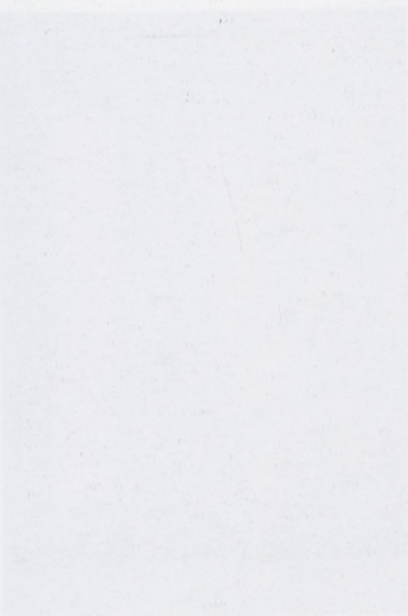


Figure 4-20. Section from a fetus papyraceus. Necrotic muscle and bone trabeculae are recognizable (HE, x125).

Figures 4-21a and b. Fetus papyraceus, viewed from both sides.



a



b

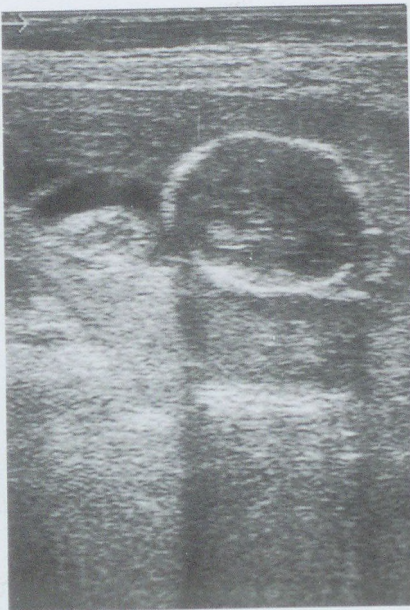


Figure 4-22a. The smaller dead fetus lies beside the normal 19-week head (ultrasound scan).

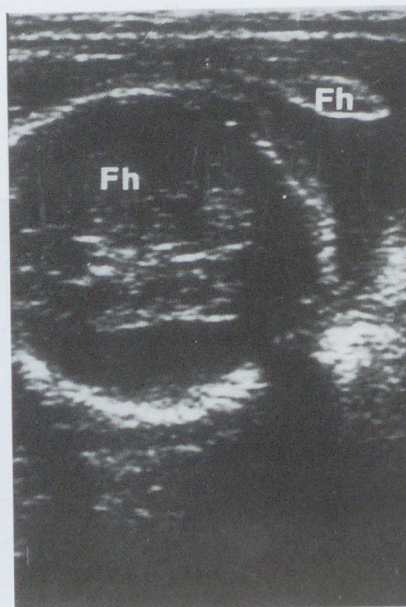


Figure 4-22b. One of twins died at ten gestational weeks and fetus papyraceus developed. Beside a normal 36-week fetal head is a small flattened structure representing the head of the fetus papyraceus. Ultrasound view (Fh = fetal heads).

Figure 4-23. Fetus papyraceus: the narrow umbilical cord is twisted several times.

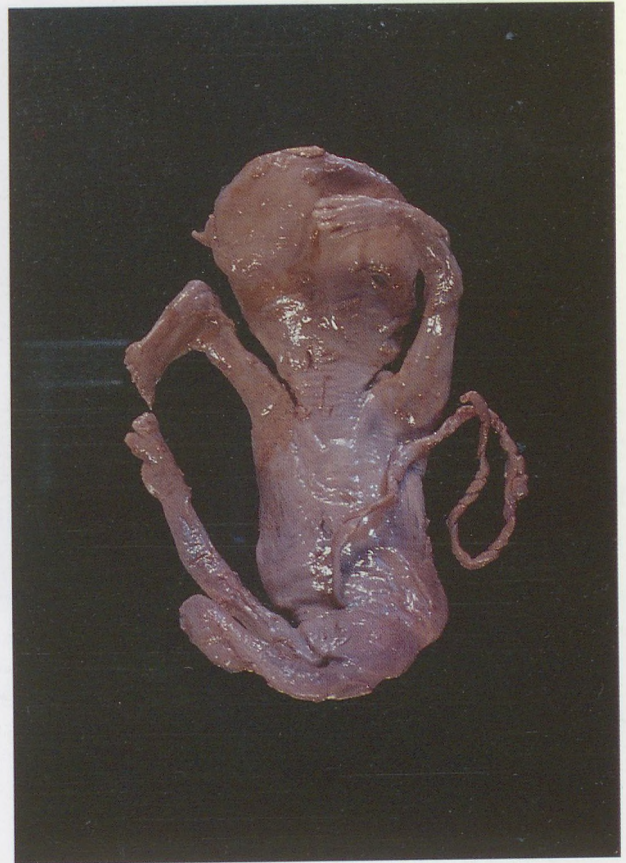


Figure 4-24. Fetus papyraceus extracted from the membranes of the placenta.



Figure 4-25. Transverse section of a fetus papyraceus. In some areas the normal outline of organs can be seen.



Figure 4-26. Congenital skin defect of the trunk, in a twin pregnancy; the defect extends through the cutis and subcutaneous tissues. This particular defect was associated with the death of the co-twin during the second trimester and the development of a fetus papyraceus.



Figure 4-27. Most commonly the scalp is involved by skin defects (local alopecia), usually over the vertex. In the older literature skin defects were thought to result from infection and adhesion between the amnion and the fetal surface. More recently these defects have been considered to be the result of thromboplastins released from a dead co-twin, which could explain the concurrence of abnormalities such as skin defects. Three-month-old infant with epilepsy.



Figure 4-28. Small scalp defect on the vertex associated with trisomy 13 in a 22-week abortus.

References

- Achiron R., Rosen N., Zakut H.** (1987)
Pathophysiologic mechanism of hydramnios development in twin transfusion syndrome. A case report.
J. Reprod. Med. 32, 305-308.
- Alter D. N., Reed K. L., Marx G. R., Anderson C. F., Shenker L.** (1988)
Prenatal diagnosis of congestive heart failure in a fetus with a sacrococcygeal teratoma.
Obstet. Gynecol. 71, 978-981.
- Anderson R. L., Golbus M. S., Curry C. J. R., Callen P. W., Hastrup W. H.** (1990)
Central nervous system damage and other anomalies in surviving fetus following 2nd trimester antenatal death of co-twin.
Prenat. Diagn. 10, 513-518.
- Apuzzio J. J., Ganesh V., Landau I., Pelosi M.** (1984)
Prenatal diagnosis of conjoined twins.
Am. J. Obstet. Gynecol. 148, 343-344.
- Baker V. V., Doering M. C.** (1982)
Fetus papyraceus: An unreported congenital anomaly of the surviving infant.
Am. J. Obstet. Gynecol. 143, 234-234.
- Barth R. A., Filly R. A., Goldberg J. D., Moore P., Silverman N. H.** (1990)
Conjoined twins. Prenatal diagnosis and assessment of associated malformations.
Radiology 177, 201-207.
- Bebbington M. W., Wittmann B. K.** (1989)
Fetal transfusion syndrome. Antenatal factors predicting outcome.
Am. J. Obstet. Gynecol. 160, 913-915.
- Benson C. B., Doubilet P. M.** (1990)
Sonography of multiple gestations.
Radiol. Clin. North Am. 28, 149-161.
- Bock B., Riess R., Wunsch P. H., Feige A.** (1990)
Prenatal diagnosis of a sacrococcygeal teratoma with fetal hydrops and hypertrophy of the placenta. Consequences for the course of pregnancy.
Geburtshilfe Frauenheilkd. 50, 647-649.
- Bolodár A., Török O., Tóth Z., Papp Z.** (1990)
Invasive intrauterine procedures in twin pregnancies discordant for fetal malformation.
Acta Chir. Hung. 31, 39-42.
- Boulot P., Hedon B., Deschamps F., Laffargue F., Viala J. L., Humeau C., Arnal F.** (1990)
Anencephaly-like malformation in surviving twin after embryonic reduction.
Lancet, 335, 1155-1156.
- Brenbridge A. N. A. G., Kraft J. L., Teja K.** (1987)
Sonographic findings in the prenatal diagnosis of cephalothoracopagus syncephalus. A case report.
J. Reprod. Med. 32, 59-62.
- Brennan J. N., Diwan R. V., Rosen M. G., Bellon E. M.** (1982)
Fetofetal transfusion syndrome: Prenatal ultrasonographic diagnosis.
Radiology 143, 535-536.
- Brown B. S. J.** (1982)
Disappearance of one gestational sac in the first trimester of multiple pregnancies. Ultrasonographic findings.
J. Can. Assoc. Radiol. 33, 273-275.
- Brown D. L., Benson C. B., Driscoll S. G., Doubilet P. M.** (1989)
Twin-twin transfusion syndrome. Sonographic findings.
Radiology 170, 61-63.
- Burke M. S.** (1990)
Single fetal demise in twin gestation.
Clin. Obstet. Gynecol. 33, 69-78.
- Campbell D. M.** (1990)
Multiple pregnancy.
Baill. Clin. Obstet. Gynec. 4, 109-127.
- Chatterjee M. S., Weiss R. R., Verma U. L., Tejani N. A., Macri J.** (1983)
Prenatal diagnosis of conjoined twins.
Prenat. Diagn. 3, 357-361.
- Chervenak F. A., Isaacson G., Touloukian R. L., Tortora M., Berkowitz R., Hobbins J. C.** (1985)
Diagnosis and management of fetal teratomas.
Obstet. Gynecol. 66, 666-671.
- Csécsei K., Molnár P., Tóth Z., Papp Z.** (1985)
Aplasia cutis congenita and fetus papyraceus.
Acta Med. Auxol. 17, 257-261.
- Csécsei K., Tóth Z., Szeifert G. T., Papp Z.** (1988)
Pathological consequences of the vanishing twin.
Acta Chir. Hung. 29, 173-182.
- Dalton M. E., Dudley D. K. L.** (1986)
Ultrasound in the antenatal management of twin gestation.
Semin. Perinatol. 10, 30-38.
- Danskin F. H., Neilson J. P.** (1989)
Twin-to-twin transfusion syndrome. What are appropriate diagnostic criteria?
Am. J. Obstet. Gynecol. 161, 365-369.
- El Qarmalawi M. A., Saddik M., Hadi F. E., Muwaffi R., Nageeb K.** (1990)
Diagnosis and management of fetal sacrococcygeal teratoma.
Int. J. Gynecol. Obstet. 31, 275-281.

- Filly R. A., Goldstein R. B., Callen P. W.** (1990)
Monochorionic twinning. Sonographic assessment.
A. J. R. 154, 459-469.
- Fisk N. M., Borrel A., Hubinont C., Tannirandorm Y., Nicolini U., Rodeck C. H.** (1990)
Fetofetal transfusion syndrome. Do the neonatal criteria apply in utero?
Arch. Dis. Child. 65, 657-661.
- Flake A. W., Harrison M. R., Adzick N. S., Laberge J. M., Warsof S. L.** (1986)
Fetal sacrococcygeal teratoma.
J. Pediatr. Surg. 21, 563-566.
- Goldhofer W., Merz E., Bauer H., Koltai I. L.** (1986)
Prenatal diagnosis of a sacrococcygeal cystic teratoma with retroperitoneal extension.
Geburtshilfe Frauenheilkd. 46, 121-123.
- Gore R. M., Filly R. A., Parer J. T.** (1982)
Sonographic antepartum diagnosis of conjoined twins. Its impact on obstetric management.
J. Am. Med. Assoc. 247, 3351-3353.
- Gross S. J., Benzie R. J., Sermer M., Skidmore M. B., Wilson S. R.** (1987)
Sacrococcygeal teratoma. Prenatal diagnosis and management.
Am. J. Obstet. Gynecol. 156, 393-396.
- Hahmann K., Issel E. P., Steinbach C.** (1982)
Prenatal diagnosis of anterior duplication anomaly (dicephalus diauchenos) by ultrasonography.
J. Perinat. Med. 10, 93-98.
- Hantman S. S., Zara H. D.** (1982)
In utero sonographic detection of abnormal twin pregnancy.
J. Clin. Ultrasound 10, 282-284.
- Hogge W. A., Thiagarajah S., Barber V. G., Rodgers B. M., Newman B. M.** (1987)
Cystic sacrococcygeal teratoma. Ultrasound diagnosis and perinatal management.
J. Ultrasound Med. 6, 707-710.
- Holzgrevé W., Mahony B. S., Glick P. L., Filly R. A., Harrison M. R., DeLorimier A. A., Holzgreve A. C., Muller K. M., Callen P. W., Aderson R. L., Golbus M. S.** (1985)
Sonographic demonstration of fetal sacrococcygeal teratoma.
Prenat. Diagn. 5, 245-257.
- Huter O., Brezinka Ch., Busch G., Pfaller Ch.** (1990)
The vanishing twin.
Geburtshilfe Frauenheilkd. 50, 989-992.
- Jauniaux E., Elkazen N., Leroy F., Wilkin P., Rodesch F., Hustin J.** (1988)
Clinical and morphologic aspects of the vanishing twin phenomenon.
Obstet. Gynecol. 72, 577-581.
- Kalchbrenner M., Weiner S., Templeton J., Losure T. A.** (1987)
Prenatal ultrasound diagnosis of thoracopagus conjoined twins.
J. Clin. Ultrasound 15, 59-63.
- Kerenyi T. D., Chitkara U.** (1981)
Selective birth in twin pregnancy with discordancy for Down's syndrome.
N. Engl. J. Med. 304, 1525-1527.
- Landy H. J., Keith L., Keith D.** (1982)
The vanishing twin.
Acta Genet. Med. Gemellol. 31, 179-194.
- Landy H. J., Winer S., Corson S. L., Batzer F. R., Bolognese R. J.** (1986)
The "vanishing twin": Ultrasonographic assessment of fetal disappearance in the first trimester.
Am. J. Obstet. Gynecol. 155, 14-19.
- Langer J. C., Harrison M. R., Schmidt K. G., Silverman N. H., Anderson R. L., Goldberg J. D., Filly R. A., Crombleholme T. M., Longaker M. T., Golbus M. S.** (1989)
Fetal hydrops and death from sacrococcygeal teratoma. Rationale for fetal surgery.
Am. J. Obstet. Gynecol. 160, 1145-1150.
- Mannino F. L., Jones K. L., Benirschke K.** (1977)
Congenital skin defects and fetus papyraceus.
Pediatrics 91, 559-564.
- Mühlhaus K., Beisler G.** (1986)
Acardia. Prenatal diagnosis and course of pregnancy in two twin pregnancies.
Z. Geburtshilfe Perinatol. 190, 98-103.
- Papp Z., Gardó S., Walawska J.** (1974)
Probably monozygotic twins with discordance for Goldenhar syndrome.
Clin. Genet. 5, 86-90.
- Patel R. B., Gibson J. Y., D'Cruz C. A., Burkhalter J. L.** (1982)
Sonographic diagnosis of cervical teratoma in utero.
A. J. R. 139, 1220-1222.
- Pretorius D., Leopold G. R., Moore T. R., Benirschke K., Sivo J. J.** (1988)
Acardiac twin. Report of Doppler sonography.
J. Ultrasound Med. 7, 413-416.
- Razavi-Encha F., Mulliez N., Benhaïem-Sigaux N., Gonzales M., Casasoprana A., Bloch G.** (1987)
Cardiovascular abnormalities in thoracopagus twins. Embryological interpretation and review.
Early Hum. Dev. 15, 33-34.
- Sherer D. M., Armstrong B., Shah Y. G., Metlay L. A., Woods J. R.** (1989)
Prenatal sonographic diagnosis, Doppler velocimetric umbilical cord studies, and subsequent management of an acardiac twin pregnancy.
Obstet. Gynecol. 74, 472-475.
- Sheth S., Nussbaum A. R., Sanders R. C., Hamper U. M., Davidson A. J.** (1988)
Prenatal diagnosis of sacrococcygeal teratoma. Sonographic-pathologic correlation.
Radiology 169, 131-136.

- Siegfried M. S., Koptik G. F.** (1983)
Prenatal sonographic diagnosis of conjoined twins.
Postgrad. Med. 73, 317-319.
- Sulak L. E., Dodson M. G.** (1986)
The vanishing twin: Pathologic confirmation of an ultrasonographic phenomenon.
Obstet. Gynecol. 68, 811-815.
- Szabó M., Varga P., Zalatnai A., Hidvégi J., Tóth Z., Papp Z.** (1985)
Sacrococcygeal teratoma and normal alpha-fetoprotein concentration in amniotic fluid.
J. Med. Genet. 22, 405-408.
- Taubert H. D., Bastert G., Dericks-Tan J. S. E.** (1986)
Maternal serum alpha-fetoprotein levels in a triplet pregnancy with 2 papyraceous fetuses.
Arch. Gynecol. 237, 127-133.
- Taylor M. B., Anderson R. L., Golbus M. S.** (1984)
One hundred twin pregnancies in a prenatal diagnosis program.
Am. J. Med. Genet. 18, 419-422.
- Teal L. N., Angtuaco T. L., Jimenez J. F., Quirk J. G.** (1988)
Fetal teratomas. Antenatal diagnosis and clinical management.
J. Clin. Ultrasound 16, 329-336.
- Turner R. J., Hankins G. D. V., Weinreb J. C., Ziaya P. R., Davis T. N., Lowe T. W., Gilstrap L. C.** (1986)
Magnetic resonance imaging and ultrasonography in the antenatal evaluation of conjoined twins.
Am. J. Obstet. Gynecol. 155, 645-649.
- Veal J. S.** (1984)
Prenatal diagnosis of twin-to-twin transfusion syndrome.
Med. Ultrasound 8, 30-32.
- Wilson D. A., Young G. Z., Crumley C. S.** (1983)
Antepartum ultrasonographic diagnosis of ischiopagus: A rare variety of conjoined twins.
J. Ultrasound Med. 2, 281-282.
- Wood M. J., Thompson H. E., Robertson F. M.** (1981)
Real-time ultrasound diagnosis of conjoined twins.
J. Clin. Ultrasound 9, 195-197.
- Yancey M. K., Brady K., Read J. A.** (1991)
Sonographic evidence of fetal hydrothorax after in utero death of monozygotic twin.
J. Clin. Ultrasound 19, 162-166.

Prenatal Cerebral Abnormalities

Hydrocephalus

Megalencephaly resulting from a pathological increase in the volume of cerebrospinal fluid (CSF) is called hydrocephalus. The excess CSF is most frequently present within the cerebral ventricles. Ventricular dilatation, due to increased CSF pressure, usually precedes the appearance of other signs, e.g., cranial enlargement, and the term ventricular dilatation (ventriculomegaly) is also used, in prenatal diagnosis, independently of the idea of hydrocephalus.

The CSF is mainly produced in the choroid plexuses of the lateral ventricles, it reaches the third ventricle through the foramen of Monro and thence the fourth ventricle through the aqueduct of Sylvius. It then passes into the subarachnoid space through the foramina of Luschka and the foramen of Magendie. Ninety per cent of the CSF is reabsorbed into the superior sagittal sinus, and any obstacle to the free outward flow of fluid leads to its accumulation.

When the obstruction is within the ventricular system, i.e., between the foramen of Monro and the foramina of Luschka and Magendie, the consequential hydrocephalus is called intraventricular obstructive, or non-communicating. When the block is between the basal cisterns and the subarachnoid space, the designation is extraventricular obstructive, or communicating, hydrocephalus.

Hydranencephaly

The term hydranencephaly denotes major deficiency of the cerebral hemispheres. An early occlusion or

developmental failure of both carotid arteries or of cerebral arteries may be the pathogenetic event: those parts of the brain receiving blood through the posterior cerebral circulation (brain stem, cerebellum, some of the occipital lobe, midbrain and basal ganglia) are well developed, and absence of the carotids can be demonstrated by postmortem angiography. The cerebral hemispheres are reduced to a gliomatous membrane which lies pressed against the internal aspect of the cranium by the CSF which fills the remaining space within the cranial cavity.

Hydranencephaly occurs as an isolated defect, not associated with malformations elsewhere, and virtually all cases are sporadic. Hydranencephaly is usually associated with polyhydramnios, and is easily diagnosable on ultrasound.

An ultrasonically normal telencephalon, in the first half of pregnancy, may develop later into hydranencephaly. In the most extreme cases of hydranencephaly pregnancy termination, or induction of premature labour, might be requested, on account of the progressive polyhydramnios and the hopeless prognosis. Although some hydranencephalic infants may survive for a few months, they do not develop neurologically after birth.

There are many more less severely affected children whose condition seems to represent loss of tissue primarily from the regions of the anterior and middle cerebral arteries (porencephaly); some of these children live for years and may even acquire a few motor skills.

Microcephaly

Microcephaly means small head, microencephaly small brain; when both are present the latter term is used, and this is always associated with developmental retardation. Microcephaly may appear as an isolated defect or may result from insults during pregnancy or later (maternal PKU, irradiation, TORCH infections, perinatal asphyxia) or be associated with chromosome abnormalities (trisomy 18) or malformation syndromes (Meckel syndrome) or skeletal dysplasias.

Some forms can probably be detected by ultrasound before the 24th week of gestation. Isolated biparietal diameter readings, even with certain dates, are less useful than serial measurements, at about fortnightly intervals, from the start of the second trimester; head/trunk ratios are also useful. Differentiation from craniosynostosis is important. In craniosynostosis the skull is small, but the brain is of normal size.

Holoprosencephaly

In the first weeks of embryonal development—the neural plate and neural groove stages—the brain consists of three recognizable parts, viz., prosencephalon, mesencephalon and rhombencephalon. Between the time of neural tube closure and the fifth gestational week the prosencephalon gives origin to telencephalon (cerebral hemispheres) and diencephalon (thalamus and hypothalamus), the mesencephalon forms the midbrain, and the rhombencephalon develops into metencephalon

(pons and cerebellum) and myelencephalon (medulla oblongata). At the time of telencephalon/diencephalon differentiation the prosencephalon also splits longitudinally—the longitudinal cerebral fissure—and the hemispheres develop on the lateral aspects of the fissure by progressive enlargement and hollowing of the cerebral vesicles. Remnants of the original septum lie in the fissure between the hemispheres.

Should the prechordal mesoderm fail to migrate normally the prosencephalon remains undivided. As a consequence a common cerebral ventricle develops, cortex and thalamus form a single structure, and the development of olfactory and optic bulbs is upset; there is abnormal differentiation and development of the nasofrontal process and the midline of the face (holoprosencephaly sequence).

Differing degrees of disorganization are reflected in the terms alobar, semilobar, and lobar.

The alobar (undivided) form is the most severe. The longitudinal cerebral fissure and the falx cerebri are completely absent, as is the pellucid septum; the corpus callosum is absent or poorly developed; instead of two separate lateral ventricles there is a single midline prosencephalic cyst.

In the semilobar (partially divided) form the posterior third of the prosencephalon has divided and the frontoparietal region remains single.

In the lobar (divided) form, the cerebral hemispheres are, for the greater part, separated. Only the most anterior aspect of the cerebrum remains as a single midline structure. In such cases there may also be fusion of the frontal or occipital horns of the lateral ventricles.

Arhinencephalia. The olfactory tracts and bulbs are lacking or, less frequently, rudimentary.

Associated facial anomalies. Some facial malformation is consistently present: the more severe the holoprosencephaly defect the more severe the facial malformation.

Cyclotia. The ears are fused below the face (otocephaly); there is a midline orbit, a supraorbital proboscis (tubular nose), and a maxillary and mandibular defect. This is the most severe and rarest of the facial defects.

Cyclopia. The eyes and the bony orbits are fused, to a variable degree, and the normal nasal bones and soft tissues are absent. There is a supraorbital proboscis.

Ethmocephaly. Extreme hypotelorism, with a proboscis lying between the two orbits.

Cebocephaly. Defect with close-set eyes, and a flattened nose consisting of a single blind-ending nostril, with no sensory cells or fila olfactoria in the nasal mucosa.

Premaxillary agenesis. Hypotelorism, a hypoplastic nose and a very severe median cleft lip.

Cleft lip and palate. Either or both of these defects may be present.

Alobar holoprosencephaly is usually incompatible with postnatal life. Children with the semilobar or lobar forms are mentally and physically severely handicapped, and many will require long-term residential care, if they survive.

Dandy-Walker Sequence

This anomaly is characterized by hypoplasia or agenesis of the cerebellar vermis and a cystic dilatation of the scala posterior. The degree of anatomical abnormality is highly variable. Hydrocephalus is caused by atresia or obliteration of the foramen of Magendie and the foramina of Luschka; there is an enormously dilated fourth ventricle and a resultant dilatation of the third ventricle and lateral ventricles, while the basal cisterns are obliterated.

Choroid plexus cysts

These are commonly bilateral and within the lateral ventricles, they resolve spontaneously before the third

trimester of pregnancy and are of no pathological importance. However, if the cysts are associated with other malformations they may indicate the presence of an underlying chromosome abnormality.

Toxoplasmosis

Intrauterine/congenital *Toxoplasma gondii* infection usually develops in the second half of pregnancy, and remains subclinical. Symptoms manifest in 10-12% of infected newborn infants, involving the nervous system (periventricular calcification, microcephaly, hydrocephalus and concomitant mental retardation), the eye (chorioretinitis, microphthalmos) and the liver (hepatitis, hepatosplenomegaly, thrombocytopenia).

Prenatal Diagnosis

Prenatal diagnosis of a hydrocephalus can be made with ultrasound. The process already begins in utero, with dilatation of the ventricles, and this is then followed by enlargement of the skull. In prenatal diagnostic practice ventricular dilatation and hydrocephalus should be clearly distinguished. Hydrocephalus includes megalencephaly, i.e., an excessive growth of the biparietal diameter, additional to a dilatation of the ventricular system.

By 14 weeks of gestation the lateral ventricles, filled with choroid plexus, can be seen on the ultrasound screen. The diagnosis of ventricular dilatation can be established by 18-20 weeks.

Obstructive ventricular dilatation is easier to diagnose in the third trimester, at which gestation also hydrocephalus, if present, can be diagnosed (BPD > 90th percentile).

One should remember that a dilated monoventricle may be associated with the alobar type of holoprosencephaly. Ventricular dilatation may also result from in utero

infection. In such cases the process is not progressive; in infection-associated cases it may even be reversible.

For the diagnosis of cerebral ventricular dilatation the lateral ventricle/hemisphere ratio is a useful index. The numerator of the fraction derives from the distance between the midline and the lateral wall of the lateral ventricle; the denominator denotes the distance between the midline and the internal bony wall of the cranium. A quotient exceeding 0.5, in the 17th week of gestation or later, suggests the ventricular system is probably dilated. However, dilatation commences in the occipital horns of the lateral ventricles, and the medial wall of the lateral ventricle is at first pressed towards the midline by the increasing volume of CSF, so that a normal quotient may not necessarily indicate the absence of dilatation.

When the ventricles are dilated the falx cerebri may appear to float or flap, moving with movements of

the scanning head. The presence of associated malformations, e.g., spina bifida, encephalocele, may help the recognition of ventricular dilatation; it may be seen together with the sonographic signs of Dandy-Walker sequence or Arnold-Chiari malformation.

In spina bifida, the biparietal diameter is often below the 10th percentile by or before the 20th week of gestation. Ventricular dilatation is then usually demonstrable, and is very often seen in cases diagnosed earlier. Isolated spina bifida, without ventricular dilatation, is rare.

Once ventricular dilatation has been diagnosed convincingly, most couples insist on pregnancy termination. One must remember that nearly two-thirds of all fetuses with a pregnancy diagnosis of hydrocephalus are born dead or die within a few days of birth. Fifty per cent of operated children die before five years of age, and only one-third of all survivors are of more or less normal intelligence.

An intrauterine shunting procedure can be considered as a possible alternative to termination, but only a few cases diagnosed before 24 weeks are suitable for this procedure, and in later pregnancy the cortical mantle is thinned to a degree that implies permanent damage.

Prenatal ultrasound diagnosis of holoprosencephaly is also practicable. In the alobar form, no falx cerebri can be detected within the longitudinal fissure; in the other forms of holoprosencephaly it is present, to a variable degree. The hypotelorism can be assessed by measurement of the interorbital distance, other midline facial defects can be detected, and the presence of cerebral tissue in the frontal areas, and of normal subtentorial structures, can be confirmed. Polyhydramnios is consistently present.

In toxoplasmosis pregnancy ultrasound may demonstrate early hydrocephalus, periventricular calcification and hepatosplenomegaly.



Figure 5-1a. Severe hydrocephalus together with radial aplasia and radial club-hand (18 gestational weeks).

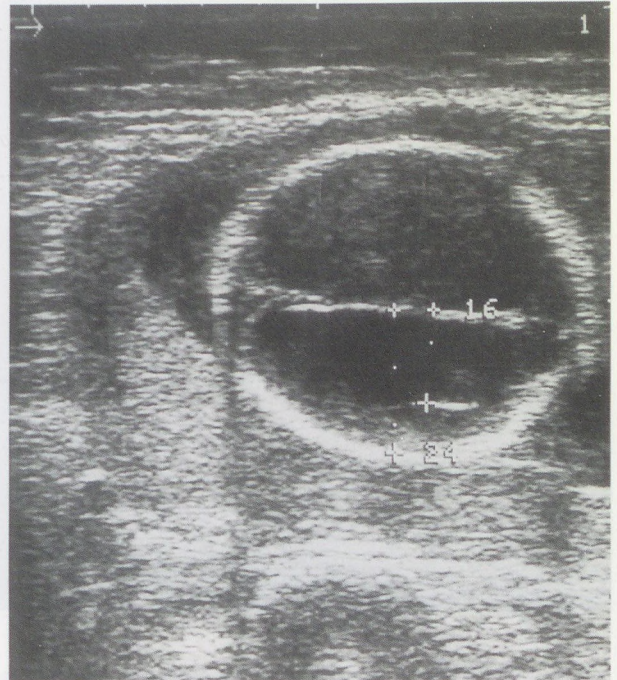
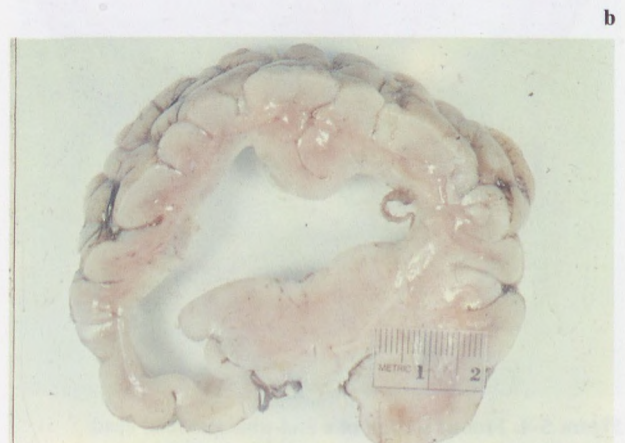
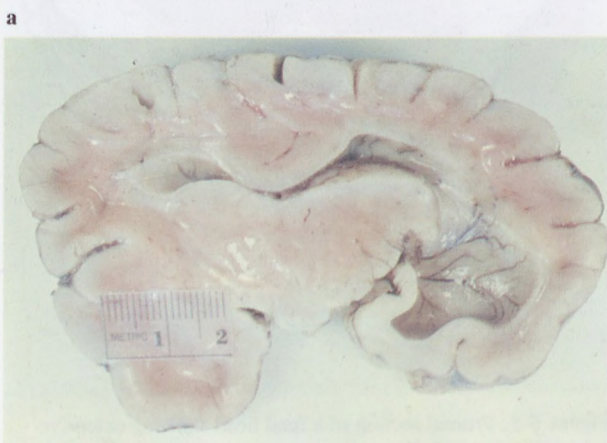


Figure 5-1b. Ultrasound technique for measurement of LVW/HW (16/24 mm) in a 20-week-old hydrocephalic fetus.



Figures 5-2a and b. Sagittal (a) and parasagittal (b) section showing holoprosencephaly in a mid-trimester fetal brain.



Figure 5-3. Frontal section of a mid-trimester brain with slight ventriculomegaly in the 3rd and lateral ventricles at the level of the foramen of Monro.



Figure 5-4. Frontal section of a mid-trimester fetal head at the level of the foramen magnum showing mild external hydrocephalus.

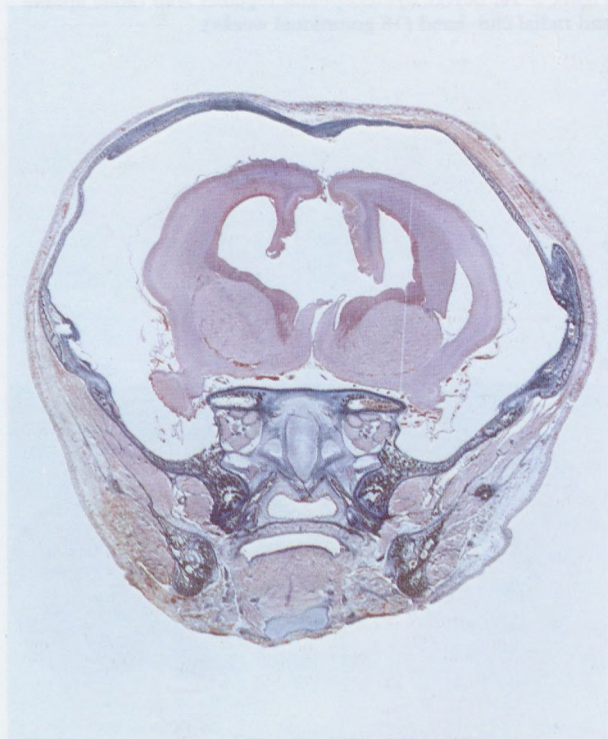
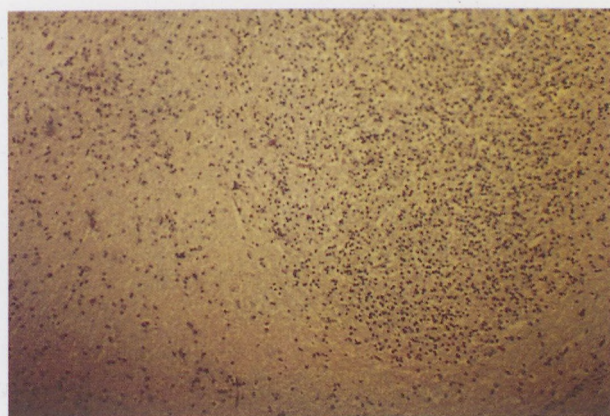
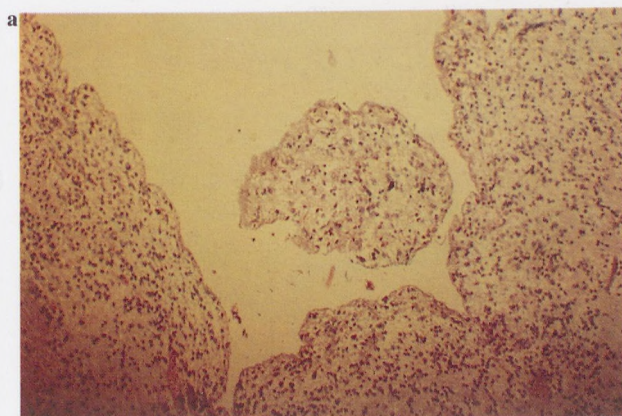


Figure 5-5. Frontal section of a fetal head showing extensive external hydrocephalus.

Figure 5-6. Hydrocephalus: moderately enlarged lateral ventricles, with scattered ependymal nodules (no signs of inflammation).



Figures 5-7a and b. Tuberous sclerosis, lining of lateral ventricle: the regular pattern of ependymal cells is replaced by an irregular collection of proliferating glial cells (a); hamartomatous glial nodule within ordinary brain tissue (b).

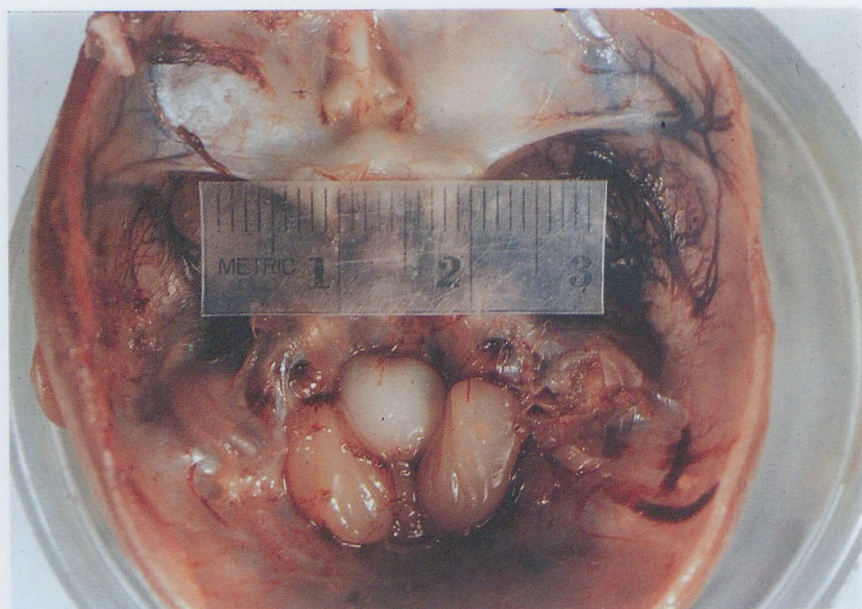


Figure 5-8. Arnold-Chiari malformation: the cerebellar tonsils have herniated through the foramen magnum.

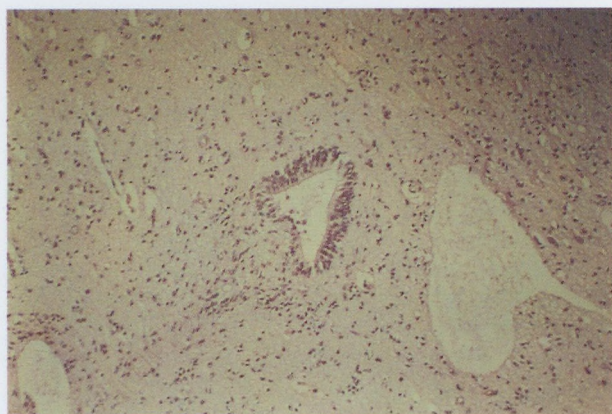


Figure 5-9. Aqueduct stenosis with hydrocephalus: although the diameter of the aqueduct is markedly reduced, the lining ependyma is intact and there is little surrounding gliosis (HE, x100).



Figure 5-10. Lateral view of a newborn with acrocephalosyndactyly (Apert) syndrome. There is a high prominent forehead with flattened occiput, hypoplastic supraorbital ridges, a short beaked nose, slightly hypoplastic maxilla and low-set dysplastic ear pinnae.

Figure 5-11. Agenesis of corpus callosum.

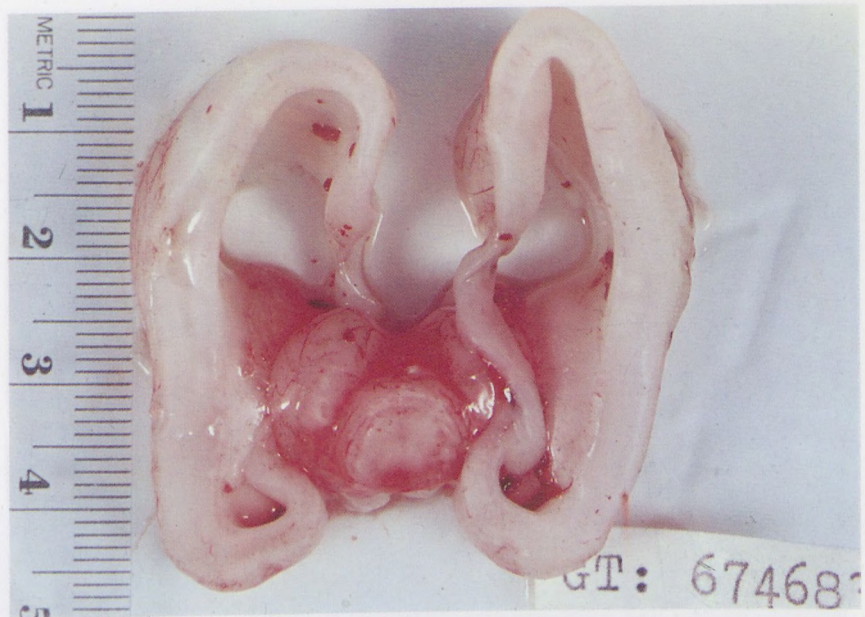


Figure 5-12. Prenatally diagnosed hydrocephalus, with moderately enlarged lateral ventricles and with agenesis of the corpus callosum.

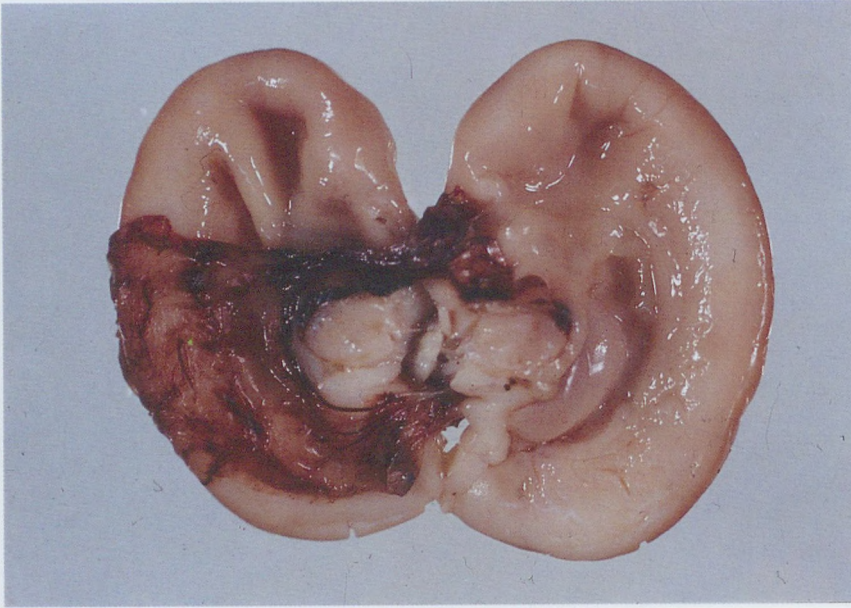


Figure 5-13. Internal hydrocephalus with dysgenesis of corpus callosum: slight dilatation of the lateral ventricles.



Figure 5-14. Internal hydrocephalus with moderate enlargement of the lateral ventricles associated with dysgenesis of corpus callosum. An internal view of the frontal lobes opened in sagittal section.



Figure 5-15a. Frontal section of a mid-trimester fetal brain at the level of the pons.

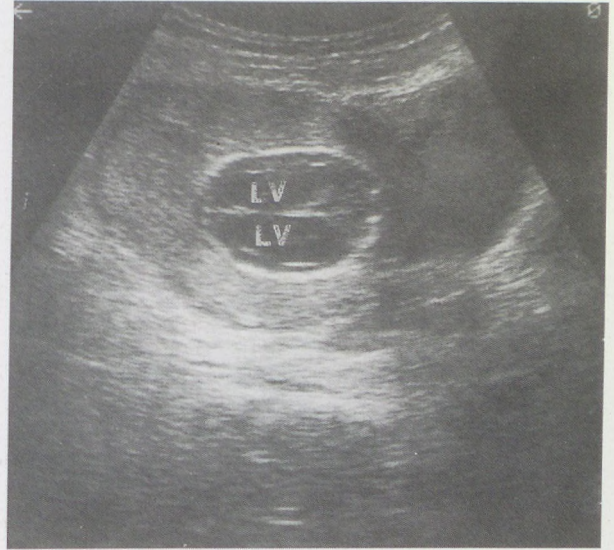


Figure 5-15b. Early dilatation of the lateral ventricles in an 18-week-old fetus (LV = lateral ventricles).



Figure 5-16a. Frontal section of a mid-trimester fetal brain. The corpus callosum is absent.

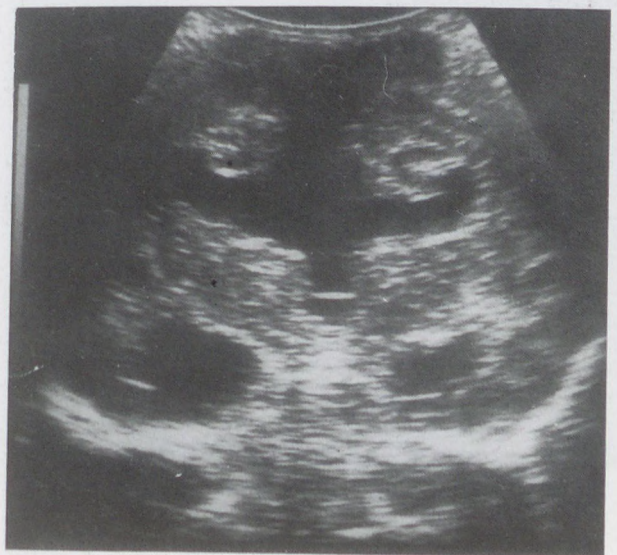


Figure 5-16b. Ultrasound view of corpus callosum dysgenesis in a newborn infant.



Figure 5-17a. Cyclops. Note the proboscis lying between the single midline orbit and the extroverted cerebral substance (exencephaly).

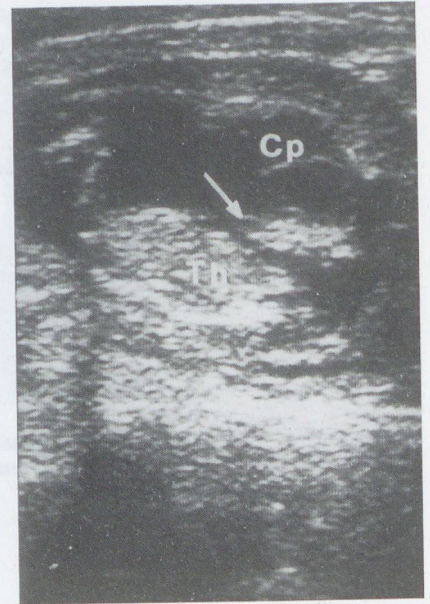


Figure 5-17b. The cranium has a cyst-like structure (Cp) in an 18-week-old exencephalic fetus. There is only a single orbit (arrow) on the ultrasound scan.



Figure 5-18. Severe microcephaly and holoprosencephaly, with midline fusion of the very hypoplastic orbits, and absence of nasal bones and nasal structures.



Figure 5-19. Cyclopia, with proboscis above a single midline eye.



Figure 5-20. Cebocephaly: hydrocephalus (holoprosencephaly), microphthalmia, hypotelorism and a suborbital proboscis with a single opening (blind-ending nostrils).



Figure 5-21. Holoprosencephalic mid-trimester fetus with hypotelorism, absence of internal nasal structures, and median cleft-lip and palate.

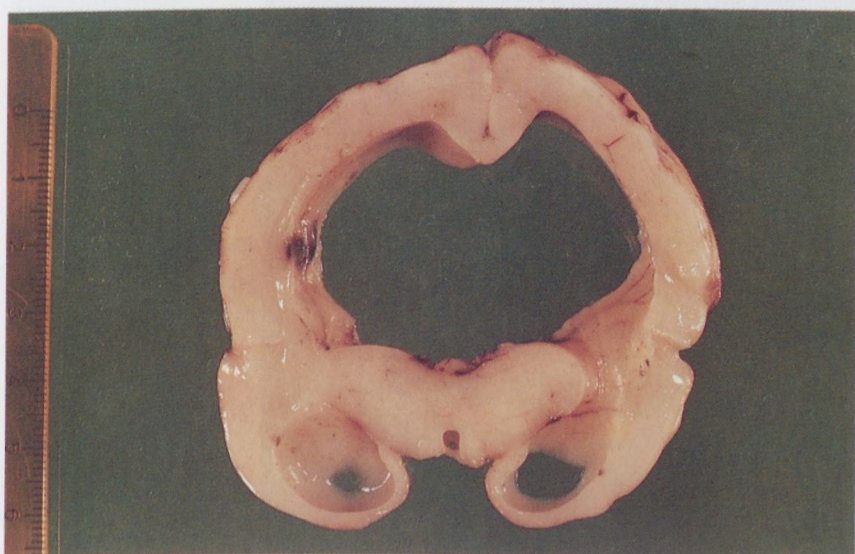
Figures 5-22a, b and c. Median sagittal section of a holoprosencephalic mid-trimester brain, with elongated cerebellum (a). Frontal (b) and temporal (c) section of the brain.



a



b



c



Figure 5-23a. Horizontal section of a mid-trimester fetal brain: holoprosencephaly.

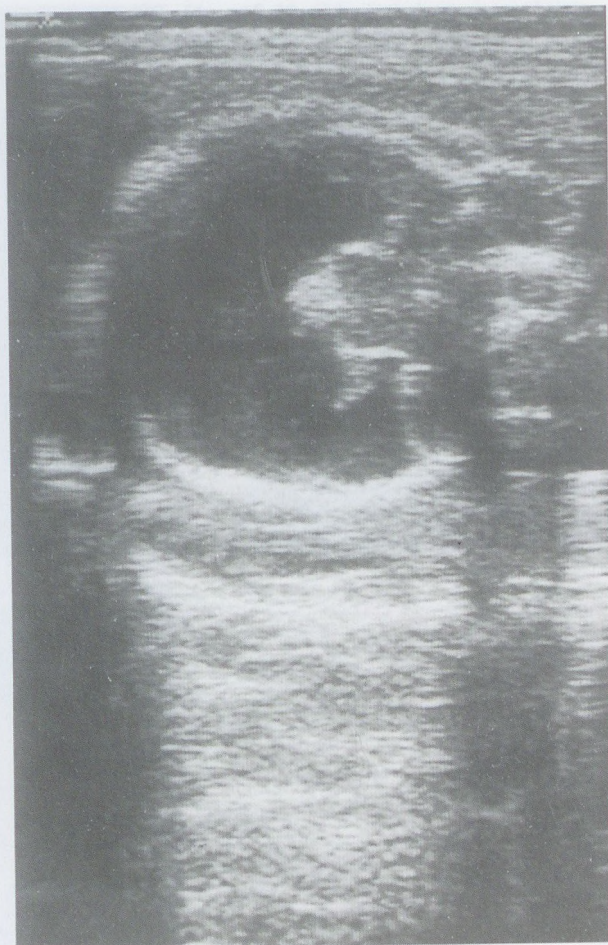


Figure 5-23b. Holoprosencephaly the midline falx echo and lateral ventricle structures are missing on ultrasound scan.

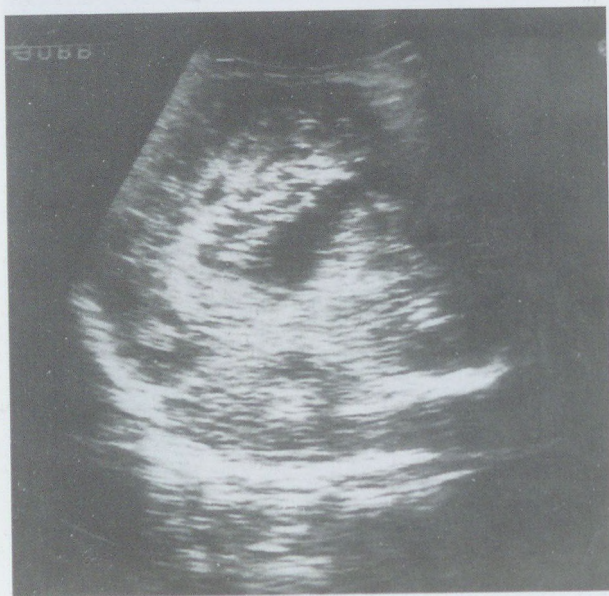


Figure 5-24. Semilobar holoprosencephaly in a newborn infant (coronal ultrasound scan).

Figures 5-25a and b. Váradi-Papp syndrome (McKusick Catalogue Number: 127717): holoprosencephaly, hypertelorism, hypoplastic nasal bones, median cleft lip and palate, postaxial polydactyly. Prenatally diagnosed mid-trimester fetus (a) and a 4-year-old child (b) in a Hungarian gipsy family.





a

Figure 5-26a. Frontal section of a fetal head showing reduced amount of cerebral tissue. The fetus has microhydranencephaly.



b

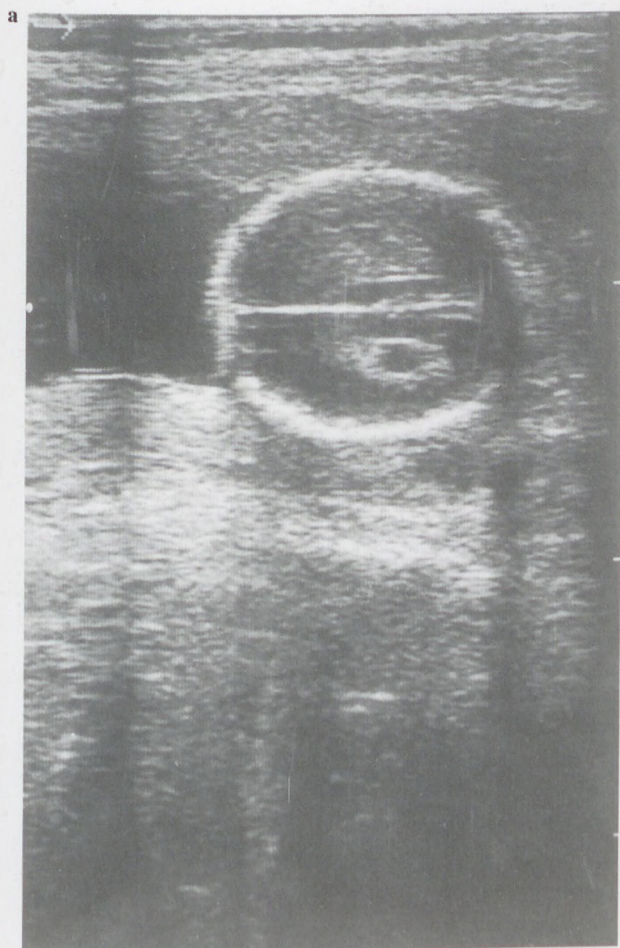
Figures 5-26b and c. Hydranencephaly in a 36-week-old fetus (b) and in a newborn infant (c). The cranial vault is completely occupied by fluid accumulation surrounding the midbrain (ultrasound view).



c

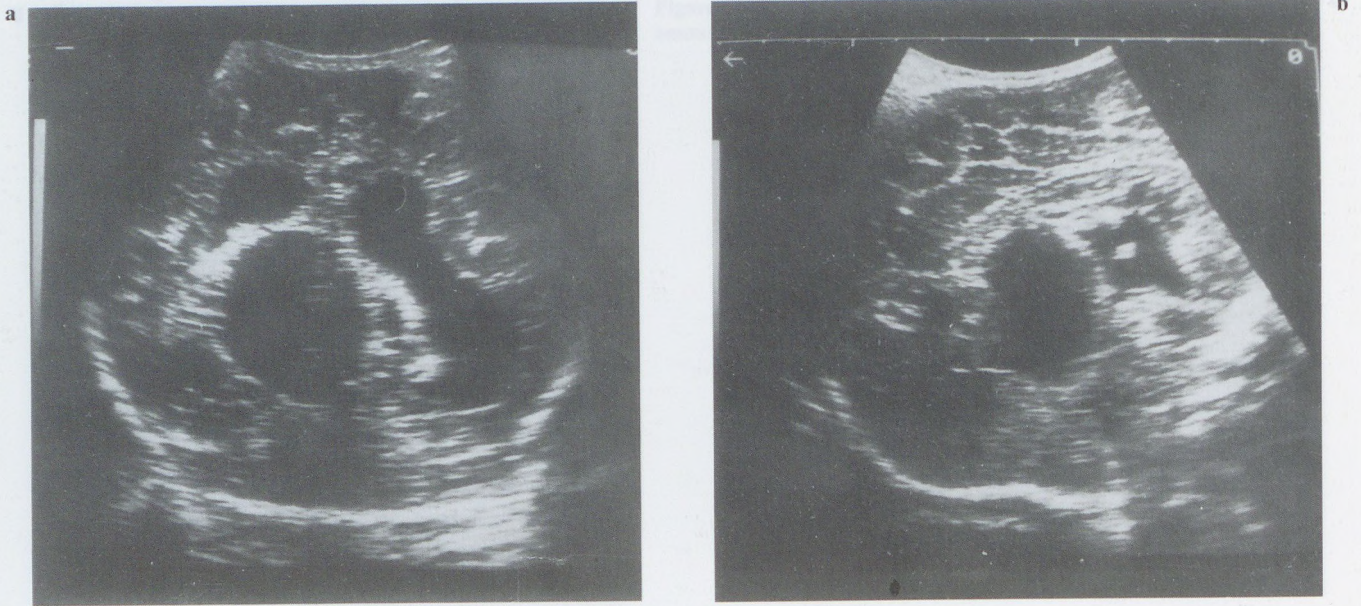


Figures 5-27a and b. Dandy-Walker cyst fills midline in posterior fossa [coronal (a) and sagittal (b) scan in newborn infant].



Figures 5-28a and b. Choroid plexus cyst detected at 19 gestational weeks (a) and resolving five weeks later (b).





Figures 5-29a and b. Coronal (a) and sagittal (b) section of a vein of Galen's aneurysm.



Figure 5-30. Congenital cystic brain tumour causing midline shift.

Figures 5-31a and b. Choroid plexus papilloma in frontal (a) and parasagittal (b) ultrasound scan in newborn infant.





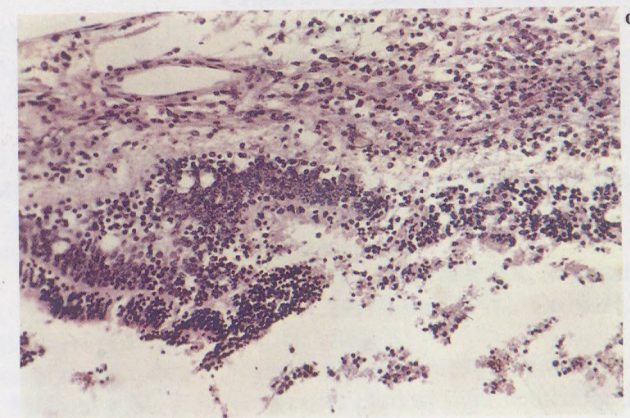
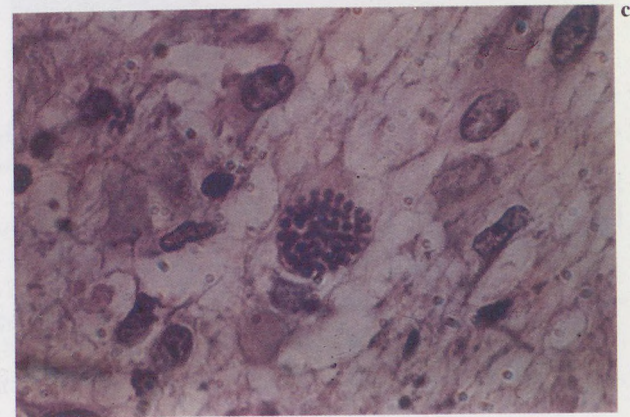
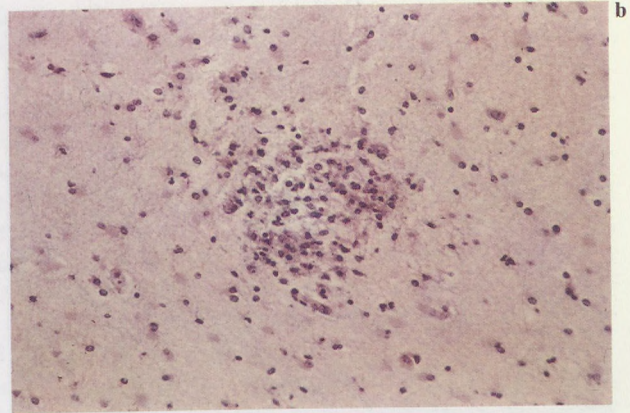
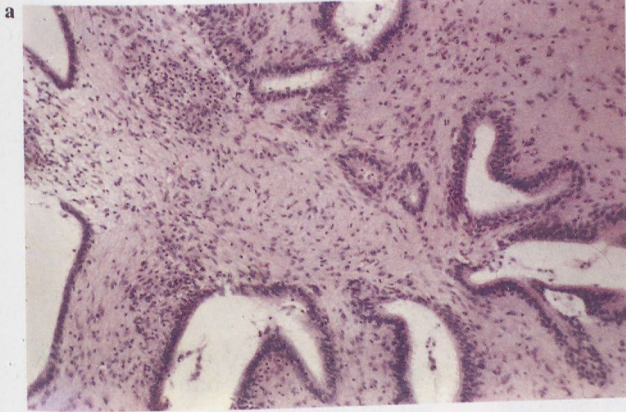
Figure 5-32. Intrauterine toxoplasmosis, with internal hydrocephalus; marked dilatation of lateral and third ventricles, and necrotic changes in the brain parenchyma.



Figure 5-33. Intrauterine toxoplasmosis: hydrocephalus, with flattening and widening of the cortical gyri.



Figure 5-34. Intrauterine toxoplasmosis: the normally oval aqueduct of Sylvius is dilated, but the fourth ventricle is normal in size.



Figures 5-35a, b, c and d. Intrauterine toxoplasmosis with hydrocephalus. **(a):** Severe glial cell proliferation and glial scarring have disorganized the aqueduct, breaking it into small compartments and causing hydrocephalus (HE, x200). **(b):** Gliotic nodule within the brain parenchyma (HE, x400). **(c):** Pseudocyst: macrophage containing large numbers of *Toxoplasma* in the cytoplasm (HE, x1000). **(d):** Destructive chorioretinitis following toxoplasmosis (HE, x400).



Figure 5-36. Klippel-Trenaunay-Weber syndrome, six weeks old infant: enlarged head with ventriculomegaly (later, hydrocephalus), with dense naevus flammeus involving part of left forehead and scalp. There was some limb asymmetry and patchy involvement of limbs and trunk with vascular naevi and lymphoedema.



Figure 5-37. Neonate with trisomy for proximal 15q found at maternal age amniocentesis; mother elected to continue the pregnancy; birth weight 5200 g at term, ventriculomegaly, plethoric face with deep-set eyes and telecanthus, intractable epilepsy from six months, severe retardation.

References

- Abramowicz J., Jaffe R.** (1988)
Diagnosis and intrauterine management of enlargement of the cerebral ventricles.
J. Perinat. Med. 16, 165-173.
- Akimoto N., Ikeda T., Satow Y., Lee J. Y., Okamoto N.** (1986)
Craniofacial and oral malformations in an autopsy population of Japanese human fetuses and newborns.
J. Craniofac. Genet. Dev. Biol. 2, 213-233.
- Benacerraf B. B.** (1988)
Fetal hydrocephalus. Diagnosis and significance.
Radiology 169, 858-859.
- Benacerraf B. B., Birnholz J. C.** (1987)
The diagnosis of fetal hydrocephalus prior to 22 weeks.
J. Clin. Ultrasound 15, 531-536.
- Benacerraf B. B., Laboda L. A.** (1989)
Cyst of the fetal choroid plexus: A normal variant?
Am. J. Obstet. Gynecol. 160, 319-321.
- Bertino R. E., Nyberg D. A., Cyr D. R., Mack L. A.** (1988)
Prenatal diagnosis of agenesis of the corpus callosum.
J. Ultrasound Med. 7, 251-260.
- Blackwell D. E., Spinnato J. A., Hirsch G., Giles H. R., Sackler J.** (1982)
Antenatal ultrasound diagnosis of holoprosencephaly: A case report.
Am. J. Obstet. Gynecol. 143, 848-849.
- Body G., Darnis E., Purcelot D., Santini J. J., Gold F., Soutoul J. H.** (1990)
Choroid plexus tumors. Antenatal diagnosis and follow-up.
J. Clin. Ultrasound 18, 575-578.
- Bordarier C., Aicardi J.** (1990)
Dandy-Walker syndrome and agenesis of the cerebellar vermis. Diagnostic problems and genetic counseling.
Dev. Med. 32, 285-294.
- Bromley B., Frigoletto F. D., Benacerraf B. R.** (1991)
Mild fetal lateral cerebral ventriculomegaly. Clinical course and outcome.
Am. J. Obstet. Gynecol. 164, 863-867.
- Bruni J. E., Delbigio M. R., Cardoso E. R., Persaud T. V. N.** (1988)
Hereditary hydrocephalus in laboratory animals and humans.
Exp. Pathol. 35, 239-246.
- Bundy A. L., Lindov H., Soliman M., Doubilet P. M.** (1988)
Antenatal sonographic diagnosis of cebocephaly.
J. Ultrasound Med. 7, 395-398.
- Busch R.** (1986)
Craniofacial malformations in perinatal mortality.
Nova Acta Leopoldina 58, 375-378.
- Chan L., Hixson J., Laifer S. A., Martin J. G., Hill L. M.** (1989)
A sonographic and karyotypic study of 2nd trimester fetal choroid plexus cysts.
Obstet. Gynecol. 73, 703-706.
- Chervenak F. A., Berkowitz R. L., Romero R., Tortora M., Mayden K., Duncan C., Mahoney M. J.** (1983)
The diagnosis of fetal hydrocephalus.
Am. J. Obstet. Gynecol. 147, 703-716.
- Chervenak F. A., Berkowitz R. L., Tortora M., Hobbins J. C.** (1985)
The management of fetal hydrocephalus.
Am. J. Obstet. Gynecol. 151, 933-942.
- Chervenak F. A., Isaacson G., Mahoney M. J., Tortona M., Mesologites T., Hobbins J. C.** (1984)
The obstetric significance of holoprosencephaly.
Obstet. Gynecol. 63, 115-121.
- Chow C. W., McKelvie P. A., Anderson R. M., Phelan E. M. D., Klug G. L., Rogers J. G.** (1990)
Autosomal recessive hydrocephalus with 3rd ventricle obstruction.
Am. J. Med. Genet. 35, 310-313.
- Clark S. L., DeVore G. R., Sabey P. L.** (1988)
Prenatal diagnosis of cysts of the fetal choroid plexus.
Obstet. Gynecol. 72, 585-587.
- Cochrane D. D., Myles S. T., Nimrod C., Still D. K., Sugarman R. G., Wittmann B. K.** (1985)
Intrauterine hydrocephalus and ventriculomegaly: Associated anomalies and fetal outcome.
Can. J. Neurol. Sci. 12, 51-59.
- Cohen M. M.** (1989)
Perspectives on holoprosencephaly. 1. Epidemiology, genetics, and syndromology.
Teratology 40, 211-235.
- Crane J. P., Beaver H. A.** (1986)
Midtrimester sonographic diagnosis of mandibulofacial dysostosis.
Am. J. Med. Genet. 25, 251-255.
- Daddario V., Kurjak A.** (1985)
Ultrasound investigation of the fetal cerebral ventricles.
J. Perinat. Med. 13, 67-77.
- Deroo T. R., Harris R. D., Sargent S. K., Denholm T. A., Crow H. C.** (1988)
Fetal choroid plexus cysts. Prevalence, clinical significance, and sonographic appearance.
A. J. R. 151, 1179-1181.
- DeRosa R., Lenke R. R., Kurczynski T. W., Persutte W. H., Nemes J. M.** (1989)
In utero diagnosis of benign fetal macrocephaly.
Am. J. Obstet. Gynecol. 161, 690-692.

- Dinh D. H., Wright R. M., Hanigan W. C.** (1990)
The use of magnetic resonance imaging for the diagnosis of fetal intracranial anomalies.
Child. Nerv. 6, 212-215.
- Doi H., Tatsuno M., Mizushima H., Matsumoto K.** (1991)
The use of 2-dimensional Doppler monography (color Doppler) in the diagnosis of hydranencephaly.
Child. Nerv. 6, 456-458.
- Dolkart L. A., Balcom R. J., Eisinger G.** (1990)
Intracranial teratoma. Prolonged neonatal survival after prenatal diagnosis.
Am. J. Obstet. Gynecol. 162, 768-769.
- Dreazen E., Tessler F., Sarti D., Crandall B. F.** (1989)
Spontaneous resolution of fetal hydrocephalus.
J. Ultrasound Med. 8, 155-157.
- Drugan A., Krause B., Canady A., Zador I. E., Sacks A. J., Evans M. I.** (1989)
The natural history of prenatally diagnosed cerebral ventriculomegaly.
J. Am. Med. Assoc. 261, 1785-1788.
- Duda V., Juhnke I.** (1990)
Permanent cysts of the choroid plexus as sonographic symptom of a genetic defect.
Z. Geburtshilfe Perinatol. 194, 236-239.
- Elejalde B. R., Elejalde M. M., Hamilton P. R., Christenson R., Broekhuizen F.** (1983)
Prenatal diagnosis of cyclopia.
Am. J. Med. Genet. 14, 15-19.
- Evans J. A., Strane L. C., Kaplan P., Hunter A. G. W.** (1989)
VACTERL with hydrocephalus. Further delineation of the syndrome(s).
Am. J. Med. Genet. 34, 177-182.
- Filice C., Maserati R., Brunetti E., Minoli L., Suter F.** (1985)
In utero sonographic diagnosis of semilobar holoprosencephaly.
Biol. Res. Pregnancy Perinatol. 6, 112-113.
- Filly R. A., Chinn D. H., Callen P. W.** (1984)
Alobar holoprosencephaly. Ultrasonographic prenatal diagnosis.
Radiology 151, 455-459.
- Foulon W., Naessens A., Mahler T., Dewaele M., Decatte L., De-meuter F.** (1990)
Prenatal diagnosis of congenital toxoplasmosis.
Obstet. Gynecol. 76, 769-772.
- Friedman J. M., Santos-Ramos R.** (1984)
Natural history of X-linked aqueductal stenosis in the second and third trimesters of pregnancy.
Am. J. Obstet. Gynecol. 150, 104-106.
- Gabrielli S., Reece E. A., Pilu G., Perolo A., Rizzo M., Bovicelli L., Hobbins J. C.** (1989)
The clinical significance of prenatally diagnosed choroid plexus cysts.
Am. J. Obstet. Gynecol. 160, 1207-1210.
- Gillerot Y., Hustin J., Koulischer L., Viteux V.** (1987)
Prenatal diagnosis of a dup(3p) with holoprosencephaly.
Am. J. Med. Genet. 26, 225-227.
- Golabi M., Edwards M. S. B., Ousterhout D. K.** (1987)
Craniosynostosis and hydrocephalus.
Neurosurgery 21, 63-67.
- Goldstein I., Reece E. A., Pilu G., O'Connor T. Z., Lockwood C. J., Hobbins J. C.** (1988)
Sonographic assessment of the fetal frontal lobe: A potential tool for prenatal diagnosis of microcephaly.
Am. J. Obstet. Gynecol. 158, 1057-1062.
- Goldstein I., Reece E. A., Pilu G., Hobbins J. C., Bovicelli L.** (1988)
Sonographic evaluation of the normal developmental anatomy of fetal cerebral ventricles.
Obstet. Gynecol. 72, 588-592.
- Gorlin R. J., Cohen M. M., Levin L. S.** (1990)
Syndromes of the Head and Neck.
Oxford University Press, Oxford-New York-Tokyo
- Greene M. F., Benacerraf B. B., Frigoletto F. D.** (1987)
Reliable criteria for the prenatal sonographic diagnosis of alobar holoprosencephaly.
Am. J. Obstet. Gynecol. 156, 687-689.
- Hadi H. A., Mashini I. S., Devoe L. D., Holzman G. B., Fadel H. E.** (1986)
Ultrasonographic prenatal diagnosis of hydranencephaly. A case report.
J. Reprod. Med. 31, 254-256.
- Hanigan W. C., Gibson J., Kleopoulos N. J., Cusack T., Zwicky G., Wright R. M.** (1986)
Medical imaging of fetal ventriculomegaly.
J. Neurosurg. 64, 575-580.
- Heiserman J., Filly R. A., Goldstein R. B.** (1991)
Effect of measurement errors on sonographic evaluation of ventriculomegaly.
J. Ultrasound Med. 10, 121-124.
- Hertzberg B. S., Kay H. H., Bowie J. D.** (1989)
Fetal choroid plexus lesions. Relationship of antenatal sonographic appearance to clinical outcome.
J. Ultrasound Med. 8, 77-82.
- Hidalgo H., Bowie J., Ram P. C., Ford K., Lipsit E.** (1982)
In utero sonographic diagnosis of fetal cerebral anomalies.
A. J. R. 139, 143-148.
- Hilpert P. L., Kurtz A. B.** (1990)
Prenatal diagnosis of agenesis of the corpus callosum using endovaginal ultrasound.
J. Ultrasound Med. 9, 363-365.
- Hoffman-Tretin J. C., Horoupian D. S., Koenigsberg M., Schnur M. J., Llena J. F.** (1986)
Lobar holoprosencephaly with hydrocephalus. Antenatal demonstration and differential diagnosis.
J. Ultrasound Med. 5, 691-697.

- Holmes L. B., Griscoll S., Atkins L.** (1974)
Genetic heterogeneity of cebocephaly.
J. Med. Genet. 11, 35-40.
- Holzgreve W., Miny P., Gullotta F.** (1985)
Sonographic diagnosis of holoprosencephaly in the 2nd trimester of pregnancy.
Geburtshilfe Frauenheilkd. 45, 813-814.
- Horwich A., Riccardi V. M., Francke U.** (1983)
Brief clinical report: Aqueductal stenosis leading to hydrocephalus. An unusual manifestation of neurofibromatosis.
Am. J. Med. Genet. 14, 577-581.
- Hughes H. E., Miskin M.** (1986)
Congenital microcephaly due to vascular disruption. In utero documentation.
Pediatrics 78, 85-87.
- Jeanty P., Romero R., Staudach A., Hobbins J. C.** (1986)
Facial anatomy of the fetus.
J. Ultrasound Med. 5, 607-616.
- Johnson M. L., Pretorius D., Clewell W. H., Meier P. R., Manchester D.** (1983)
Fetal hydrocephalus: Diagnosis and management.
Semin. Perinatol. 7, 83-89.
- Jovanovic W., Rauskolb R., Fuhrmann W.** (1983)
Prenatal ultrasound diagnosis of microencephalus.
Arch. Gynecol. 235, 444-445.
- Jörgensen C., Ingemarsson I., Svenningsen N. W.** (1983)
Prenatal diagnosis of fetal brain ventricle dilatation.
Br. J. Obstet. Gynaecol. 90, 162-166.
- Jörgensen C., Ingemarsson I., Svalenius E., Montan S., Svenningsen N. W.** (1986)
Ultrasound measurement of the fetal cerebral ventricles: A prospective, consecutive study.
J. Clin. Ultrasound 14, 185-190.
- Khoury M. J., Cordero J. F., Mulinare J., Opitz J. M.** (1989)
Selected midline defect associations. A population study.
Pediatrics 84, 266-272.
- Khousam M. N., Hooker J. G.** (1989)
The significance of prenatal diagnosis of choroid plexus cysts.
Prenat. Diagn. 9, 213-216.
- Koga Y., Mizumoto M., Matsumoto Y., Hattori T., Tanaka S., Fujimoto S.** (1991)
Prenatal diagnosis of fetal intracranial calcifications.
Am. J. Obstet. Gynecol. 163, 1543-1545.
- Komarniski C. A., Cyr D. R., Mack L. A., Weinberger E.** (1990)
Prenatal diagnosis of schizencephaly.
J. Ultrasound Med. 9, 305-307.
- Kushnir U., Shalev J., Bronstein M., Bider D., Lipitz S., Nebel L., Mashiach S., Benrafael Z.** (1989)
Fetal intracranial anatomy in the 1st trimester of pregnancy. Transvaginal ultrasonographic evaluation.
Neuroradiology 31, 222-225.
- Lemire R. J., Cohen M. M., Beckwith J. B., Kokich V. G., Siebert J. R.** (1981)
The facial features of holoprosencephaly in anencephalic human specimens. I. Historical review and associated malformations.
Teratology 23, 297-303.
- Litschgi M.** (1986)
Antenatal ultrasound diagnosis of severe congenital microcephaly.
Geburtshilfe Frauenheilkd. 46, 250-252.
- Lockwood C. J., Ghidini A., Aggarwal R., Hobbins J. C.** (1988)
Antenatal diagnosis of partial agenesis of the corpus callosum. A benign cause of ventriculomegaly.
Am. J. Obstet. Gynecol. 159, 184-186.
- Manchester D. K., Pretorius D. H., Avery C., Manco-Johnson M. L., Wiggins J., Meier P. R., Clewell W. H.** (1988)
Accuracy of ultrasound diagnoses in pregnancies complicated by suspected fetal abnormalities.
Prenat. Diagn. 8, 109-117.
- Mann T. P.** (1989)
Colour Atlas of Paediatric Facial Diagnosis.
Clinical Press, Kluwer Academic Publishers, Dordrecht, Boston, London
- Martinovic J., Sibalic D., Djordjevic M., Stefanovic B., Nagulic M.** (1982)
Frequency of toxoplasmosis in the appearance of congenital hydrocephalus.
J. Neurosurg. 56, 830-834.
- Mayden K. L., Tortora M., Berkowitz R. L., Bracken M., Hobbins J. C.** (1982)
Orbital diameters: A new parameter for prenatal diagnosis and dating.
Am. J. Obstet. Gynecol. 144, 289-297.
- McCorkell S. J., Ohlsson A., Probst F.** (1985)
Cebocephaly. CT and sonographic findings.
A. J. N. R. 6, 647-649.
- McLeary R. D., Kuhns L. R., Barr M.** (1984)
Ultrasonography of the fetal cerebellum.
Radiology 151, 439-442.
- Meholic A. J., Freimani. A. K., Stucka J., Lo Piccolo M. L.** (1991)
Sonographic in utero diagnosis of Klippel-Trenaunay-Weber syndrome.
J. Ultrasound Med. 10, 111-114.
- Meizner I., Barki Y., Hertzanu Y.** (1987)
Prenatal sonographic diagnosis of agenesis of corpus callosum.
J. Clin. Ultrasound 15, 262-264.
- Meizner I., Mazor M., Drawall D., Katz M.** (1987)
Sonographic findings in a rare case of fetal cyclopia.
Isr. J. Med. Sci. 23, 910-912.

- Michejda M., Queenan J. T., McCullough D. (1986)**
Present status of intrauterine treatment of hydrocephalus and its future.
Am. J. Obstet. Gynecol. 155, 873-882.
- Mones M. L., Wiegel U., Schuler A. (1988)**
Prenatal toxoplasmosis. Diagnosis and prevention.
Dtsch. Med. Wochenschr. 113, 847-850.
- Monteagudo A. N. A., Reuss M. L., Timor-Tritsch I. E. (1991)**
Imaging the fetal brain in the second and third trimesters using transvaginal sonography.
Obstet. Gynecol. 77, 27-32.
- Mor Z., Schreyer P., Wainraub Z., Hayman E., Caspi E. (1988)**
Nonimmune hydrops fetalis associated with angioosteohypertrophy (Klippel-Trenaunay) syndrome.
Am. J. Obstet. Gynecol. 159, 1185-1186.
- Munke M. (1989)**
Clinical, cytogenetic, and molecular approaches to the genetic heterogeneity of holoprosencephaly.
Am. J. Med. Genet. 34, 237-245.
- Nolla-Salas J., Ricart C., D'Ollhaberriague L., Gali F., Lamarca J. (1987)**
Hydrocephalus. An unusual CT presentation of cerebral toxoplasmosis in a patient with acquired immunodeficiency syndrome.
Eur. Neurol. 27, 130-132.
- Nyberg D. A., Cyr D. R., Mack L. A., Fitzsimmons J., Hickok D., Mahony B. S. (1988)**
The Dandy-Walker malformation. Prenatal sonographic diagnosis and its clinical significance.
J. Ultrasound Med. 7, 65-71.
- Nyberg D. A., Mack L. A., Hirsch J., Pagon R. O., Shepard T. H. (1987)**
Fetal hydrocephalus: Sonographic detection and clinical significance of associated anomalies.
Radiology 163, 187-191.
- Nyberg D. A., Mack L. A., Bronstein A., Hirsch J., Pagon R. A. (1987)**
Holoprosencephaly. Prenatal sonographic diagnosis.
A. J. R. 149, 1051-1058.
- Nyberg D. A., Mack L. A., Bronstein A., Hirsch J., Pagon R. A. (1987)**
Holoprosencephaly. Prenatal sonographic diagnosis.
A. J. N. R. 8, 871-876.
- Nyberg D. A., Mahony B. S., Hegge F. N., Hickok D., Luthy D. A., Kapur R. (1991)**
Enlarged cisterna magna and the Dandy-Walker malformation: Factors associated with chromosome abnormalities.
Obstet. Gynecol. 77, 436-442.
- Patterson J. A., Gold W. D., Sanz L. E., McCullough D. C. (1981)**
Antenatal evaluation of fetal hydrocephalus with computed tomography.
Am. J. Obstet. Gynecol. 140, 344-345.
- Persutte W. H., Kurczynski T. W., Chaudhury K., Lenke R. R., Woldenberg L. (1990)**
Prenatal diagnosis of autosomal dominant microcephaly and postnatal evaluation with magnetic resonance imaging.
Prenat. Diagn. 10, 631-642.
- Persutte W. H., Lenke R. R., DeRosa R. T. (1990)**
Prenatal ultrasonographic appearance of the agnathia malformation complex.
J. Ultrasound Med. 9, 725-728.
- Pescia G., Nguyen-The H., Deonna T. (1983)**
Prenatal diagnosis of genetic microcephaly.
Prenat. Diagn. 3, 363-365.
- Pilu G., Reece E. A., Romero R., Bovicelli L., Hobbins J. C. (1986)**
Prenatal diagnosis of craniofacial malformations with ultrasonography.
Am. J. Obstet. Gynecol. 155, 45-50.
- Pilu G., Reece E. A., Goldstein I., Hobbins J. C., Bovicelli L. (1989)**
Sonographic evaluation of the normal developmental anatomy of the fetal cerebral ventricles. 2. The atria.
Obstet. Gynecol. 73, 250-256.
- Pilu G., Rizzo M., Orsini L. F., Bovicelli L. (1986)**
Antenatal recognition of cerebral anomalies.
Ultrasound Med. Biol. 12, 319-326.
- Pilu G. L., Romero R., Depalma L., Rivoisecc. M., Jeanty P., Copel J. A., Bovicelli L., Hobbins J. C. (1986)**
Antenatal diagnosis and obstetric management of Dandy-Walker syndrome.
J. Reprod. Med. 31, 1017-1022.
- Renier D., Sainte-Rose C., Pierre-Kahn A., Hirsch J. F. (1988)**
Prenatal hydrocephalus. Outcome and prognosis.
Childs Nerv. Syst. 4, 213-222.
- Russ P. D., Pretorius D. H., Johnson M. J. (1989)**
Dandy-Walker syndrome. A review of fifteen cases evaluated by prenatal monography.
Am. J. Obstet. Gynecol. 161, 401-406.
- Saltzman D. H., Benacerraf B. B., Frigoletto F. D. (1986)**
Diagnosis and management of fetal facial clefts.
Am. J. Obstet. Gynecol. 155, 377-379.
- Schinzel A., Savoldelli G., Briner J., Schmid W. (1984)**
Prenatal ultrasonographic diagnosis of holoprosencephaly 2 cases of cebocephaly and 2 of cyclopia.
Arch. Gynecol. 236, 47-53.
- Schmidt R., Boos R., Schmidt W. (1986)**
Diagnosis of holoprosencephaly with cyclopia in the fetus.
Geburtshilfe Frauenheilkd. 46, 470-472.

- Serlo W., Kirkinen P., Heikinen E., Jouppila P.** (1985)
Antenatal and postnatal evaluation of the Dandy-Walker syndrome.
Childs Nerv. Syst. 1, 148-151.
- Shalev E., Romano S., Nseir T., Zuckerman H.** (1988)
Klippel-Trenaunay syndrome: Ultrasonic prenatal diagnosis.
J. Clin. Ultrasound 16, 268-270.
- Siebert J. R., Kokich V. G., Beckwith J. B., Cohen M. M., Lemire R. J.** (1981)
The facial features of holoprosencephaly in anencephalic human specimens. II. Craniofacial anatomy.
Teratology 23, 305-315.
- Smith P. A., Johansson D., Tzannatos C., Campbell S.** (1986)
Prenatal measurement of the fetal cerebellum and cisterna cerebellomedullaris by ultrasound.
Prenat. Diagn. 6, 133-141.
- Stango S.** (1980)
Congenital toxoplasmosis.
Am. J. Dis. Child. 134, 635-637.
- Tassin G. B., Maklad N. F., Stewart R. R., Bell M. E.** (1991)
Cytomegalic inclusion disease. Intrauterine sonographic diagnosis using findings involving the brain.
Am. J. Neuror. 12, 117-122.
- Teebi A. S., Naguib K. K.** (1988)
Autosomal recessive nonsyndromal hydrocephalus.
Am. J. Med. Genet. 31, 467-470.
- Thorp J. M., Seeds J. W., Herbert W. N. P., Bowes W. A., Maslow A. S., Cefalo R. C., Chescheir N., Katz V. L.** (1988)
Prenatal management and congenital toxoplasmosis.
N. Engl. J. Med. 319, 372-373.
- Tolmie J. L., McNay M., Stephenson J. B., Doyle D., Connor J. M.** (1987)
Microcephaly. Genetic counseling and antenatal diagnosis after the birth of an affected child.
Am. J. Med. Genet. 27, 583-594.
- Toma P., Costa A., Magnano G. M., Cariati M., Lituania M.** (1990)
Holoprosencephaly. Prenatal diagnosis by sonography and magnetic resonance imaging.
Prenat. Diagn. 10, 429-436.
- Toma P., Lucigrai G., Ravegnani M., Cariati M., Magnano G., Lituania M.** (1990)
Hydrocephalus and porencephaly. Prenatal diagnosis by ultrasound and MR imaging.
J. Comput. Assist. Tomogr. 14, 843-845.
- Tóth Z., Csécsi K., Szeifert G. T., Török O., Papp Z.** (1986)
Early prenatal diagnosis of cyclopia associated with holoprosencephaly.
J. Clin. Ultrasound 14, 550-553.
- Tóth Z., Csécsi K., Szeifert G. T., Papp Z.** (1988)
Prenatal diagnosis by ultrasound of midface defects associated with holoprosencephaly.
Acta Chir. Hung. 29, 215-221.
- Tzannatos C.** (1988)
Morphometry of the second trimester fetal brain: Measurements of anterior and posterior horns of the lateral ventricles in the prenatal diagnosis of hydrocephalus.
J. Pathol. 154, 78-78.
- Van Egmond-Linden A., Wladimiroff J. W., Jahoda M. G. J., Niermeijer M. F., Sachs B. P., Stefanko S.** (1983)
Prenatal diagnosis of X-linked hydrocephaly.
Prenat. Diagn. 3, 245-248.
- Van Egmond-Linden A., Wladimiroff J. W., Niermeijer M. F., Stewart P. A.** (1986)
Fetal hydrocephaly. Diagnosis, prognosis and management.
Ultrasound Med. Biol. 12, 939-944.
- Váradi V., Csécsi K., Szeifert G. T., Tóth Z., Papp Z.** (1987)
Prenatal diagnosis of X-linked hydrocephalus without aqueductal stenosis.
J. Med. Genet. 24, 207-209.
- Váradi V., Szabó L., Papp Z.** (1980)
Syndrome of polydactyly, cleft lip/palate or lingual lump, and psychomotor retardation in endogamic gypsies.
J. Med. Genet. 17, 119-122.
- Váradi V., Tóth Z., Török O., Papp Z.** (1988)
Heterogeneity and recurrence risk for congenital hydrocephalus (ventriculomegaly). A prospective study.
Am. J. Med. Genet. 29, 305-310.
- Vintzileos A. M., Campbell W. A., Weinbaum P. J., Nochimson D. J.** (1987)
Perinatal management and outcome of fetal ventriculomegaly.
Obstet. Gynecol. 69, 5-11.
- Vintzileos A. M., Ingardia C. J., Nochimson D. J.** (1983)
Congenital hydrocephalus: A review and protocol for perinatal management.
Obstet. Gynecol. 62, 539-549.
- Willems P. J.** (1988)
Heterogeneity in familial hydrocephalus.
Am. J. Med. Genet. 31, 471-472.
- Williamson R. A., Schauburger C. W., Varner M. W., Aschenbrener C. A.** (1984)
Heterogeneity of prenatal onset hydrocephalus: Management and counseling implications.
Am. J. Med. Genet. 17, 497-508.
- Williamson R. A., Weiner C. P., Yuh W. T. C., Abu-Yousef M. M.** (1989)
Magnetic resonance imaging of anomalous fetuses.
Obstet. Gynecol. 73, 952-956.

Neural Tube Defects

The neural tube differentiates into the central nervous system, consisting of the brain and spinal cord. Neural tube defects (NTDs) constitute the most frequently encountered group of severe congenital malformations. In very early embryogenesis the neural plate develops into a tube-like structure, and disturbed development at that stage results in persistently open structures derived from that tube. Three major types of malformation result: anencephaly/exencephaly, spina bifida, and encephalocele. The first two account for 95% of all NTDs, and encephalocele for 5%.

Anencephaly/Exencephaly

Apparent failure of closure at the cranial pole results in anencephaly, a gross malformation incompatible with survival postnatally. The calvarium is largely or totally absent, the frontal, parietal and occipital bones being present only in a rudimentary form. The bony orbits are shallow, with associated exophthalmos. The neural tube lesion is covered by an abundantly vascularized spongy connective tissue, the area cerebrovasculosa, containing some glial cells, and a disordered choroid plexus, and fibrovascular stroma. Primordial remnants of the brain stem and basal ganglia can be recognized beneath this transparent membrane.

The cranial defect may continue downwards as a cleft involving the whole length of the spinal column (craniorachischisis) or, more frequently, be accompanied by a sepa-

rate lumbosacral spina bifida. In some cases the skull vault is entirely absent (acrania).

Defective closure of the neural tube (encephaloschisis) is the primary factor leading to anencephaly, subsequent extroversion of the brain is a secondary factor, and gradual degeneration of the exposed tissues a tertiary one. Ultrasound in the first half of pregnancy will pretty consistently show some exposed cerebral tissue (exencephaly). On serial ultrasound this initially extruded mass becomes smaller, a regression brought about by the large number of macrophages present in the fetal circulation and the amniotic fluid ("scavenger function"). This cellular reaction can be identified in the amniotic fluid, and is useful in prenatal diagnosis.

"Classical" anencephaly is seen mainly in the second half of gestation; before the 20th week one finds exencephaly more frequently. To differentiate the two is important only at the time of diagnosis; in statistics on malformation both forms are registered as anencephaly.

Anencephaly is found more frequently in female fetuses; many die in utero, and the remainder within a few hours of birth.

Spina Bifida

Spina bifida results from defective neural tube closure along some or all the length of the vertebral column. When no tissue is extruded through the defect, and it is covered by normal skin, it is termed spina bifida occulta. When the defect forms a

protruding sac, the term spina bifida cystica is used. It is this latter that is ordinarily meant by the simple designation "spina bifida"; this group can be subdivided into closed defects (the sac is covered by intact skin or thick opaque membrane) (not to be confused with spina bifida occulta!), and open defects, covered by a reddish semitransparent oozing membrane, the area medullovasculosa, which at its edges merges into the more normal surrounding skin (this represents a primary tissue defect and contains remnants of the original protecting membrane: both this membrane and the neighbouring intact skin are very easily injured).

When the sacular formation contains cerebrospinal fluid and extruded meningeal tissue, but no neural elements, it is called a meningocele. When spinal cord tissue and/or nerves are present, it is termed a myelomeningocele. Occasionally there is no protective membrane, the neural tube is completely open, like a book, not covered by skin, vertebral arch or meninges, and the defect exposes the central canal of the cord (myeloschisis, rachischisis). All the above are frequently associated with malformations of the fourth ventricle and medulla (Arnold-Chiari malformation) and with hydrocephalus.

Spina bifida cystica is a severe malformation often leading to death in the neonatal period. Surgical treatment includes direct closure of the defect (skin grafting), insertion of shunts to relieve hydrocephalus, and operations to relieve urinary and intestinal obstruction. None-

theless, many of the survivors suffer from paralysis of the lower limbs and urinary and faecal incontinence, and some from mental retardation, focal neurological damage and unrelieved hydrocephalus.

Criteria for selective surgery have been introduced, taking into account the severity, extent and location of the neural tube lesion, the presence or absence of associated malformations, the general condition of the newborn baby, and the attitudes of the parents. Only one-third of babies live-born with open spina bifida reach the age of five years, and among these survivors 80% suffer from severe handicaps; only 5-10% are able to lead a completely normal life. For babies with closed spina bifida lesions detected at birth the prognosis is somewhat better, but 60-70% of them have a persisting handicap.

Encephalocele

An encephalocele is a hernia-like protrusion of meninges and/or brain tissue through an opening in the cranium. The occipital bone is most frequently involved. Sphenopharyngeal, sphenoorbital and frontoethmoidal forms sometimes occur.

Many affected infants die, despite surgical treatment, and survivors usually exhibit serious neurological handicaps.

Iniencephaly

The Greek word *inion* indicates occiput. Iniencephaly is a gross malformation of the occipital region, the spine and the central nervous system: the occipital bone itself, and the cervical and thoracic vertebrae, are partly or completely absent, remaining vertebrae are irregularly fused, with defective closure of the vertebral arches. The neck is practically absent, with the facial skin continuing directly onto the chest. There is extreme lordosis in the cervicothoracic region, with a hyperextended "stargazing" head, and the trunk is shortened. The underlying nervous tissue (medulla, cervical and thoracic spinal cord, etc.) is disorganized; there is usually an open spina bifida. Associated malformations may be present; polyhydramnios consistently occurs. The defect is more often seen in female fetuses. It is a condition incompatible with survival.

Iniencephaly is usually sporadic, but occurs in some families with other neural tube defects.

Prenatal Diagnosis

All anencephalic babies die early, about or shortly after the time of birth. Some spina bifida babies also die very early, but others survive for varying periods, often with a high

degree of handicap, imposing a heavy burden on their families and on society. Many couples with a previous spina bifida baby, or at high risk of an NTD pregnancy (identified on screening) request prenatal diagnosis. Diagnosis can be made by ultrasound, AFP and AChE assays and by exfoliative cytology of the amniotic fluid.

Polyhydramnios is easy to demonstrate with ultrasound. In anencephaly absence of the calvaria results in an open bowl-like or flower-like echo, and "exophthalmos" is obvious. In exencephaly and encephalocele the extracranial tissue is usually easily seen and a lack of continuity of the vault bones can be demonstrated. In spina bifida, the two posterior lines of the vertebral column diverge at the level of the defect; in transverse section a "U" or "V" pattern is seen instead of a circular one. Due to the sharp outline of the excess tissue, closed forms are easier to recognize than open spina bifida. With spina bifida, dilated or abnormally shaped cerebral ventricles can often be demonstrated. The recent identification of easily recognizable cranial and cerebellar signs by Campbell will facilitate the detection rate of spina bifida at the routine booking scan. (Lemon sign: scalloping of the frontal bones; banana sign: anterior curvature of the cerebellar hemispheres.)



Figure 6-1a. Anterior view of a 19-week-old fetus with anencephaly and a bilateral cleft-lip and palate.

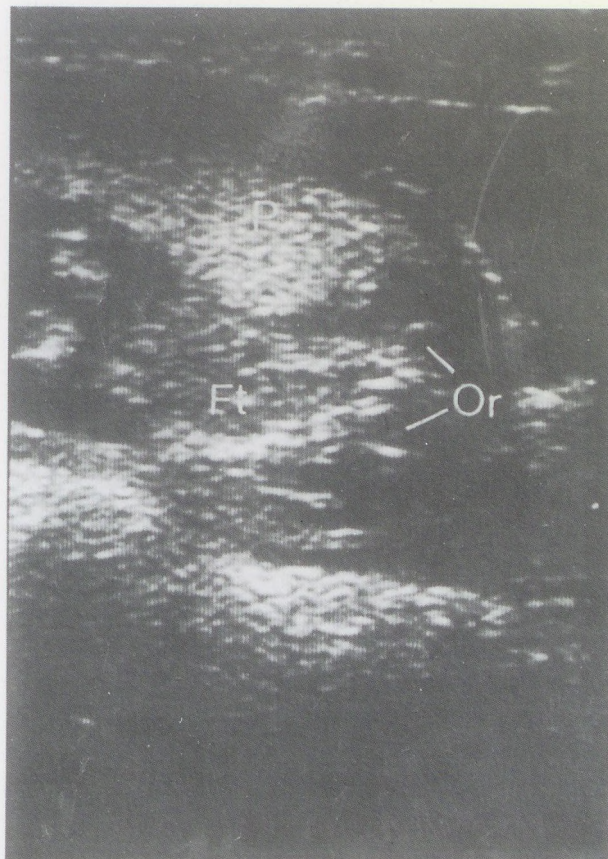


Figure 6-1b. Ultrasound view of an 18-week-old anencephalic fetus. Note the absence of the cranial vault above orbit level (Ft = fetal trunk, Or = orbits).



Figure 6-2. Sagittal section of an anencephalic, mid-trimester fetal head.



Figure 6-3. Posterior view of an anencephalic fetal head. Note the extruded fibrovascular tissue and disorganized brain tissue (yellow).

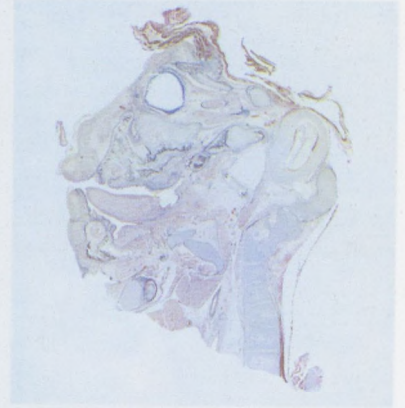


Figure 6-4a. Sagittal section of an anencephalic fetal head. The cranial vault is absent, the remnants of the brain and meninges are seen at the base of the cranium.

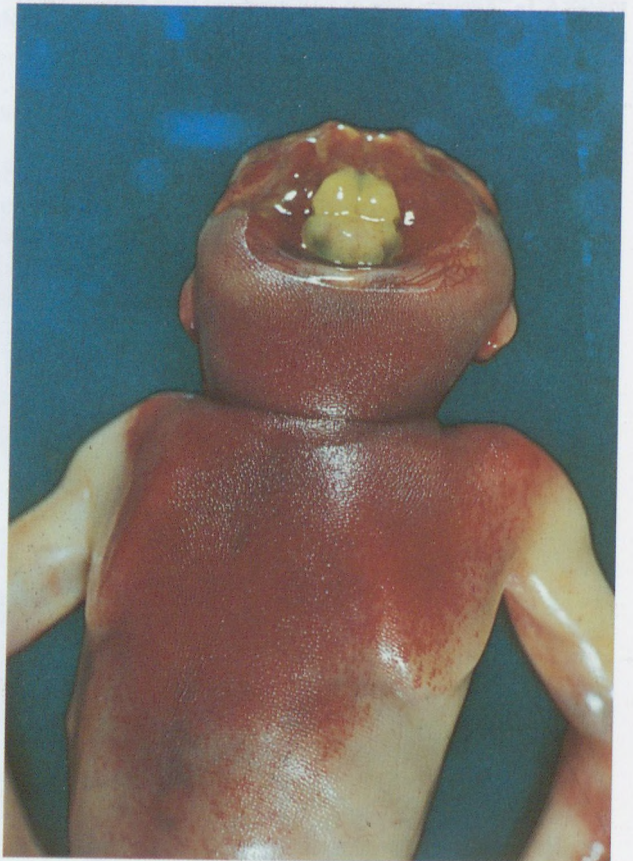


Figure 6-4b. Anencephaly. Yellowish brain is seen in the centre of the cranial cavity, surrounded by deep-red fibrovascular tissues. Note the sharp edge to the normal skin, contrasting with the adjacent hyperaemic connective tissue of the calvarium.



Figure 6-5a. Anencephaly, together with open cervical and upper thoracic spina bifida. The brain stem and cervical part of the spinal cord remain uncovered.



Figure 6-5b. Posterolateral view of an anencephalic fetal head: fibrovascular tissue is found in place of the brain.



Figure 6-6a. Posterior view of an anencephalic fetal head.

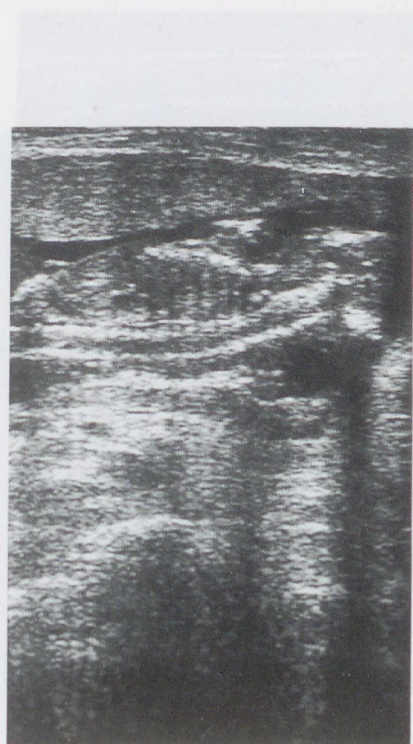


Figure 6-6b. Longitudinal scan of an anencephalic fetus with an absent cranial vault. The spine is intact.



Figure 6-7. Posterior view of a 17-week-old fetus suffering from anencephaly, an open thoracolumbar spina bifida and a large omphalocele.

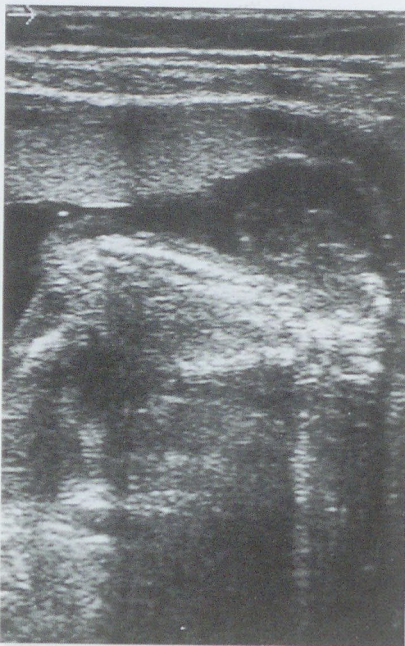


Figure 6-8a. Ultrasound view of exencephaly. The extroverted cerebral material is situated in the amniotic fluid.



Figure 6-8b. Anterior view of a fetus with exencephaly.

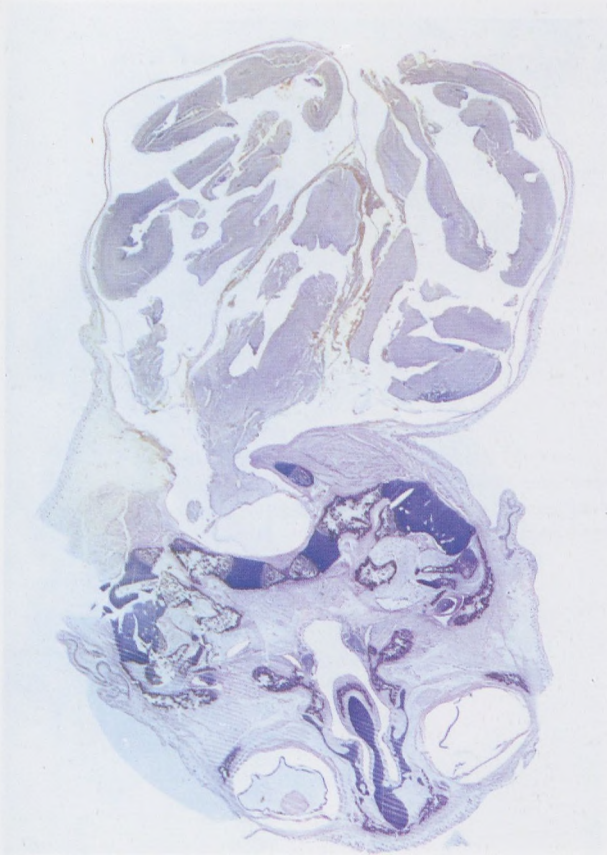


Figure 6-9a. Transverse section of a fetal head at the level of the orbits. A large occipital meningoencephalocele is seen.

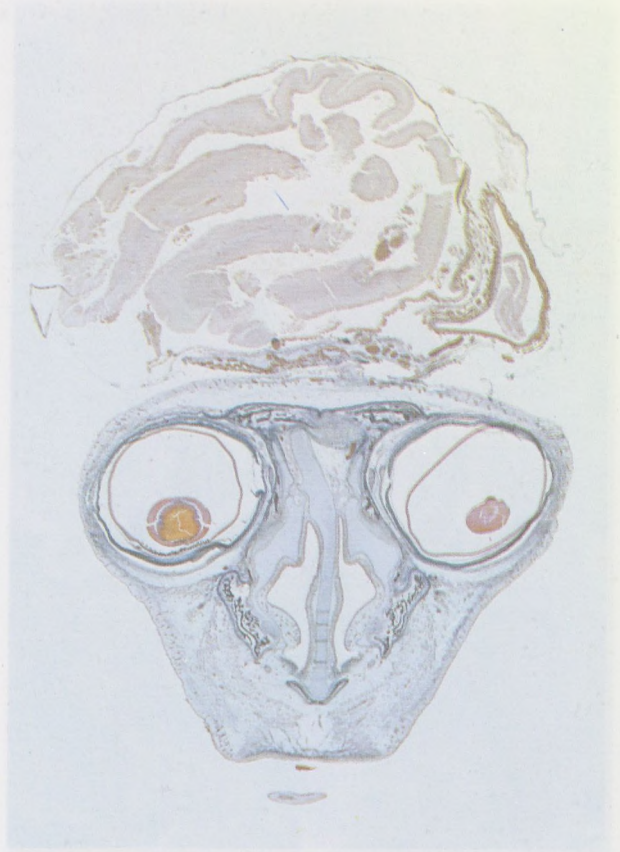
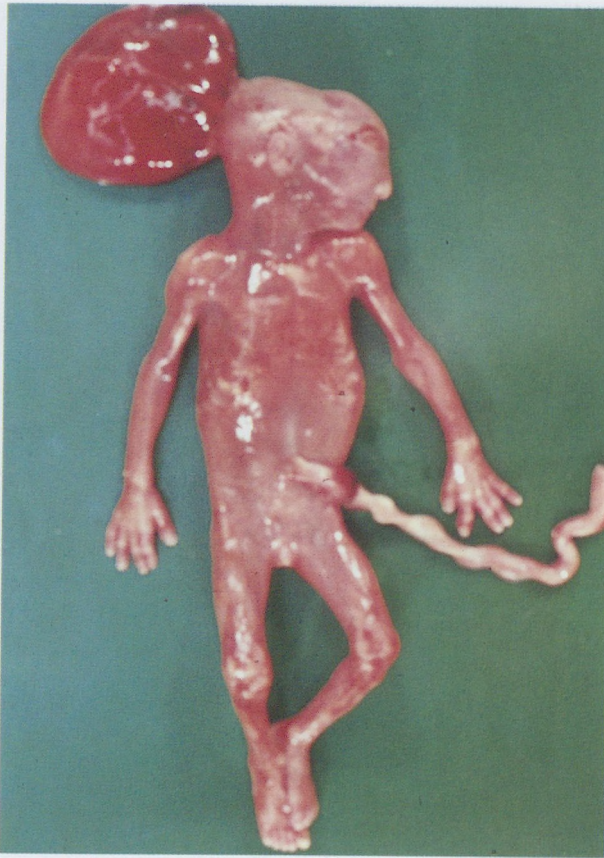


Figure 6-9b. Frontal section of an exencephalic fetal head at the level of the orbits. The exposed cerebral tissue shows an irregular pattern. Normal lateral ventricles are not seen.



Figure 6-10. Medium-sized occipital meningoencephalocele: most of the brain lies within the sac.

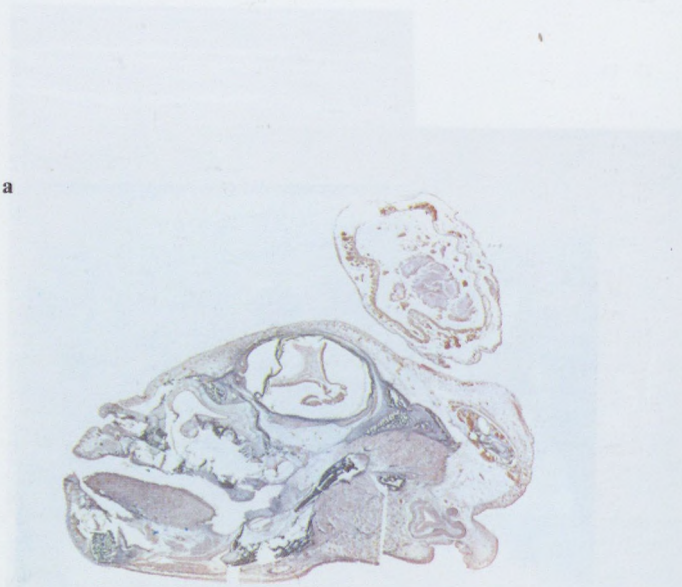


a



b

Figures 6-11a and b. Prenatally diagnosed occipital meningoencephalocele (**a**). Frontal section of the head at the level of the orbits. The remnant of brain tissue is seen above the right orbit (**b**).

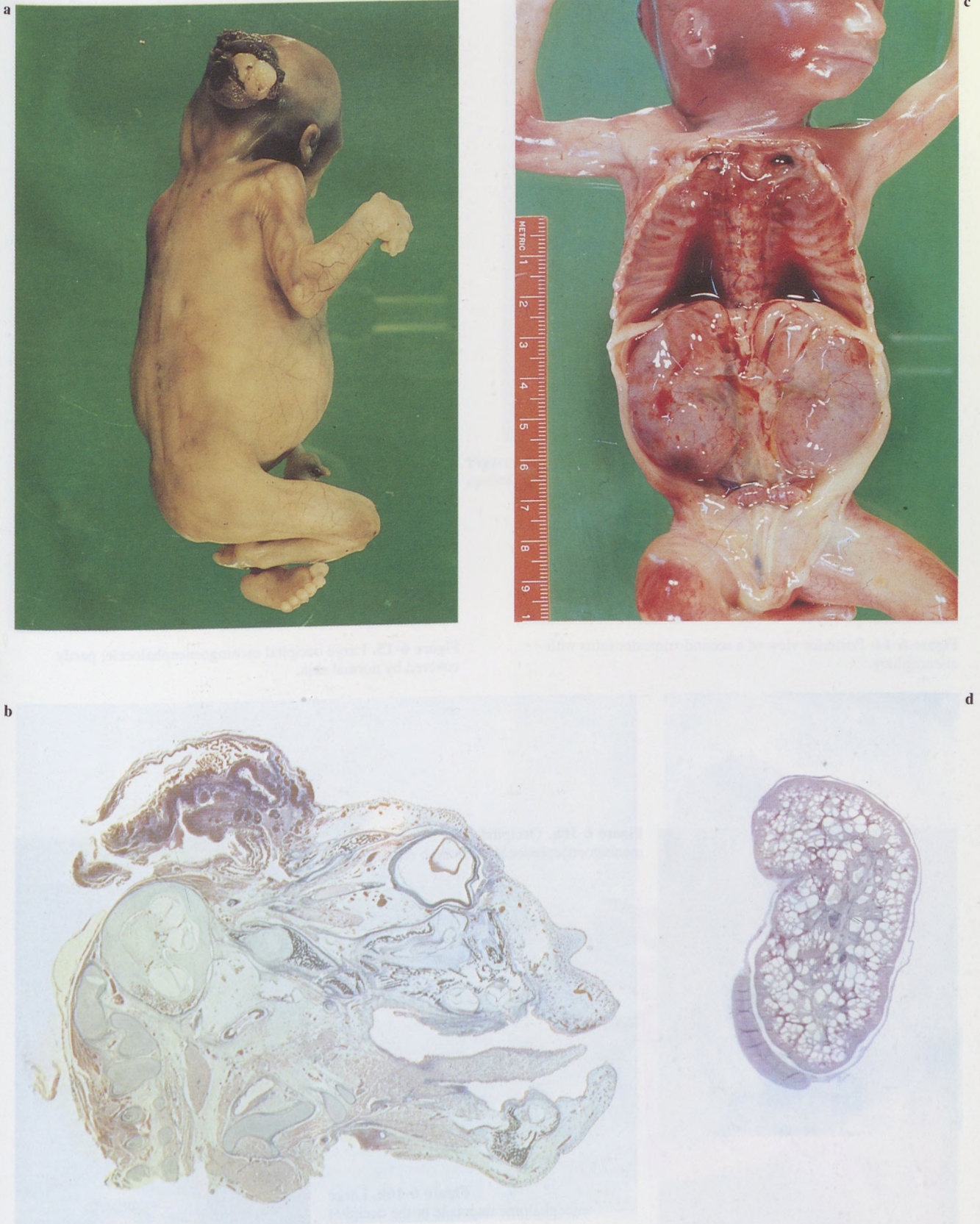


a



b

Figures 6-12a and b. Sagittal section of a fetal head with exencephaly. The bones of the cranial vault are absent and the cerebral tissue is exposed (**a**). The uncovered brain tissue remains relatively intact. The flattened (platen-like) frontal bone is covered by normal skin tissue (**b**).



Figures 6-13a, b, c and d. Meckel syndrome, second-trimester fetus: major features include brain malformation (the occipital encephalocele is typical) (a and b), cystic kidneys (c and d), and polydactyly (six toes can be seen on one foot) (a).



Figure 6-14. Posterior view of a second-trimester fetus with anencephaly.



Figure 6-15. Large occipital meningoencephalocele, partly covered by normal skin.



Figure 6-16a. Occipital meningoencephalocele with limb reduction.



Figure 6-16b. Large encephalomeningocele in the occipital region of a 20-week-old fetus. Herniated brain tissue can be recognized within the sac (ultrasound scan).



Figures 6-17a and b. Cystic neural tube defect: spina bifida cystica, upper thoracic, with associated meningocele.



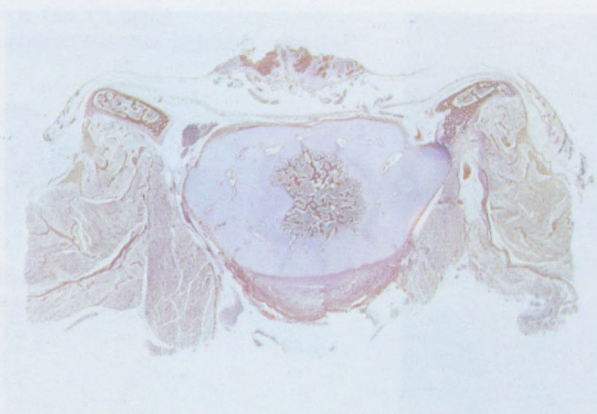
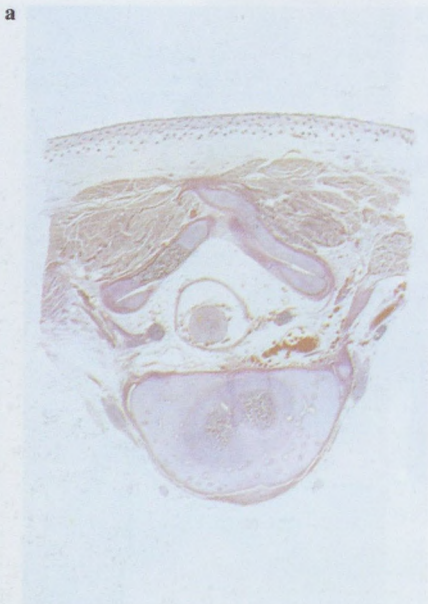
Figure 6-17c. Medium-sized occipital meningoencephalocele.



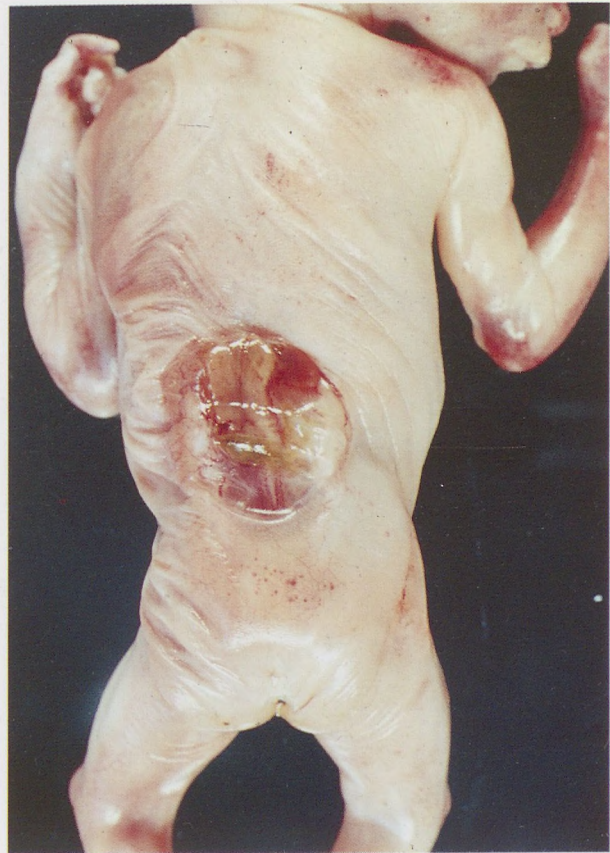
Figure 6-18. Newborn infant with large lumbar spina bifida cystica.



Figure 6-19. Prenatally diagnosed rachischisis (18 gestational weeks).



Figures 6-20a and b. Transverse section of a normal thoracic vertebra and spinal cord. The overlying skin is intact (a). Transverse section of a thoracic vertebra with spina bifida. The vertebral arch is open and the neural tissue is exposed on the surface (b).



Figures 6-21a and b. Large thoracolumbar spina bifida cystica (a). Note the opened book-like appearance of the spinal cord (b).



Figure 6-22. Transverse sonogram showing an open spinal tube at 24 weeks.

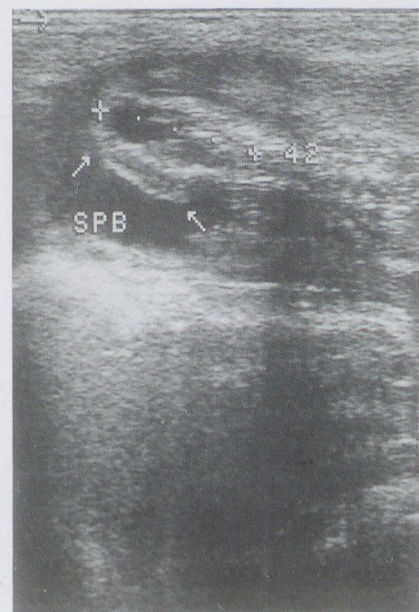


Figure 6-23. Longitudinal scan through the lumbar spina bifida (SPB). The defect is recognized as a widening of parallel echoes representing the affected part of the spine. The defect is covered with a cystic extension of the meninges (arrows).

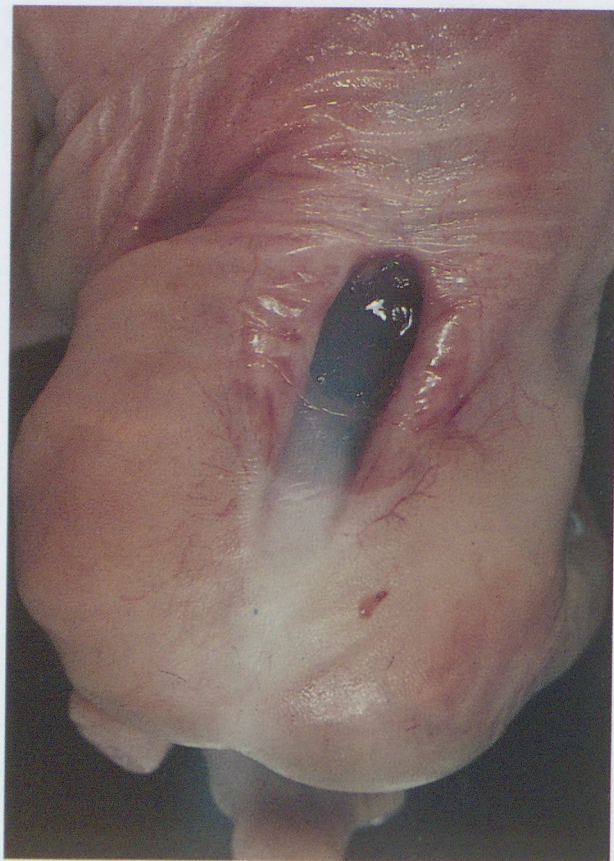
a



b

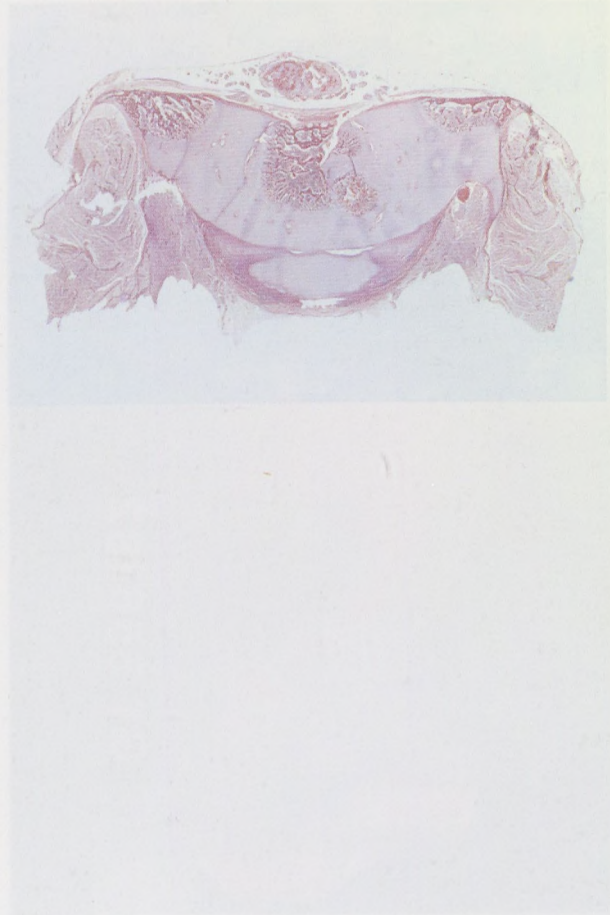
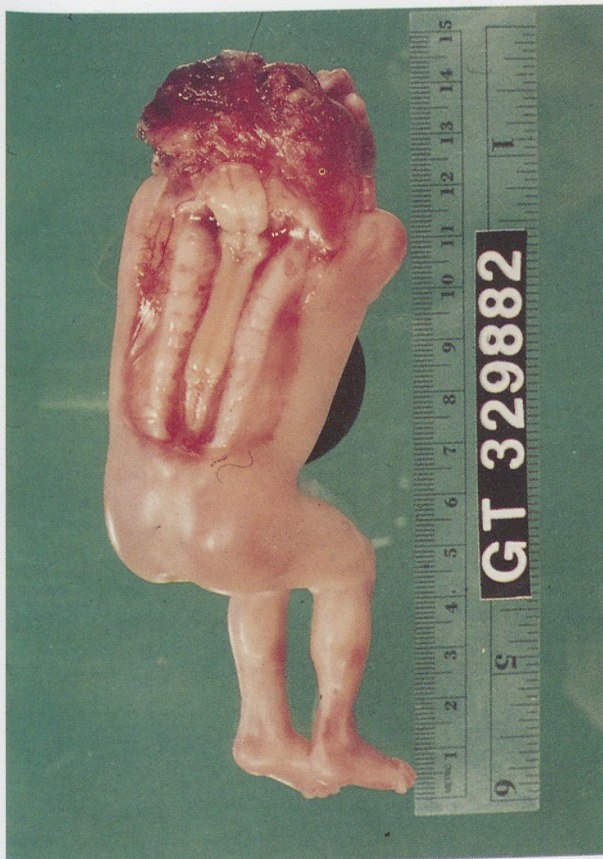


c



d





Figures 6-25a and b. Craniorachischisis. The most severe form of neural tube defect. Absence of brain tissue (anencephaly) is associated with an opening up of the vertebral arches throughout the whole length of the spine. The uncovered medulla and spinal cord are flattened and resemble an opened book (**a**). Transverse section of a lumbar vertebra with open vertebral arch shows the exposed spinal cord (**b**).

Figures 6-24a, b, c and d. Mid-trimester fetuses with extensive open thoracolumbar (**a**), lumbar (**b**), lumbosacral (**c**) and cervico-thoracolumbar (**d**) spina bifida.



Figures 6-26a and b. Large open thoracolumbar defect (spina bifida) and club foot (a). Transverse section of the trunk showing open spina bifida at the level of the liver and stomach (b).



Figure 6-27. Open lumbosacral spina bifida with associated myelomeningocele.

Figure 6-28. Iniencephaly, posterior view with open cervicothoracic defect.

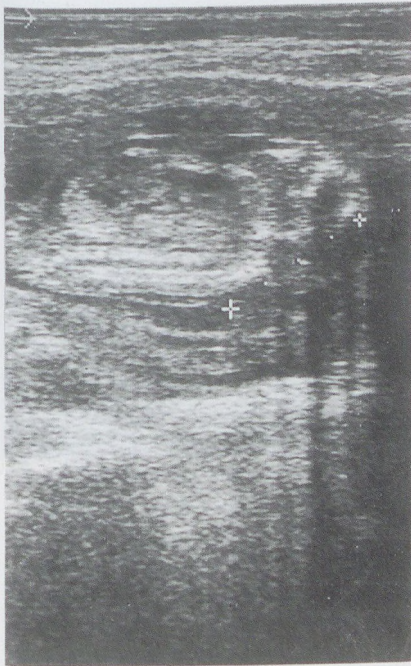


Figure 6-29a. Longitudinal ultrasound view of 19-week-old iniencephalic fetus. The fetal head is unduly close to the trunk. A large meningocele is present.

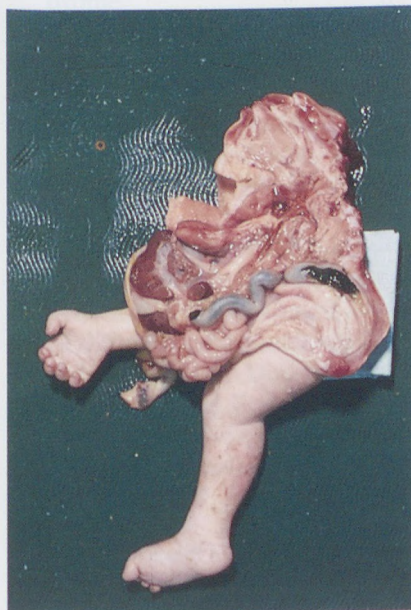
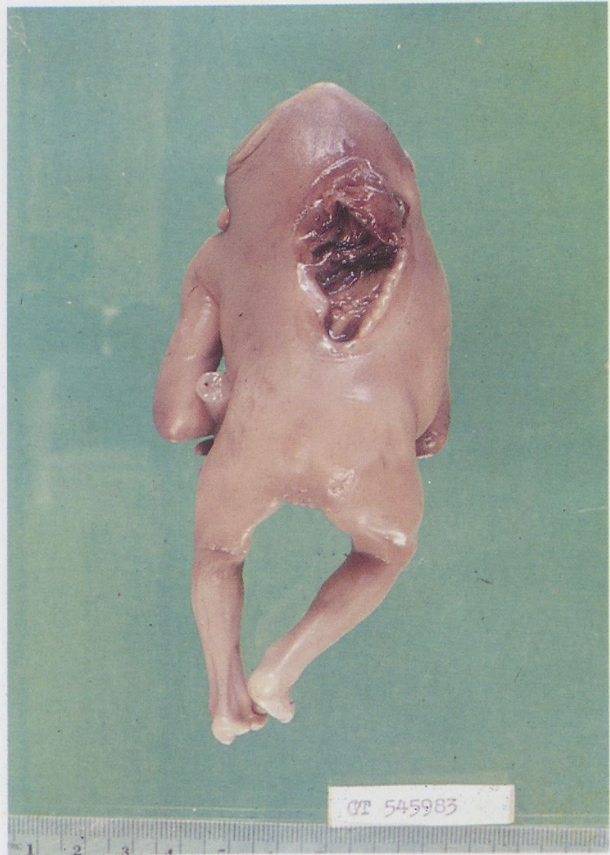
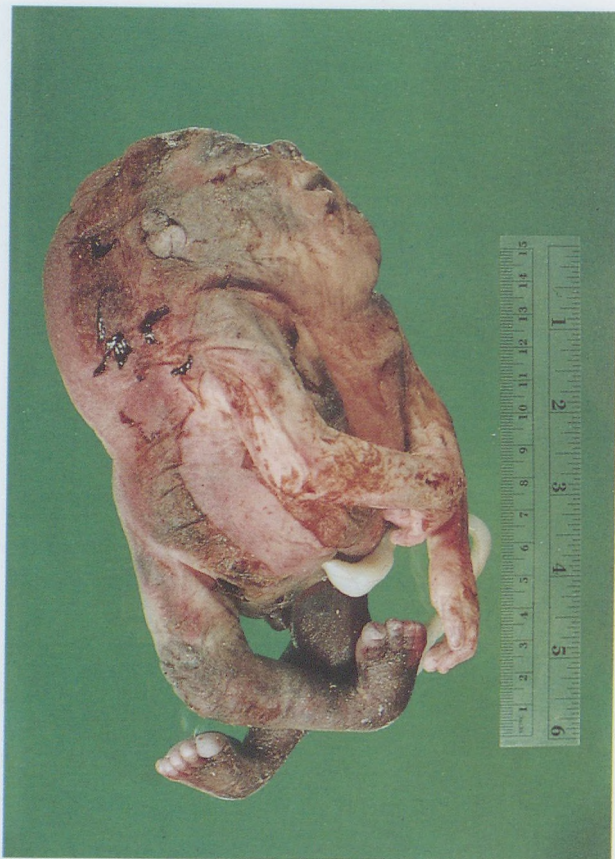
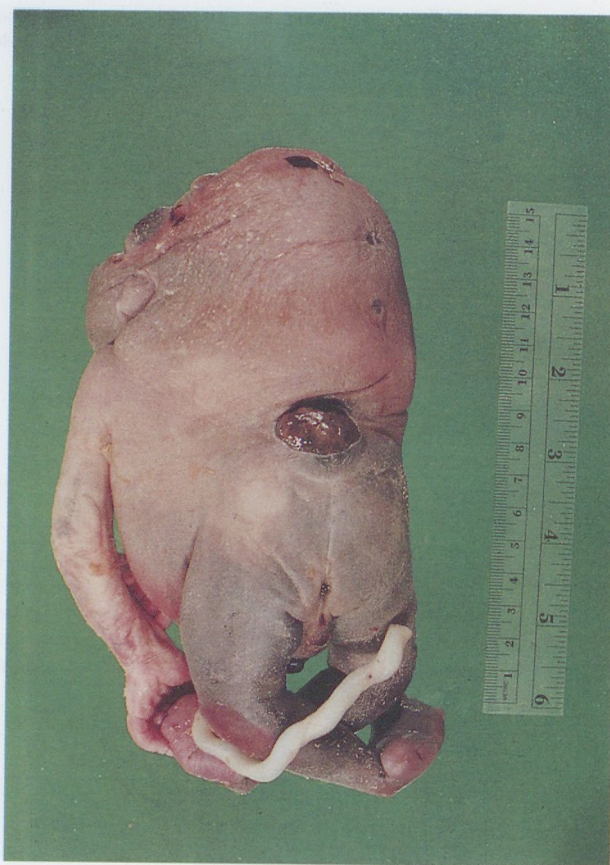


Figure 6-29b. Sagittal section through the trunk of an iniencephalic fetus. No vertebrae can be identified. A large omphalocele is also seen.

a



b



c



Figures 6-30a, b and c. Iniencephaly, with open thoracic neural tube defect and bilateral talipes: lateral view (a), posterior view (b) and lateral X-ray (c).

References

- Abrams S. L., Filly R. A. (1985)**
Congenital vertebral malformations. Prenatal diagnosis using ultrasonography.
Radiology 155, 762-762.
- Abumusa A., Hata T., Senoh D., Makihara K., Aoki S., Hata K., Takamiya O., Mochida T., Kitao M., Tanaka O. (1990)**
Antenatal sonographic diagnosis of exencephaly.
Gynecol. Obstet. Invest. 29, 75-77.
- Agamanol D. P., Hite S. H., Platt M. S., Boeckman C. R. (1986)**
Arnold-Chiari malformation. Report of 4 cases with contamination of the central nervous system by amniotic contents.
Surg. Neurol. 25, 261-266.
- Ahdab-Barmada M., Claassen D. (1990)**
A distinctive triad of malformations of the central nervous system in the Meckel-Gruber syndrome.
J. Neuropathol. Exp. Neurol. 49, 610-620.
- Bell J. E. (1979)**
Central nervous system defects in early human abortuses.
Dev. Med. Child Neurol. 21, 321-332.
- Bell J. E. (1989)**
The pathology of central nervous system defects in human fetuses of different gestational ages.
Adv. Study Birth Defects 7, 1-17.
- Bell J. E., Green R. J. L. (1982)**
Studies on the area cerebrovasculosa of anencephalic fetuses.
J. Pathol. 137, 315-328.
- Benacerraf B. B., Stryker J. M., Frigoletto F. D. (1989)**
Abnormal ultrasonography appearance of the cerebellum (banana sign). Indirect sign of spina bifida.
Radiology 171, 151-153.
- Brock D. J. H. (1982)**
Early Diagnosis of Fetal Defects. Churchill Livingstone, Edinburgh-London
- Campbell J., Gilbert W. M., Nicolaides K. H., Campbell S. (1987)**
Ultrasound screening for spina bifida: Cranial and cerebellar signs in a high-risk population.
Obstet. Gynecol. 70, 247-250.
- Chambers S. E., Muir B. B., Bell J. E. (1988)**
"Bullet"-shaped head in fetuses with spina bifida: A pointer to the spinal lesion.
J. Clin. Ultrasound 16, 25-28.
- Chatterjee M. S., Bondoc B., Adhate A. (1985)**
Prenatal diagnosis of occipital encephalocele.
Am. J. Obstet. Gynecol. 153, 646-647.
- Chervenak F. A., Isaacson G., Mahoney M. J., Berkowitz R. L., Tortora M., Hobbins J. C. (1984)**
Diagnosis and management of fetal cephalocele.
Obstet. Gynecol. 64, 86-91.
- Coicaud C. (1988)**
Antenatal ultrasound diagnosis of spina bifida.
Neurochirurgie 34, 35-39.
- Cox G. G., Rosenthal S. J., Holsapple J. W. (1985)**
Exencephaly: Sonographic findings and radiologic-pathologic correlation.
Radiology 155, 755-756.
- Csécsei K., Szeifert G. T., Tóth Z., Papp Z. (1986)**
Prenatal detection and morphology of dysplastic kidneys in Meckel syndrome.
In: Tankó A., Berik I., Petri E. (eds) *Practical Aspects of Gynaecourology*. Akadémiai Kiadó, Budapest, pp. 425-430.
- Cullen M. T., Athanassiadis A. P., Romero R. (1990)**
Prenatal diagnosis of anterior parietal encephalocele with transvaginal sonography.
Obstet. Gynecol. 75, 489-491.
- Delacruz R., Millan J. M., Miralles M., Munoz M. J. (1989)**
Cranial sonographic evaluation in children with meningomyelocele.
Child. Nerv. 5, 94-98.
- Filly R. A., Cardoza J. D., Goldstein R. B., Barkovich A. J. (1989)**
Detection of fetal central nervous system anomalies. A practical level of effort for a routine sonogram.
Radiology 172, 403-408.
- Fink I. J., Chinn D. H., Callen P. W. (1983)**
A potential pitfall in the ultrasonographic diagnosis of fetal encephalocele.
J. Ultrasound Med. 2, 313-314.
- Foderaro A. E., Abu-Yousef M. M., Benda J. A., Williamson R. A., Smith W. L. (1987)**
Antenatal ultrasound diagnosis of iniencephaly.
J. Clin. Ultrasound 15, 550-554.
- Freeman P. C., Jeanty P. (1991)**
Iniencephaly.
The Fetus 1, 7402-7404.
- Furness M. E., Barbary J. E., Verco P. W. (1987)**
Fetal head shape in spina bifida in the second trimester.
J. Clin. Ultrasound 15, 451-453.
- Garel L., Boisvert J., Filiatra D., Grignon A., Perreaul G., Patriqui H. (1989)**
Fetal sonography. 1. Neural tube defects.
Pediatr. Radiol. 19, 157-162.
- Goldstein R. B., Filly R. A. (1988)**
Prenatal diagnosis of anencephaly. Spectrum of sonographic appearances and distinction from the amniotic band syndrome.
A. J. R. 151, 547-550.
- Goldstein R. B., Filly R. A., Callen P. W. (1989)**
Sonography of anencephaly: Pitfalls in early diagnosis.
J. Clin. Ultrasound 17, 397-402.

- Graham D., Johnson R. B., Winn K., Sanders R. C.** (1982)
The role of sonography in the prenatal diagnosis and management of encephalocele.
J. Ultrasound Med. 1, 111-115.
- Gray D. L., Crane J. P., Rudloff M. A.** (1988)
Prenatal diagnosis of neural tube defects. Origin of midtrimester vertebral ossification centers as determined by sonographic water-bath studies.
J. Ultrasound Med. 7, 421-427.
- Hendricks S. K., Cyr D. R., Nyberg D. A., Raabe R., Mack L. A.** (1988)
Exencephaly. Clinical and ultrasonic correlation to anencephaly.
Obstet. Gynecol. 72, 898-901.
- Hobbins J. C.** (1991)
Diagnosis and management of neural tube defects today.
N. Engl. J. Med. 324, 690-691.
- Hori A., Fiebig I., Stichnoth F. A.** (1988)
Neural-tube defect associated with thoracoabdominal evisceration.
Ann. Pathol. 8, 321-324.
- Johnson A., Losure T. A., Weiner S.** (1985)
Early diagnosis of fetal anencephaly.
J. Clin. Ultrasound 13, 503-505.
- Johnson V. P., Holzwarth D. R.** (1984)
Prenatal diagnosis of Meckel syndrome. Case reports and literature review.
Am. J. Med. Genet. 18, 699-711.
- Katz V. L., Aylsworth A. S., Albright S. G.** (1989)
Iniencephaly is not uniformly fatal.
Prenat. Diagn. 9, 595-599.
- Kurjak A. (ed)** (1985)
The Fetus as a Patient.
Excerpta Medica, Amsterdam-New York-Oxford
- Lemire R. J.** (1988)
Neural tube defects.
J. Am. Med. Assoc. 259, 558-562.
- Lemire R. J., Siebert J. R.** (1990)
Anencephaly. Its spectrum and relationship to neural tube defects.
J. Cran. Genet. 10, 163-174.
- Lindfors K. K., McGahan J. P., Tennant F. R., Hanson F. W., Walter J. P.** (1987)
Midtrimester screening for open neural tube defects. Correlation of sonography with amniocentesis results.
A. J. R. 149, 141-146.
- Main D. M., Mennuti M. T.** (1986)
Neural tube defects. Issues in prenatal diagnosis and counseling.
Obstet. Gynecol. 67, 1-16.
- Mannes E. J., Crelin E. S., Hobbins J. S., Viscomi G. N., Alcebo L.** (1982)
Sonographic demonstration of fetal acrania.
A. J. R. 139, 181-182.
- Meizner I., Barziv J.** (1987)
Prenatal ultrasonic diagnosis of a rare case of iniencephaly aperitus.
J. Clin. Ultrasound 15, 200-203.
- Meizner I., Maor E., Katz M., Bar-david E.** (1987)
Prenatal early sonographic diagnosis of Meckel syndrome.
Isr. J. Med. Sci. 23, 902-904.
- Mórocz I., Szeifert G. T., Molnár P., Tóth Z., Csécssei K., Papp Z.** (1986)
Prenatal diagnosis and pathoanatomy of iniencephaly.
Clin. Genet. 30, 81-86.
- Nyberg D. A., Hallesy D., Mahony B. S., Hirsch J. H., Luthy D. A., Hickok D.** (1990)
Meckel-Gruber syndrome. Importance of prenatal diagnosis.
J. Ultrasound Med. 9, 691-696.
- Nyberg D. A., Mack L. A., Hirsch J., Mahony B. S.** (1988)
Abnormalities of fetal cranial contour in sonographic detection of spina bifida. Evaluation of the lemon sign.
Radiology 167, 387-392.
- Nyberg D. A., Shepard T. H., Mack L. A., Hirsch J., Luthy D. A., Fitzsimmons J.** (1988)
Significance of a single umbilical artery in fetuses with central nervous-system malformations.
J. Ultrasound Med. 7, 265-273.
- Oi S., Kokunai I., Okuda Y., Sasagaki M., Matsumoto S.** (1990)
Identical embryopathogenesis for exencephaly and myeloschisis. An experimental study.
J. Neurosurg. 72, 450-457.
- Pachi A., Giancotti A., Torcia F., DeProsperi V., Maggi E.** (1989)
Meckel-Gruber syndrome. Ultrasonographic diagnosis at 13 weeks gestational age in an at risk case.
Prenat. Diagn. 9, 187-190.
- Paetau A., Salonen R., Haltia M.** (1985)
Brain pathology in the Meckel syndrome. A study of 59 cases.
Clin. Neurol. Neurosurg. 4, 56-62.
- Papp Z., Berta I., Árvay A.** (1973)
Early antenatal diagnosis of anencephaly.
Lancet 1, 729-729.
- Papp Z., Csécssei K., Tóth Z., Polgár K., Szeifert G. T.** (1986)
Exencephaly in human fetuses.
Clin. Genet. 30, 440-444.
- Papp Z., Tóth Z., Szabó M., Csécssei K., Török O.** (1985)
Prenatal screening for neural tube defects and other malformations by both serum AFP and ultrasound.
In: Kurjak A. (ed.) *The Fetus as a Patient*. Elsevier Science Publishers B. V., Amsterdam, New York, Oxford, pp. 167-180.
- Papp Z., Tóth Z., Török O., Szabó M.** (1987)
Prenatal diagnosis policy without routine amniocentesis in pregnancies with a positive family history for neural tube defects.
Am. J. Med. Genet. 26, 103-110.

- Pearce J. M., Griffin D., Campbell S.** (1985)
The differential prenatal diagnosis of cystic hygromata and encephalocele by ultrasound examination.
J. Clin. Ultrasound 13, 317-320.
- Petrikovsky B. M.** (1990)
Fruit signs and neural tube defects.
Prenat. Diagn. 10, 134-134.
- Pilu G., Romero R., Reece E. A., Goldstein I., Hobbins J. C., Bovicelli L.** (1988)
Subnormal cerebellum in fetuses with spina bifida.
Am. J. Obstet. Gynecol. 158, 1052-1056.
- Platt L. D., Golde S. H.** (1983)
Neural tube defects in infants of diabetic mothers.
Am. J. Obstet. Gynecol. 145, 384-385.
- Rahilly R. O., Müller F.** (1986)
The normal and abnormal development of the nervous system in the early human embryo.
Pediatr. Neurosci. 2, 89-94.
- Rehder H., Labbe F.** (1981)
Prenatal morphology in Meckel's syndrome.
Prenat. Diagn. 1, 161-172.
- Roberts C. J., Hibbard B. M., Roberts E. E., Evans K. T., Laurence K. M., Robertson I. B.** (1983)
Diagnostic effectiveness of ultrasound in detection of neural tube defects.
Lancet 1, 1068-1069.
- Salonen R.** (1984)
The Meckel syndrome. Clinico-pathological findings in 67 patients.
Am. J. Med. Genet. 18, 671-689.
- Sanders R. C., Blakemore K.** (1989)
Lethal fetal anomalies. Sonographic demonstration.
Radiology 172, 1-6.
- Siebert J. R., Lemire R. J., Cohen M. M.** (1990)
Aberrant morphogenesis of the central nervous system.
Clin. Perinatol. 17, 569-595.
- Silver R. K., Marzocchi M., Farrell E. E., McLone D. G.** (1989)
The perinatal management of central nervous system anomalies.
Clin. Perinatol. 16, 939-953.
- Spirit B. A., Oliphant M., Gordon L. P.** (1990)
Fetal central nervous system abnormalities.
Radiol. Clin. North Am. 28, 59-73.
- Stumpf D. A.** (1990)
The infant with anencephaly.
N. Engl. J. Med. 322, 669-674.
- Thiagarajah S., Henke J., Hogge W. A., Abbitt P. L., Breeden N., Ferguson J. E.** (1990)
Early diagnosis of spina bifida. The value of cranial ultrasound markers.
Obstet. Gynecol. 76, 54-57.
- Toms D., Brown B. S. J.** (1982)
Prenatal ultrasonographic diagnosis of spina bifida: Timing of examination.
J. Can. Assoc. Radiol. 33, 276-278.
- Török O., Papp Z.** (1991)
Are the neurulation and canalization forms of neural tube defects causally distinct?
Am. J. Med. Genet. 39, 241-241.
- Trenouth M. J.** (1989)
Craniofacial shape in the anencephalic human fetus.
J. Anat. 165, 215-224.
- Van den Hof M. C., Nicolaides K. H., Campbell J., Campbell S.** (1990)
Evaluation of the lemon and banana signs in 130 fetuses with open spina bifida.
Am. J. Obstet. Gynecol. 162, 322-327.
- Warkany J.** (1971)
Congenital Malformations. Notes and Comments.
Year Book Medical Publishers, Chicago
- Warkany J., Lemire R. J., Cohen M. M.** (1981)
Mental Retardation and Congenital Malformations of the Central Nervous System.
Year Book Medical Publishers, Chicago-London
- Weaver D. D., Hogge W. A., Thiagarajah S., Ferguson J. E., Schnatterly P. T., Harbert G. M.** (1989)
The role of ultrasonography and amniocentesis in the evaluation of pregnancies at risk for neural tube defects.
Am. J. Obstet. Gynecol. 161, 520-524.
- Weinstein P., Weinstein L., Doters D., Bedrick A., Anderson C.** (1983)
Prenatal diagnosis of occipital encephalocele by ultrasound scanning.
Neurosurgery 12, 680-683.
- Wilson G. N., Raj A., Waterson J. R., Bush M., Baty E., Parker J., Hamman J., Louwsma G., Barr M.** (1986)
Detection of neural tube defects with alpha-fetoprotein measurement in amniotic fluid. A protocol for managing elevated values.
J. Reprod. Med. 31, 157-161.
- Wood L. R., Smith M. T.** (1984)
Generation of anencephaly: 1. aberrant neurulation and 2. conversion of exencephaly to anencephaly.
J. Neuropathol. Exp. Neurol. 43, 620-633.

- 101-102, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000.

Cervical, Thoracic and Abdominal Malformations

Malformations of the heart, the lungs and the diaphragm. Prenatal diagnosis is possible with high-resolution ultrasound.

Congenital Heart Defects

Echocardiography has been used successfully in the prenatal assessment of fetal cardiac function and structure, and has led to the diagnosis of most cardiac abnormalities. However, it should be emphasized that the majority of published reports refer to the prenatal diagnosis of moderate to major defects and lesions with lesser haemodynamic significance for the fetus, such as small ventricular septal defects, are as yet beyond the resolving capacity of ultrasound equipment.

The optimum time for fetal cardiac scanning is 18-24 weeks' gestation. Transverse section of the thorax reveals the "four-chamber view" of the fetal heart, which occupies approximately one-third of the thorax. M-mode echocardiography improves the accuracy of the cross-sectional scan in the diagnosis of cardiac defects and provides additional information on cardiac geometry and function. This modality is particularly useful in the diagnosis and evaluation of dysrhythmias and the monitoring of *in utero* antiarrhythmic therapy.

Ectopia cordis. The heart is displaced outside the thoracic cavity. It is usually associated with an open pericardium (pericardial sac) and widely separated halves of the sternum. Frequently there are associated malformations. Ectopia cordis

results from faulty development of the sternum and pericardium, which may result from failure of complete fusion of the lateral folds in the thoracic region during the fourth week. Ectopia may represent part of the ADAM complex. It is easily seen on prenatal ultrasound.

Hypoplastic left heart. The left ventricle (and atrium) is grossly hypoplastic or absent. Death usually occurs within hours or days of birth; major corrective surgery is impossible. Mostly an isolated defect. It is easily detectable on ultrasound.

Ventricular septal defect (VSD). Most cases are isolated and of multifactorial origin. When recording family data one should note that 10-25% of defects close spontaneously in childhood. (Eisenmenger complex: ventricular septal defect with severe pulmonary hypertension and right ventricular hypertrophy.)

Tetralogy of Fallot. Pulmonary stenosis, ventricular septal defect, aortic dextroposition and hypertrophy of the right ventricle.

Pulmonary stenosis (PS). The stenosis may be subvalvular, valvular, supra-valvular, or multiple peripheral. Characteristically severe valvular stenosis occurs in Noonan syndrome; multiple peripheral stenoses in Alagille syndrome. PS may be combined with other heart defects, e.g., tetralogy of Fallot. Most cases are isolated.

Ebstein anomaly. Malformation of the tricuspid valve: the posterior and the septal valves adhere to the right ventricular wall, the anterior valve to the annulus fibrosus. This is usually an isolated malformation.

Transposition of the great vessels/great arteries (TGV, TGA). Laterality defects associated with malrotation of the heart can involve the atria, the ventricles and the great arteries. The pulmonary artery may take origin from an anatomical left ventricle, the aorta from an anatomical right ventricle. The degree of circulatory disturbance depends also on the atrial connections, and on the presence or absence of septal defects and valvular stenoses, as well as on extracardiac defects (PDA, coarctation). The terms "corrected transposition" and "uncorrected transposition" have been used. There may sometimes be laterality disturbances elsewhere, e.g., asplenia/polysplenia, midline stomach (Ivemark sequence). Ultrasound diagnosis in pregnancy is extremely difficult, and lies in the province of the paediatric cardiologist.

Cardiac tumours. In fetal life rhabdomyomata are frequently present in tuberous sclerosis. They may be detected on ultrasound and used, in high-risk pregnancies, as a marker for this disorder.

Some congenital heart defects (ectopia cordis, hypoplastic left heart) are easily diagnosable with mid-trimester ultrasound. Others, such as transpositions, are extremely difficult and call for very special experience. Some heart defects are inoperable, and some are markers for more serious disease elsewhere. Some are relatively trivial, and easily managed or repaired in childhood. High quality ultrasound techniques should be backed up by informed genetic counselling.

Malformations of the Lung

Pulmonary agenesis/aplasia develops as part of some more complex congenital malformation. *Pulmonary hypoplasia* is always secondary to other problems (e.g., renal agenesis, oligohydramnios sequence).

Congenital cystic adenomatoid malformation of the lung. The most common of the isolated lung malformations is congenital cystic adenomatoid malformation. In this condition a large part of the lung is occupied by cysts of variable size. The malformation may sometimes resemble a tumour. It can be uni- or bilateral, extensive or localized. Polyhydramnios is consistently present, and the fetus may be hydropic, in which case survival is most unlikely.

The lung changes, the polyhydramnios and the oedema can be demonstrated with pregnancy ultrasound.

Diaphragmatic Hernia

The pleuroperitoneal canal may fail to close normally at 8-10 weeks' gestation, leaving an opening through which abdominal organs herniate into the thorax. In rare instances, not only the stomach, spleen, and most of the intestines, but the liver and kidneys also pass into the thoracic cavity and displace the lungs and heart. The hernial opening is usually posterolateral (foramen of Bochdalek); retrosternal hernia is rare. The defect occurs five times more often on the left side than on the right. The lungs are compressed by the herniated abdominal organs; the alveoli are hypoplastic, and with reduced pulmonary movement development of the bronchial tree is also retarded.

Diaphragmatic hernia is consistently accompanied by polyhydramnios. Some fetuses die *in utero*, and without surgery most live-born infants would be lost within hours of birth. Left-sided hernias may result in a more rapid onset of symptoms: respiratory distress and apparent

dextrocardia. Operation is attempted when the general condition of the newborn infant permits: the herniated viscera are replaced in the abdomen, and the hernial opening is closed.

In 50% of cases the diaphragmatic hernia is isolated. The other 50% are associated with other malformations—the result of teratogen exposure, a chromosome abnormality or a monogenic multiple congenital anomaly syndrome; many of these fetuses die *in utero*.

Pregnancy ultrasound shows a break in diaphragmatic continuity, with unusual solid or cystic structures (liver, stomach, intestines etc.) within the thorax, a shift of the mediastinum, and polyhydramnios. The differential diagnosis includes situs inversus, cystic adenomatoid malformation, lobar emphysema and mediastinal cyst. Amniotography may be helpful. Following pregnancy diagnosis arrangements should be made to deliver the baby with good neonatal paediatric and surgical facilities immediately available.

Omphalocele and Gastroschisis

Omphalocele and gastroschisis are frequent malformations diagnosable prenatally, and correctable in the neonatal period. These malformations both involve a variable-sized defect of the abdominal wall with polyhydramnios; in other respects they largely differ from each other.

Omphalocele is always located in the midline and involves the umbilical cord. The herniated viscera are covered by a thin transparent membrane composed of peritoneum and amniotic epithelium of the umbilical cord, and are not in immediate contact with the amniotic fluid; they remain morphologically and functionally intact. Fifty per cent of cases are isolated, and the remainder are associated with other malformations. An *umbilical hernia* differs from an omphalocele in that the protruding mass (omentum, or

loop of bowel) is covered by subcutaneous tissue and skin.

In *gastroschisis*, the herniated viscera are not covered by membrane and float freely in the amniotic fluid. The intestines may be damaged and their surface covered by a gelatinous deposit. Gastroschisis has a paramedian location (usually on the right). Since it does not involve the umbilical cord, *paromphalocele* is its alternative name. (The term *gastroschisis*, which means "split, or open stomach", is a misnomer, because it is the anterior abdominal wall that is split, not the stomach.) The defect is usually more common in males than in females. Most cases represent isolated defects.

Omphalocele and gastroschisis should be unequivocally differentiated from each other by ultrasound. The extent of the defect should be assessed and other malformations should be looked for. A proper prognosis cannot be given otherwise.

Large omphaloceles are usually associated with other abnormalities (Wiedemann-Beckwith syndrome), and the prognosis is poor. Isolated omphaloceles are likely to have a more favourable outcome. Intervention is not necessary before term. When bladder exstrophy, anal atresia and vertebral abnormalities are associated with omphalocele the condition is termed *cloacal exstrophy*: only mild cases can be corrected surgically.

In gastroschisis, neonatal surgery may be too late to prevent serious damage to the bowel. But if bowel function has been preserved to term then the prognosis may be good. Generally, it is reasonable to consider preterm delivery and operating for gastroschisis soon after making a prenatal diagnosis, the size and general condition of the fetus permitting.

Many fetuses with omphalocele or gastroschisis die *in utero*. Serial ultrasound has shown that, from the time of the first diagnosis, an omphalocele gradually enlarges under the influence of increasing abdomi-

nal pressure. When visceral extroversion is demonstrated before the 20th week of gestation, the prognosis is almost uniformly poor. There is no doubt that prenatal diagnosis of omphalocele and gastroschisis is desirable. Before 20 weeks, if the parents request, pregnancy termination is justifiable. Later in pregnancy one has to consider the surgical possibilities and the optimum timing of delivery.

Ultrasound plays the major role in prenatal diagnosis, identifying both the degree of herniation and the extent of the abdominal wall defect.

Oesophageal Atresia

Oesophageal atresia is associated with a tracheo-oesophageal fistula (usually communicating with the distal oesophagus) in 90% of cases. Fifty per cent of cases are associated with multiple malformations elsewhere.

Tracheo-oesophageal fistula results from incomplete division of the foregut into the respiratory and digestive portions during the fourth and fifth weeks. Incomplete fusion of the tracheo-oesophageal folds results in a defective tracheo-oesophageal septum, leaving a communication between the trachea and the oesophagus. The most common variety of the abnormality is for the upper portion of the oesophagus to end blindly (oesophageal atresia) and for the lower portion to join the trachea near its bifurcation.

Oesophageal atresia can be diagnosed on the prenatal ultrasound. The fetus cannot swallow amniotic fluid, the stomach remains empty, and polyhydramnios develops. The stomach normally contains a little fluid, which can be seen on the scan, but with oesophageal atresia it cannot be identified, either on the longitudinal or transverse views of the upper abdomen. This is so even in the presence of a fistula.

Isolated cases can be operated on successfully: the rate of survival is

improving steadily, and following prenatal diagnosis one should aim to deliver the baby at the optimum time and with good surgical facilities immediately available.

Duodenal Atresia

During the solid stage of duodenal development, the lumen is completely filled with epithelial cells. If reformation of the lumen fails to occur by a process of vacuolization, a short segment of the *duodenum* is *occluded*. Obstruction of the duodenum can also be caused by an *annular pancreas*, resulting from the two parts of the developing pancreas surrounding the duodenum. Most atresias involve the descending (second) and horizontal (third) parts of the duodenum, and are located distal to the opening of the bile duct. Polyhydramnios usually occurs because the duodenal atresia prevents normal absorption of the amniotic fluid from the intestine. About half of all duodenal atresias is associated with malformations elsewhere. The most significant association is with Down syndrome.

Prenatal diagnosis is possible, based on abnormal ultrasound ("double bubble" and polyhydramnios), and elevated bile acid concentration in the amniotic fluid.

The prognosis for survival, following operation in isolated cases, is good.

Cystic Fibrosis

Cystic fibrosis (CF) is the most common autosomal recessive disease in Europe. Although present treatment is not directed towards this defect, substantial improvements in life expectancy have been achieved; in some countries half or more of affected infants live into adulthood.

Despite improving prospects this is still a crippling disorder, and many parents of affected children seek prenatal diagnosis for subsequent pregnancies. Effective prenatal di-

agnosis has been available since the early 1980s, but by DNA only from 1986/7.

All mucus-producing tissues are affected, in particular the respiratory and gastrointestinal tracts and the epididymis. The glandular ducts are obstructed by tenacious mucus, and the gland parenchyma develops cystic degeneration. Dense mucus may form meconium plugs already *in utero*, leading to intestinal obstruction (*meconium ileus*). The intestinal wall may perforate, and meconium entering the abdominal cavity produces a foreign-body-type fibrinous reaction and concomitant peritoneal calcification (*meconium peritonitis*, *meconium pseudocyst*).

In cases without meconium obstruction, no signs, except perhaps unusually thick or viscid meconium, call attention, in the newborn infant, to the presence of the disease.

Pathological confirmation of the diagnosis is easier in older children than in newborn infants or fetuses. Excess connective tissue, and cystic degeneration, are seen histologically in both pancreas and lungs in at least 80-85% of the cases.

Estimating the efficacy/accuracy of prenatal diagnostic methods depends not only on the scrupulously thorough follow-up and testing of all live-born infants submitted to prenatal diagnosis, but also on the careful postmortem examination of all terminated fetuses, with evidence that histological changes which are not found in similar-aged normal fetuses, are present in the affected fetuses, already by 18 weeks' gestation. We believe such changes are demonstrable, though they are not so striking as in affected CF infants dying after live birth.

Following unsuccessful or unreliable attempts at prenatal diagnosis, in the 1970s, attention turned to the microvillar enzymes which are secreted directly into the gut lumen. These enzymes, due to fetal intestinal movements, normally reach the amniotic fluid from 11-12 weeks onwards; a low activity in the am-

niotic fluid may be of value in the diagnosis of intestinal obstruction. It was shown that at 16-20 weeks of gestation the amniotic fluid activity of some isoenzymes of alkaline phosphatase, gamma-glutamyltranspeptidase and certain disaccharida-

ses (trehalase), was low in most pregnancies involving a CF fetus.

The CF gene has now been mapped to chromosome 7 and cloned and this permits prenatal diagnosis in almost all couples. The analysis is performed from CVS sample ob-

tained at 8-12 weeks' gestation. (DNA can now sometimes be obtained, if critical for the analysis, from Guthrie blood-spots of dead babies—amplification with polymerase chain reaction has been successful.)

Figures 7-1a and b. Newborn infant with hygroma colli.



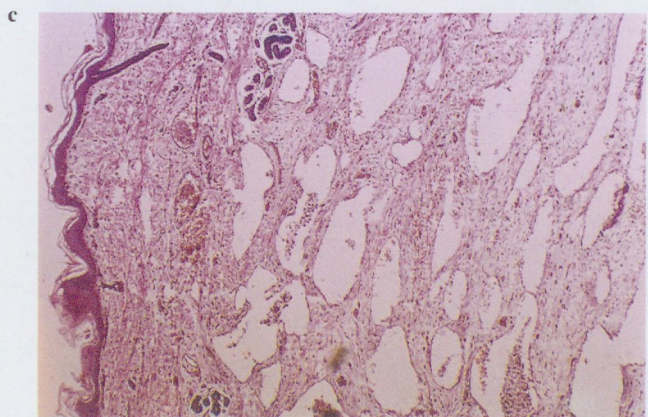
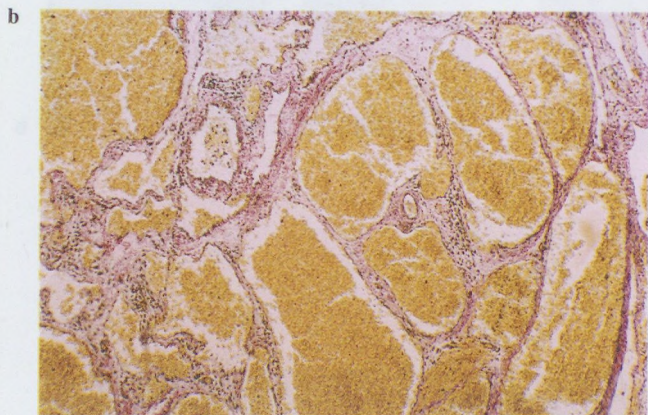
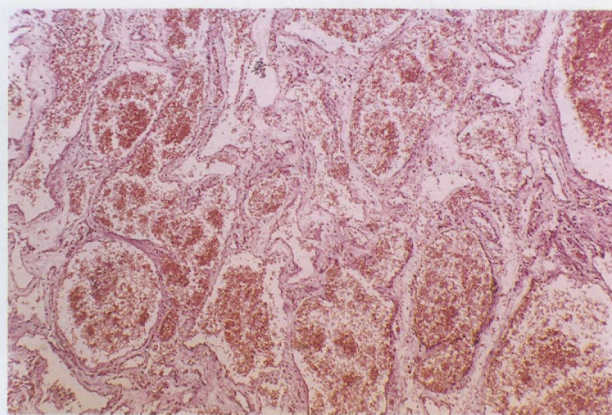
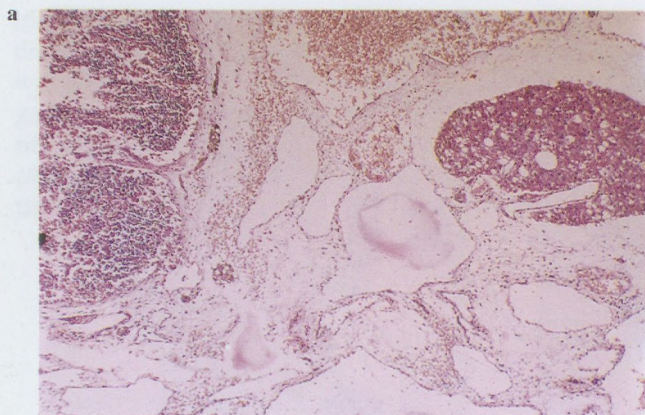
a



b



Figure 7-2. Hygroma colli: autopsy findings.



Figures 7-3a, b, c and d. Hygroma colli: dilated, thin-walled vessels filled with blood, and some empty vessels also seen (HE, x100).



Figure 7-4. Longitudinal section of the thorax showing normal relations of the organs.

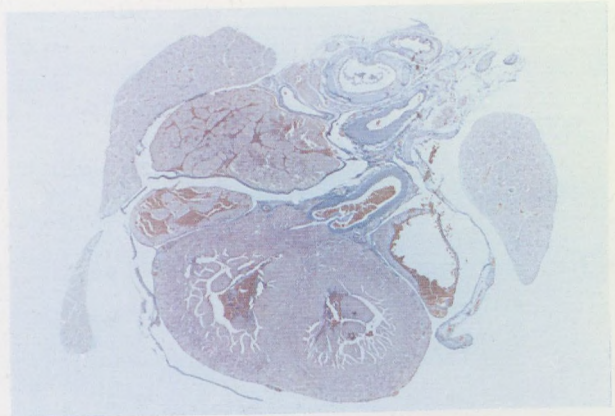
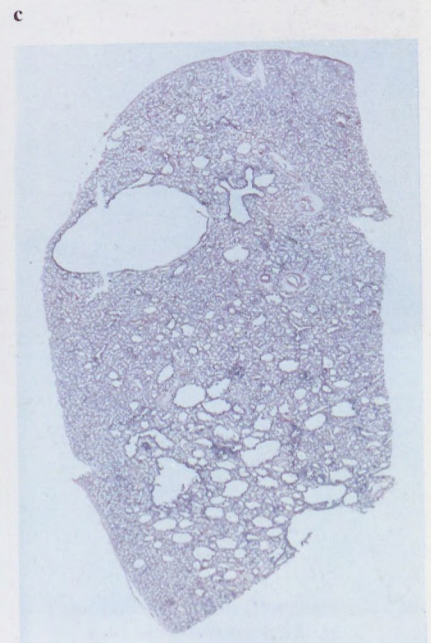
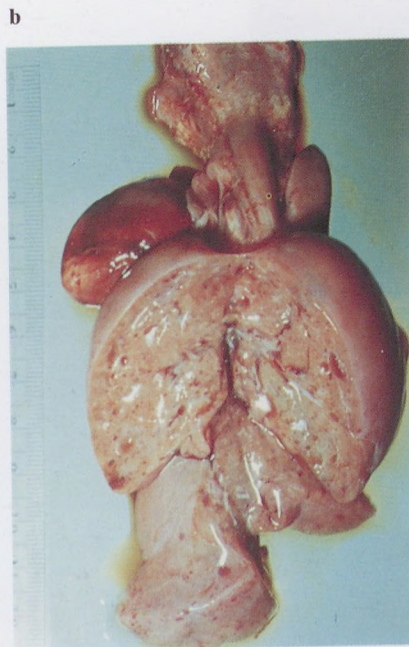
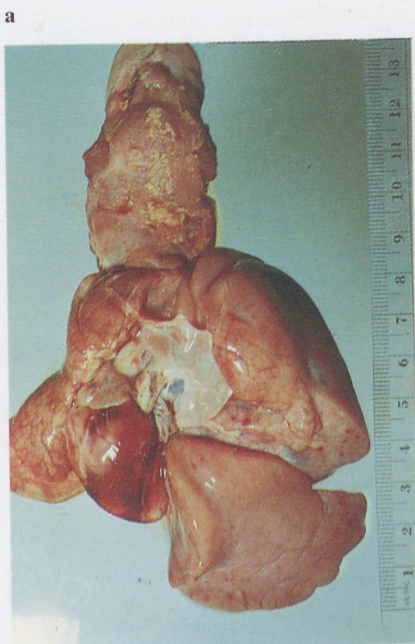


Figure 7-5. Transverse section of the thorax showing hypoplastic lungs.

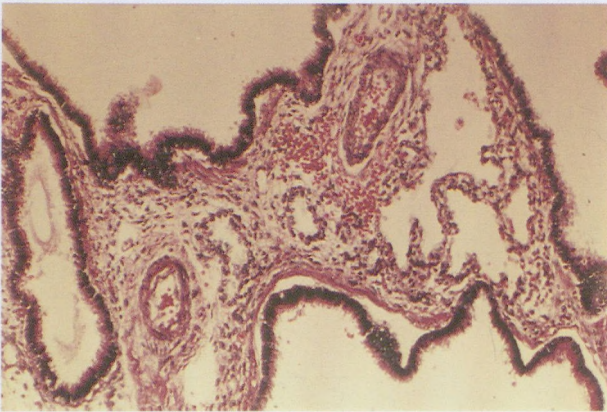


Figures 7-6a, b and c. Prenatally diagnosed congenital cystic adenomatoid malformation of the lungs (**a, b**); many cystic spaces of varying size are seen scattered in the parenchyma (**c**).

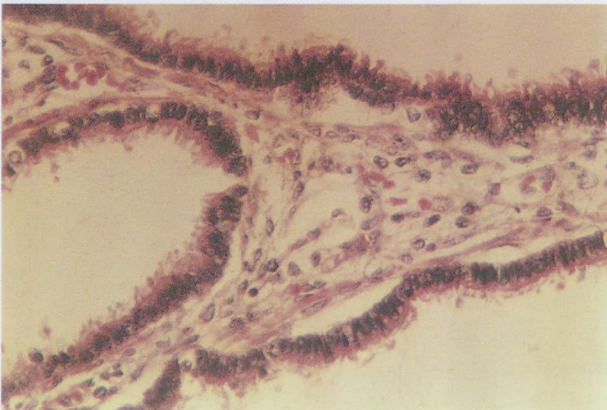
a



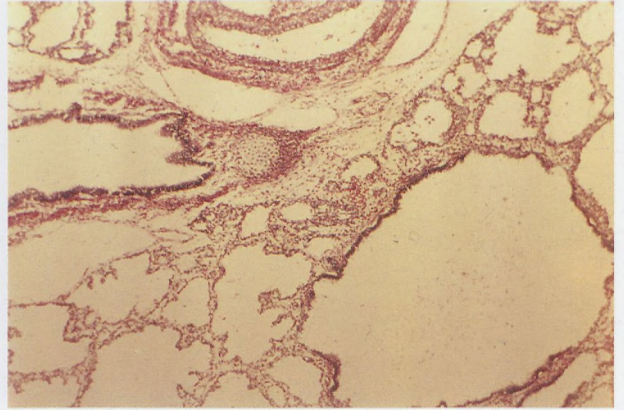
b



c



d



Figures 7-7a, b, c and d. Congenital cystic adenomatoid malformation (CCAM): (a) multiple lung cysts (HE, x200); (b) lung cysts lined by pseudostratified columnar epithelium (HE, x200); (c) cysts lined by ciliated columnar epithelium (HE, x400); (d) cystic changes, with residual islands of cartilage (HE, x100).

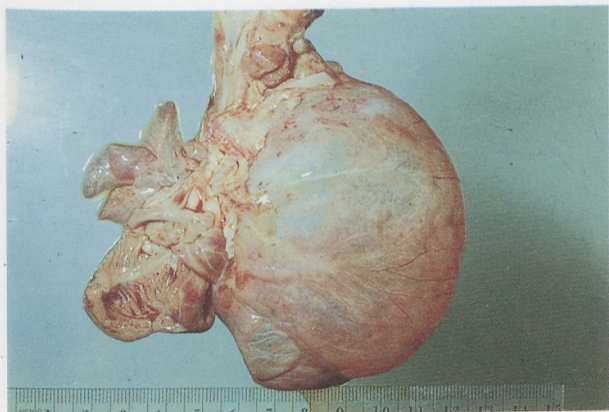
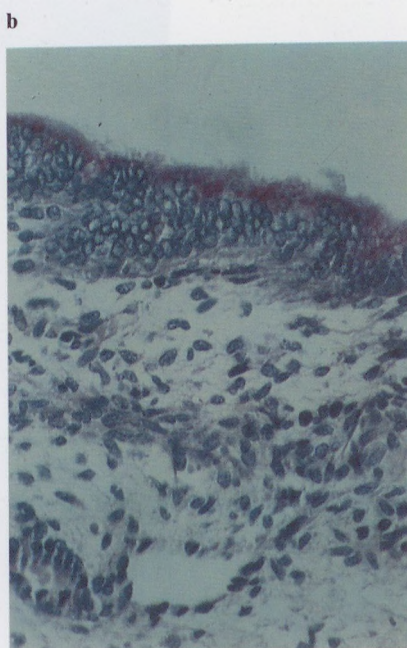
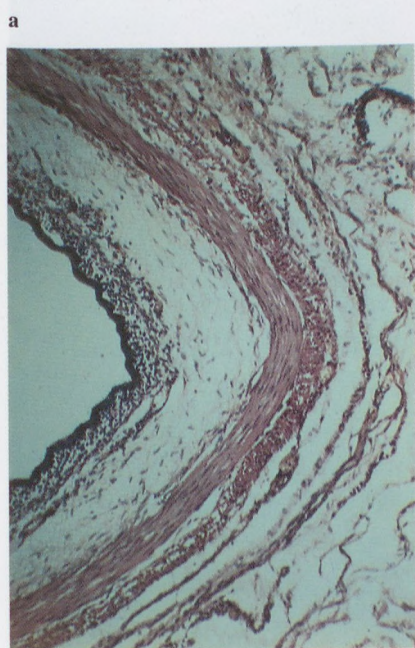


Figure 7-8a. Cyst of the lung, associated with a congenital cystic adenomatoid malformation on the other side.



Figure 7-8b. Cystic adenomatoid malformation. A transverse ultrasound scan of the fetal chest shows replacement of normal pulmonary tissue by cysts of varying sizes (CY = cysts; HA = heart).



Figures 7-9a and b. Branchiogenic cyst: the inner surface is covered by a PAS-positive pseudostratified columnar epithelium (a: HE, x100; b: PAS, x400).



Figure 7-10. Ectopia cordis. The heart and thymus lie outside the thoracic cavity with the diaphragm at the base of the oval thoracic wall defect.

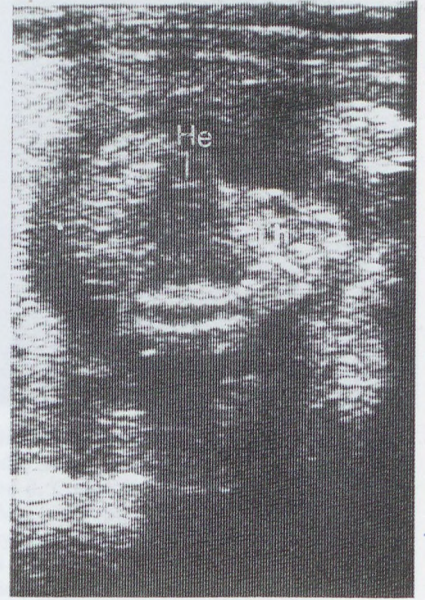


Figure 7-11. Ectopia cordis. Longitudinal ultrasound scan through the chest shows evidence of cardiac structures anterior to the chest (He = heart; Th = thorax).



Figure 7-12. Ectopia cordis with oval-shaped midline thoracic wall defect.

Figure 7-13. Trisomy 21: ventricular septal defect.

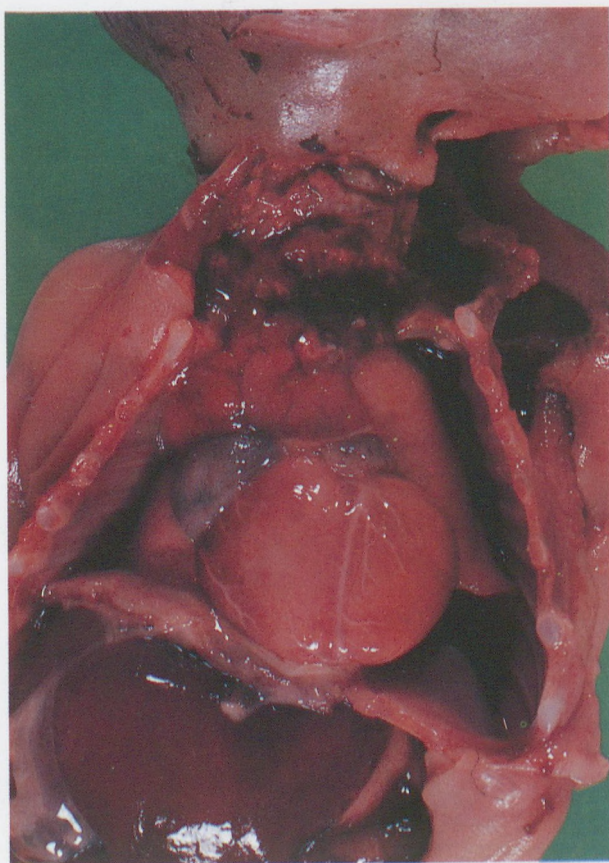
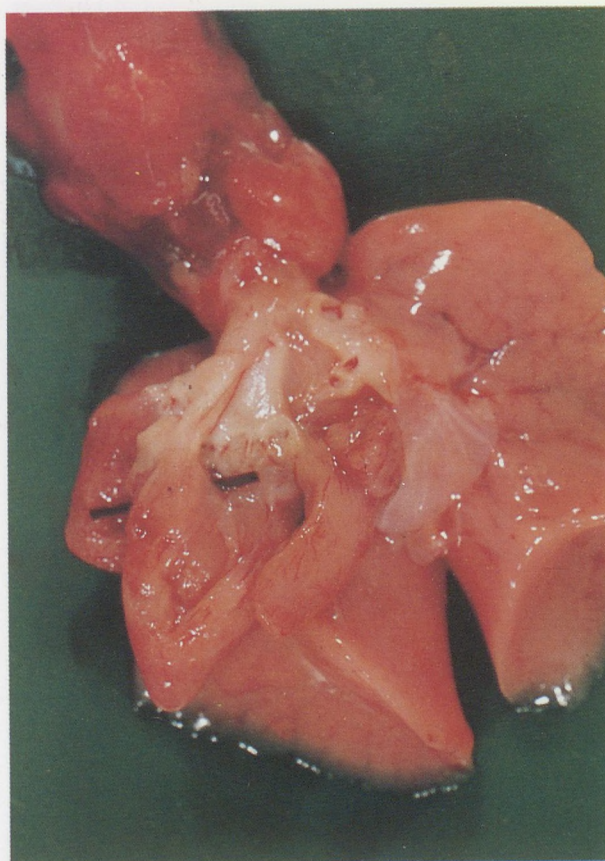


Figure 7-14. Large rounded heart in a fetus with Potter sequence. Dilated ventricles and ventricular septal defect were found.

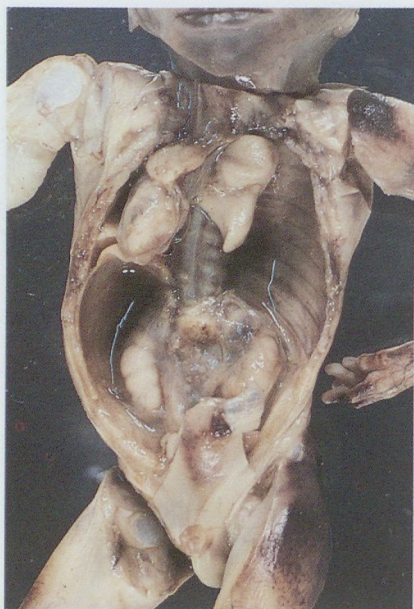


Figure 7-15. Severe diaphragmatic hernia in an 18-week-old fetus.

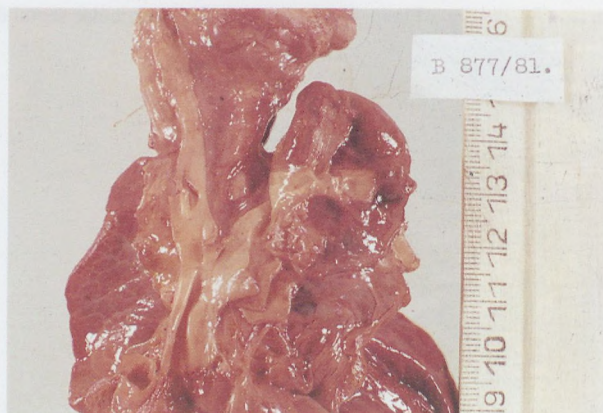
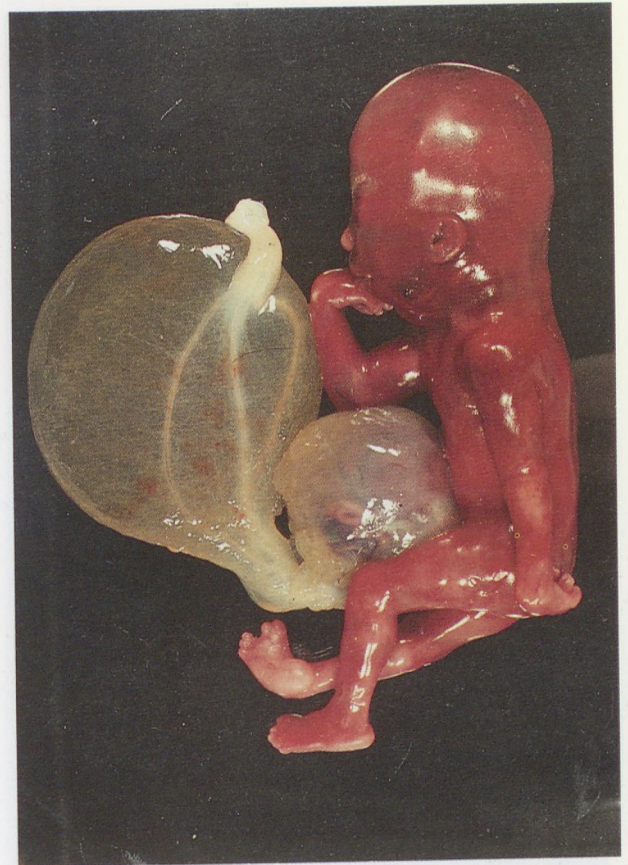


Figure 7-16. Tracheo-oesophageal fistula.



Figure 7-17. Duodenal atresia: extreme dilatation of the stomach in a fetus with trisomy 21.

Figure 7-18. Omphalocele and an enormous cystic abnormality of the umbilical cord. The two umbilical arteries and the umbilical vein are easily recognizable in the wall of the cyst.



Figures 7-19a, b and c. Large omphalocele in a 17-week-old fetus (a); after removing the membrane covering the herniated viscera (b); ultrasound view of the herniated viscera and intestinal loops (c).

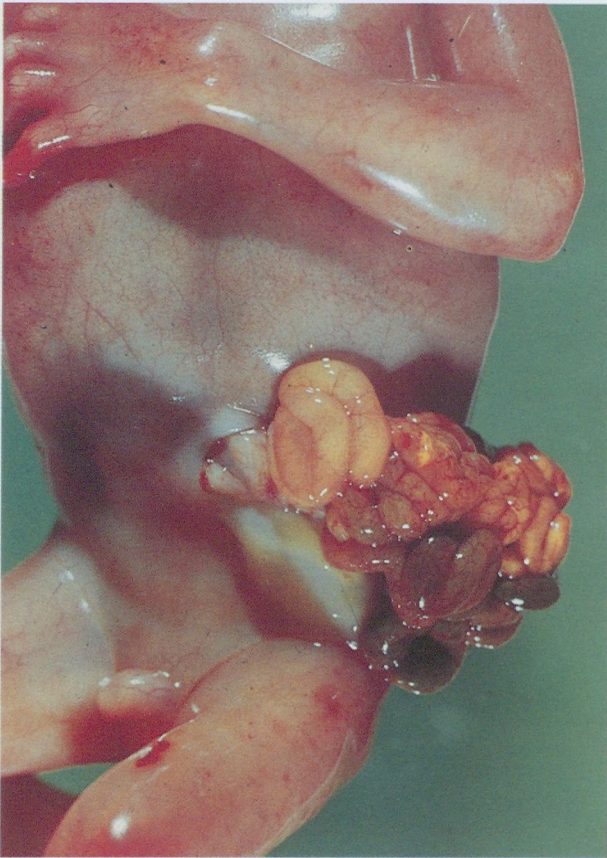


Figure 7-20. Ruptured omphalocele: the eventrated intestines show early signs of strangulation.

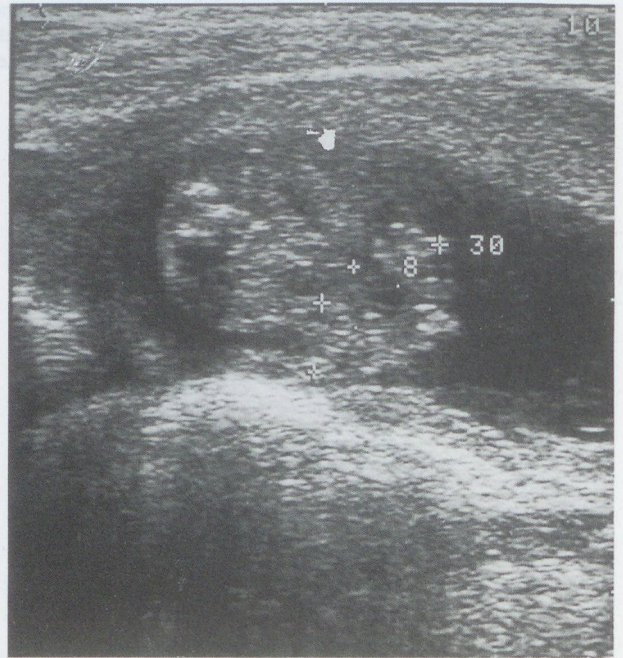


Figure 7-21. Transverse sonogram showing intestinal loops floating freely in the amniotic fluid in a case of gastroschisis.

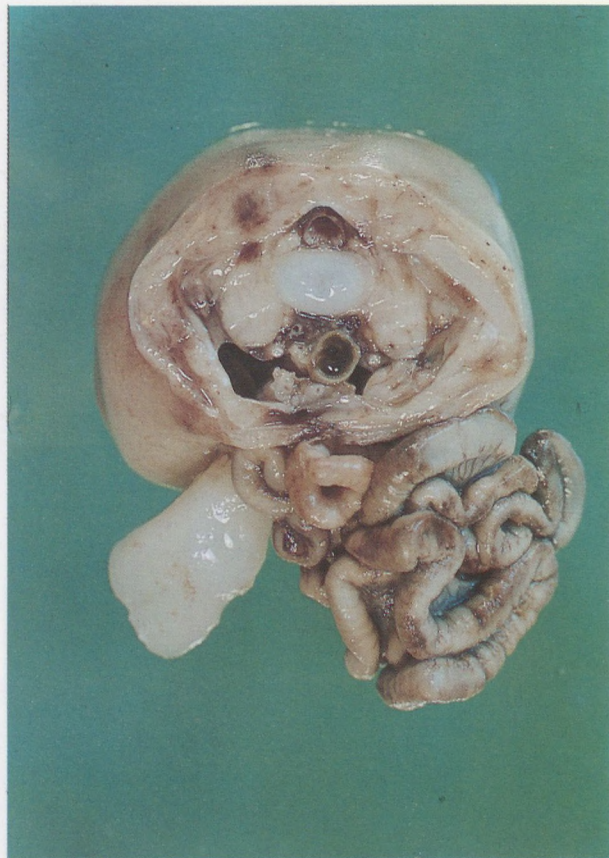


Figure 7-22. Ruptured omphalocele in an 18-week-old fetus.

a



b



Figures 7-23a and b. Second-trimester fetus with ruptured omphalocele: transverse section above the level of the cord insertion next to which can be seen the narrow opening of the omphalocele (a); transverse section at the level of the cord insertion (b).



Figure 7-24a. Strangulation ileus resulting from a ruptured omphalocele in a newborn infant. *In utero* vomiting was diagnosed prenatally.

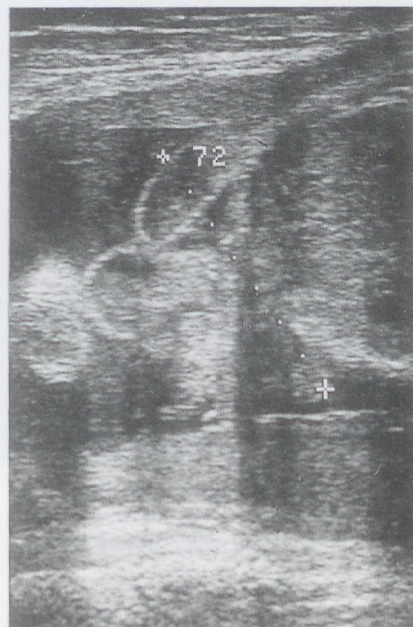


Figure 7-24b. Distended loops of bowel are seen outside the fetal abdomen (ultrasound view).

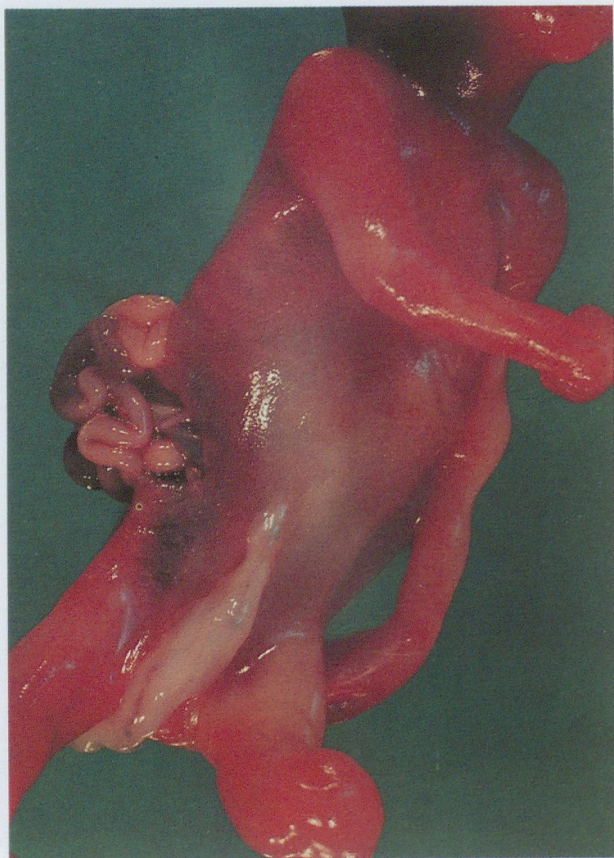


Figure 7-25. Paraumbilical abdominal wall defect with eventration of small intestines (gastroschisis).



Figure 7-26. Severe gastroschisis: the herniated viscera are not covered by membrane. The umbilical cord is not involved.

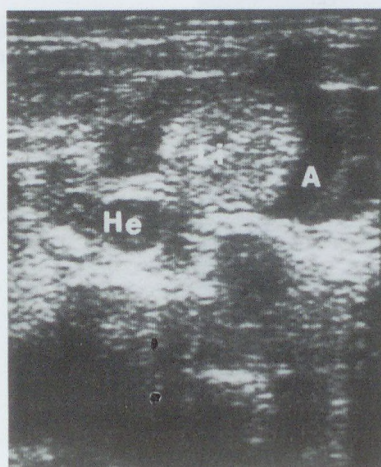


Figure 7-27. A large defect on ultrasound scan, involving the lower sternum and abdominal wall, permitting both liver (Li), heart (He) and bowel to herniate into the amniotic fluid (A).

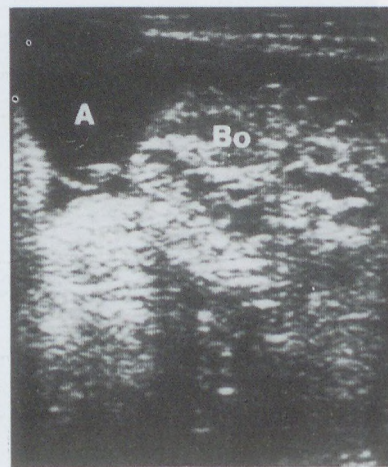


Figure 7-28. Herniated viscera and bowel (Bo) are visible in the amniotic fluid (A).

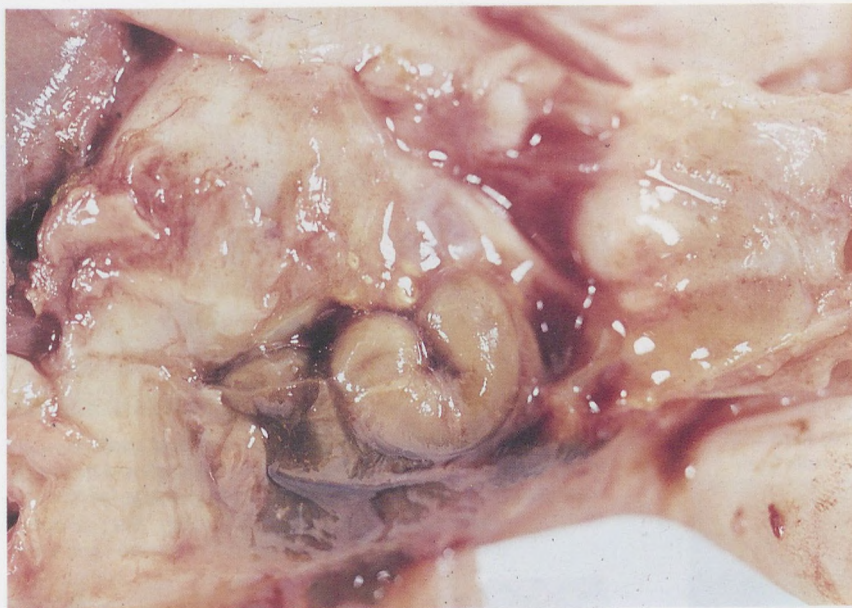


Figure 7-29. Meconium ileus with rupture of the cecum and meconium peritonitis, in a 32-week-old fetus suffering from cystic fibrosis.



Figure 7-30a. Segmental dilatation of the large bowel in a premature infant with cystic fibrosis.

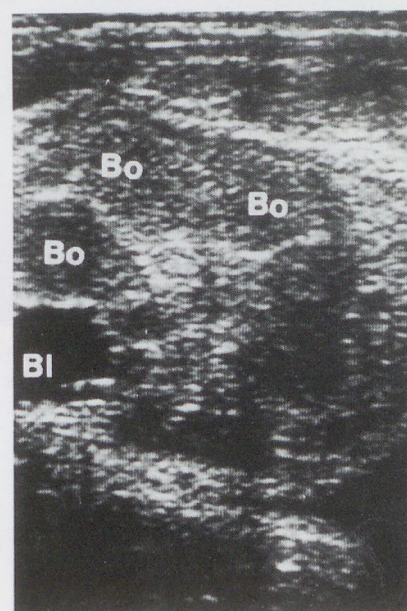


Figure 7-30b. Ultrasound scan of dilated bowel (Bo) with echogenic meconium plugs in a case of meconium ileus at 38 weeks (Bl = bladder).

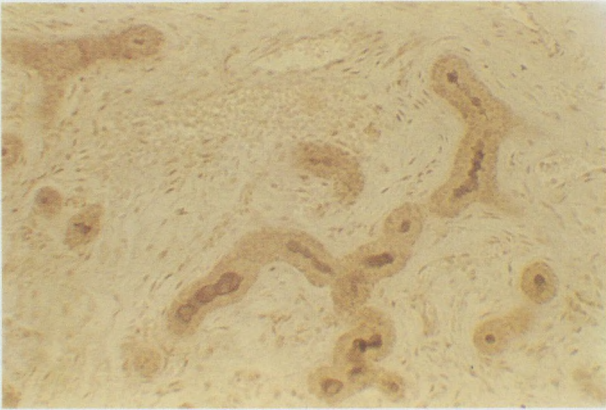


Figure 7-31a. Salivary gland from an 18-week-old fetus with cystic fibrosis: the strong iron-diamine reaction results from increased amounts of sulphomucins (x200).

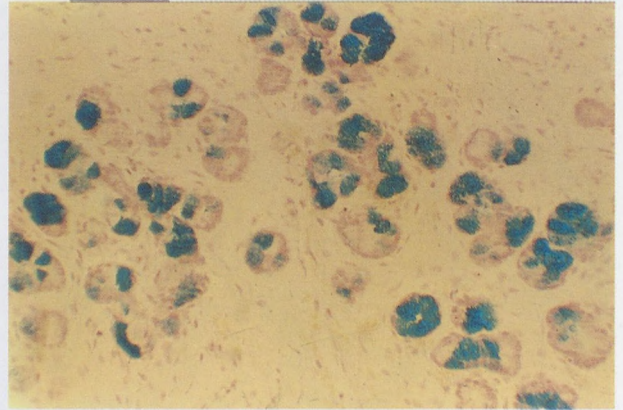


Figure 7-31b. Marked "stains-all" histochemical reaction for sialomucins in salivary gland from an 18-week-old normal fetus (x200). In cystic fibrosis this reaction is nearly failed.

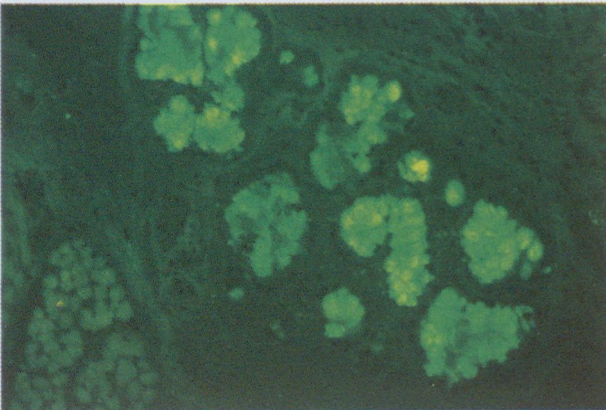


Figure 7-31c. Decreased DBA-lectin positivity in the salivary gland of a second-trimester fetus with cystic fibrosis (x200).

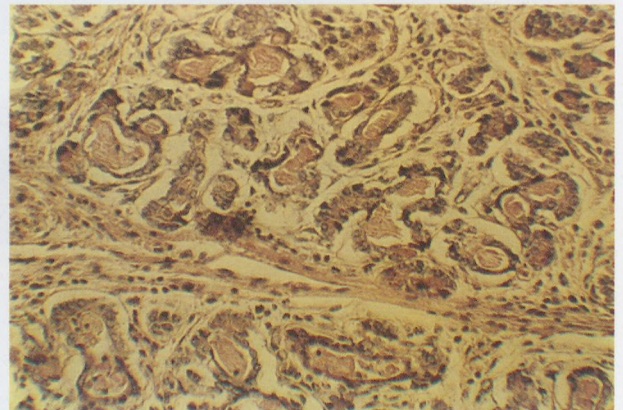
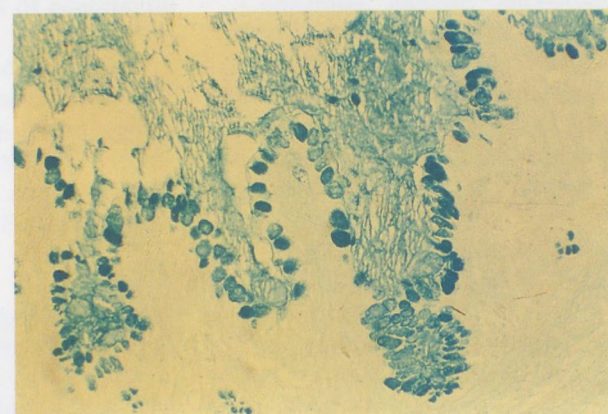
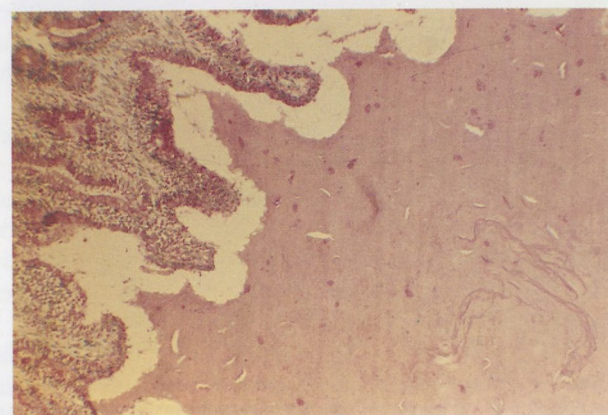
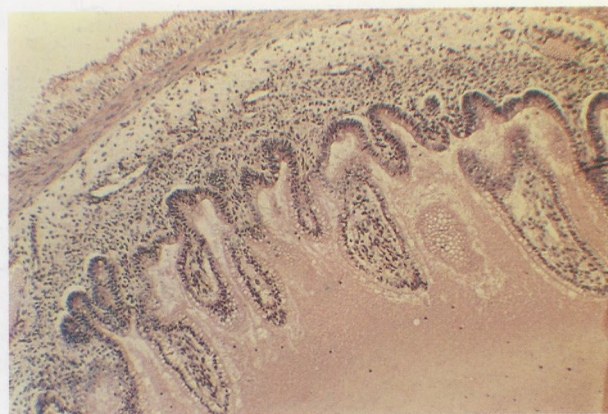
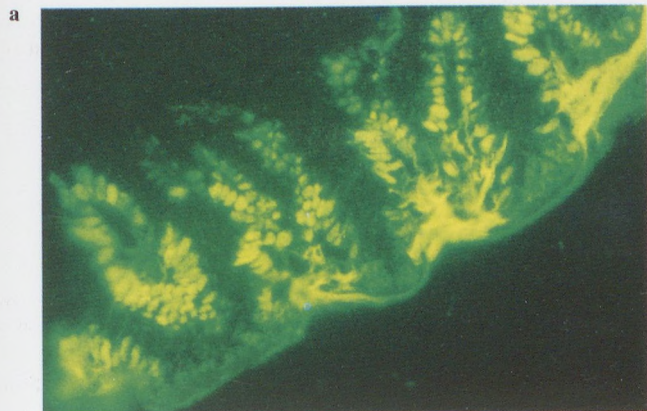


Figure 7-31d. Retention of acidophilic secretions within the exocrine pancreas: second-trimester fetus with cystic fibrosis (HE, x200).



Figures 7-32a, b, c and d. Second-trimester fetus with cystic fibrosis: (a) increased PNA-lectin positivity in gastric mucosa (x200); (b) small intestine: the lumen is filled with eosinophilic secretions (HE, x100); (c) mucin plug in the lumen of the large intestine (PAS-reaction, x100); (d) strong alcianophilic reaction in large intestine goblet cells (Alcian blue, x200).



Figures 7-33a and b. Wiedemann-Beckwith syndrome in a neonate: prominent tongue, plethoric face, extensive naevus flammeus involving glabella and upper eyelids, high sloping forehead, and deep earlobe creases (omphalocele was also present).



References

- Achiron R., Malinger G., Zaidel L., Zakut H. (1988)**
Prenatal sonographic diagnosis of endocardial fibroelastosis secondary to aortic stenosis. *Prenat. Diagn.* 8, 73-77.
- Adzick N. S., Harrison M. R., Glick P. L., Golbus M. S., Anderson R. L., Mahony B. S., Callen P. W., Hirsch J. H., Luthy D. A., Filly R. A. (1985)**
Fetal cystic adenomatoid malformation. Prenatal diagnosis and natural history. *J. Pediatr. Surg.* 20, 483-488.
- Adzick N. S., Vacanti J. P., Lillehei C. W., Orouke P. P., Crone R. K., Wilson J. M. (1989)**
Fetal diaphragmatic hernia. Ultrasound diagnosis and clinical outcome in 38 cases. *J. Pediatr. Surg.* 24, 654-658.
- Allan L. D. (1983)**
Early detection of congenital heart disease in prenatal life. *Clin. Obstet. Gynaecol.* 10, 507-514.
- Allan L. D., Tynan M., Campbell S., Anderson R. H. (1981)**
Normal fetal cardiac anatomy. A basis for the echocardiographic detection of abnormalities. *Prenat. Diagn.* 1, 131-139.
- Avni E. F., Van der Elst A., Van Gansbeke D., Shils J., Rodesch F. (1986)**
Antenatal diagnosis of pulmonary tumors. Report of 2 cases. *Pediatr. Radiol.* 16, 190-192.
- Axel L. (1983)**
Real-time sonography of fetal cardiac anatomy. *A. J. R.* 141, 283-288.
- Bair J. H., Russ P. D., Pretorius D. H., Manchester D., Manco-Johnson M. L. (1986)**
Fetal omphalocele and gastroschisis. A review of 24 cases. *A. J. R.* 147, 1047-1051.
- Baxi L. V., Yeh M.-N., Blanc W. A., Schullinger J. N. (1983)**
Antepartum diagnosis and management of in utero intestinal volvulus with perforation. *N. Engl. J. Med.* 308, 1519-1521.
- Benacerraf B. B., Adzick N. S. (1987)**
Fetal diaphragmatic hernia. Ultrasound diagnosis and clinical outcome in 19 cases. *Am. J. Obstet. Gynecol.* 156, 573-576.
- Benacerraf B. B., Frigoletto F. D. (1987)**
Prenatal ultrasonographic diagnosis of isolated congenital cystic hygroma, unassociated with lymphedema or other morphologic abnormality. *J. Ultrasound Med.* 6, 63-66.
- Benacerraf B. B., Saltzman D. H., Sanders S. P. (1989)**
Sonographic sign suggesting the prenatal diagnosis of coarctation of the aorta. *J. Ultrasound Med.* 8, 65-69.
- Bernaschek G., Schaller A. (1985)**
The prenatal differential diagnosis of congenital hernias of the abdominal wall and umbilical cord. *Z. Geburtshilfe Perinatol.* 189, 259-264.
- Bisker J. (1983)**
Sonographic antepartum demonstration of cystic hygroma colles. *Med. Ultrasound* 7, 178-179.
- Björnstaahl H., Kullendorff C. M., Westgren M. (1983)**
Gastroschisis diagnosed in utero by ultrasound. Case report. *Acta Obstet. Gynecol. Scand.* 62, 283-284.
- Bovicelli L., Rizzo N., Orsini L. F., Pilu G. (1983)**
Prenatal diagnosis and management of fetal gastrointestinal abnormalities. *Semin. Perinatol.* 7, 109-117.
- Böhm N. (1981)**
Documentation of vascular malformations by postmortal angiography of the fetus and the newborn. *Pathol. Res. Pract.* 171, 423-426.
- Brons J. T. J., VanGeijn H. P., Wladimiroff J. W., Van der Harten J. J., Kwee M. L., Sobotka-Plojhar M., Arts N. F. T. (1988)**
Prenatal ultrasound diagnosis of the Holt-Oram syndrome. *Prenat. Diagn.* 8, 175-181.
- Bronstein M., Siegler E., Yoffe N., Zimmer E. Z. (1990)**
Prenatal diagnosis of ventricular septal defect and overriding aorta at 14 weeks gestation, using transvaginal sonography. *Prenat. Diagn.* 10, 697-702.
- Brown B. S. J. (1985)**
The prenatal ultrasonographic features of omphalocele. A study of 10 patients. *J. Can. Assoc. Radiol.* 36, 312-316.
- Brown D. L., Emerson D. S., Cartier M. S., Felker R. E., Disessa T. G., Smith W. C. (1989)**
Congenital cardiac anomalies. Prenatal sonographic diagnosis. *A. J. R.* 153, 109-114.
- Brown D. L., Emerson D. S., Shulman L. P., Carson S. A. (1989)**
Sonographic diagnosis of omphalocele during 10th week of gestation. *A. J. R.* 153, 825-826.
- Brown J., Gunn T. R., Mora J. D., Mok P. M. (1986)**
The prenatal ultrasonographic diagnosis of cardiomegaly due to tricuspid incompetence. *Pediatr. Radiol.* 16, 440-440.
- Brühwiler H., Luscher K. P. (1988)**
Jejunal atresia. A contribution to prenatal ultrasound diagnosis. *Geburtshilfe Frauenheilkd.* 48, 448-449.

- Calisti A., Manzoni C., Pintus C., Perrelli L. (1986)**
Prenatal diagnosis and management of some fetal intrathoracic abnormalities.
Eur. J. Obstet. Gynecol. 22, 61-68.
- Calisti A., Manzoni C., Perrelli L. (1987)**
The fetus with an abdominal wall defect: Management and outcome.
J. Perinat. Med. 15, 105-111.
- Caplan M. S., MacGregor S. N. (1989)**
Perinatal management of congenital diaphragmatic hernia and anterior abdominal wall defects.
Clin. Perinatol. 16, 917-938.
- Carlan S. J., Knuppel R. A., Perez J., Flasher J. (1990)**
Antenatal fetal diagnosis and maternal transport in gastro-schisis. A maternal-infant case report.
Clin. Pediatr. 29, 378-381.
- Caspi B., Elchalal U., Lancet M., Chemke J. (1988)**
Prenatal diagnosis of cystic fibrosis: Ultrasonographic appearance of meconium ileus in the fetus.
Prenat. Diagn. 8, 379-382.
- Cave A. P. D., Adam A. E. (1984)**
Cystic adenomatoid malformation of the lung (Stocker type III) found on antenatal ultrasound examination.
Br. J. Radiol. 57, 176-178.
- Chan F. Y., Woo S. K., Ghosh A., Tang M., Lam C. (1990)**
Prenatal diagnosis of congenital fetal arrhythmias by simultaneous pulsed Doppler velocimetry of the fetal abdominal aorta and inferior vena cava.
Obstet. Gynecol. 76, 200-205.
- Chao A., Monoson R. F. (1990)**
Neonatal death despite fetal therapy for cystic adenomatoid malformation.
J. Reprod. Med. 35, 655-657.
- Chervenak F. A., Isaacson G., Tortora M. (1985)**
A sonographic study of fetal cystic hygromas.
J. Clin. Ultrasound 13, 311-315.
- Chiba Y., Kanzaki T., Kobayashi H., Murakami M. (1990)**
Evaluation of fetal structural heart disease using color flow mapping.
Ultrasound Med. Biol. 16, 221-229.
- Chinn D. H., Filly R. A., Callen P. W., Nakayama D. K., Harrison M. R. (1983)**
Congenital diaphragmatic hernia diagnosed prenatally by ultrasound.
Radiology 148, 119-123.
- Chitayat D., Kalousek D. K., Bamforth S. J., (1989)**
Lymphatic abnormalities in fetuses with posterior cervical cystic hygroma.
Am. J. Med. Genet. 33, 352-356.
- Chitayat D., McGillivray B. C., Diamant S., Wittmann B. K., Sandor G. B. S. (1988)**
Role of prenatal detection of cardiac tumors in the diagnosis of tuberous sclerosis. Report of two cases.
Prenat. Diagn. 8, 577-584.
- Chitayat D., Rothchil. A., Ling E., Friedman J. M., Couch R. M., Yong S. L., Baldwin V. J., Hall J. G. (1990)**
Apparent postnatal onset of some manifestations of the Wiedemann-Beckwith syndrome.
Am. J. Med. Genet. 36., 434-439.
- Clair M. R., Rosenber E. R., Ram P. C., Bowie J. D. (1983)**
Prenatal sonographic diagnosis of meconium peritonitis.
Prenat. Diagn. 3, 65-68.
- Clark E. B. (1986)**
Cardiac embryology. Its relevance to congenital heart disease.
Am. J. Dis. Child. 140, 41-44.
- Cloutier M. G., Fried A. M., Selke A. C. (1983)**
Antenatal observation of midgut volvulus by ultrasound.
J. Clin. Ultrasound 11, 286-288.
- Cobellis G., Iannoto P., Stabile M., Lonardo F., Della-Bruna M., Caliendo E., Ventruto V. (1988)**
Prenatal ultrasound diagnosis of macroglossia in the Wiedemann-Beckwith syndrome.
Prenat. Diagn. 8, 79-81.
- Comstock C. H. (1986)**
The antenatal diagnosis of diaphragmatic anomalies.
J. Ultrasound Med. 5, 391-396.
- Copel J. A., Pilu G., Kleinman C. S. (1986)**
Congenital heart disease and extracardiac anomalies. Associations and indications for fetal echocardiography.
Am. J. Obstet. Gynecol. 154, 1121-1132.
- Copel J. A., Pilu G., Green J., Hobbins J. C., Kleinman C. S. (1987)**
Fetal echocardiographic screening for congenital heart disease. The importance of the 4-chamber view.
Am. J. Obstet. Gynecol. 157, 648-655.
- Crawford D. C., Chita S. K., Allan L. D. (1988)**
Prenatal detection of congenital heart disease: Factors affecting obstetric management and survival.
Am. J. Obstet. Gynecol. 159, 352-356.
- Crawford D. C., Drake D. P., Kwaitkowski D., Chapman M. G., Allan L. D. (1986)**
Prenatal diagnosis of reversible cardiac hypoplasia associated with congenital diaphragmatic hernia. Implications for postnatal management.
J. Clin. Ultrasound 14, 718-721.
- Cullen M. T., Gabrielli S., Green J. J., Rizzo N., Mahoney M. J., Salafia C., Bovicelli L., Hobbins J. C. (1990)**
Diagnosis and significance of cystic hygroma in the 1st trimester.
Prenat. Diagn. 10, 643-651.

- Curtis J. A., Watson L. (1988)**
Sonographic diagnosis of omphalocele in the 1st trimester of fetal gestation.
J. Ultrasound Med. 7, 97-100.
- Damjanovich L., Szeifert G. T., Szabó M., Papp Z. (1990)**
Pathological confirmation of foetal cystic fibrosis following prenatal diagnosis.
Acta Morph. Hung. 38, 141-148.
- Davidson J. M., Johnson T. R. B., Rigdon D. T., Thompson B. H. (1984)**
Gastroschisis and omphalocele: Prenatal diagnosis and perinatal management.
Prenat. Diagn. 4, 355-363.
- Davis G. K., Farquhar C. M., Allan L. D., Crawford D. C., Chapman M. G. (1990)**
Structural cardiac abnormalities in the fetus. Reliability of prenatal diagnosis and outcome.
Br. J. Obstet. Gynaecol. 97, 27-31.
- Deareaujo L. M., Schmidt K. G., Silverman N. H., Finkbeiner W. E. (1987)**
Prenatal detection of truncus arteriosus by ultrasound.
Pediatr. Cardiol. 8, 261-263.
- Deeg K. H., Voigt H. J., Hofbeck M., Singer H., Kraus J. (1990)**
Prenatal ultrasound diagnosis of multiple cardiac rhabdomyomas.
Pediatr. Radiol. 29, 291-292.
- DeVore G. R. (1985)**
The prenatal diagnosis of congenital heart disease. A practical approach for the fetal sonographer.
J. Clin. Ultrasound 13, 229-245.
- DeVore G. R., Steiger R. M., Larson E. J. (1987)**
Fetal echocardiography. The prenatal diagnosis of a ventricular septal defect in a 14-week fetus with pulmonary artery hypoplasia.
Obstet. Gynecol. 69, 494-497.
- Dibbins A. W., Curci M. R., McCrann D. J. (1985)**
Prenatal diagnosis of congenital anomalies requiring surgical correction. Implications for the future.
Am. J. Surg. 149, 528-533.
- Diwan R. V., Brennan J. N., Philipson E. H., Jain S., Bellon E. M. (1983)**
Ultrasonic prenatal diagnosis of type III congenital cystic adenomatoid malformation of lung.
J. Clin. Ultrasound 11, 218-221.
- Donnenfeld A. E., Mennuti M. T., Templeton J. M., Gabbe S. G. (1989)**
Prenatal sonographic diagnosis of a vesicoallantoic abdominal wall defect.
J. Ultrasound Med. 8, 43-45.
- Engelhardt W., Lehnen H., Grabitz R., Von Bernuth G. (1990)**
Diagnosis and management of fetal bradyarrhythmias.
Z. Geburtshilfe Perinatol. 194, 153-157.
- Exalto N., Van Zalen R. M., Van Brandenburg W. J. A. (1985)**
Early prenatal diagnosis of cystic hygroma by real-time ultrasound.
J. Clin. Ultrasound 13, 655-658.
- Ferrazzi E., Fesslova V., Bellotti M., Agostoni G., Pardi G., Makowski E. L. (1989)**
Prenatal diagnosis and management of congenital heart disease.
J. Reprod. Med. 34, 207-214.
- Filkins K., Russo J., Flowers W. K. (1985)**
3rd trimester ultrasound diagnosis of intestinal atresia following clinical evidence of polyhydramnios.
Prenat. Diagn. 5, 215-220.
- Fine C., Adzick N. S., Doubilet P. M. (1988)**
Decreasing size of a congenital cystic adenomatoid malformation in utero.
J. Ultrasound Med. 7, 405-408.
- Fitzgerald E. J., Toi A. (1986)**
Antenatal ultrasound diagnosis of a cystic adenomatoid malformation of the lung.
J. Can. Assoc. Radiol. 37, 48-49.
- Frigoletto F. D., Birnholz J. C., Driscoll S. G., Finberg H. J. (1980)**
Ultrasound diagnosis of cystic hygroma.
Am. J. Obstet. Gynecol. 136, 962-964.
- Fyfe D. A., Kline C. H. (1990)**
Fetal echocardiographic diagnosis of congenital heart disease.
Pediatr. Clin. North Am. 37, 45-67.
- Garden A. S., Benzie R. J., Miskin M., Gardner H. A. (1986)**
Fetal cystic hygroma colli: Antenatal diagnosis, significance and management.
Am. J. Obstet. Gynaecol. 154, 221-225.
- Gava G., Buoso G., Beltrame G. L., Memo L., Visentin S., Cavarzerani A. (1991)**
Cardiac rhabdomyoma as a marker for the prenatal detection of tuberous sclerosis. Case report.
Br. J. Obstet. Gynaecol. 97, 1154-1157.
- Gembruch U., Bald R., Hansmann M. (1990)**
Diagnosis of fetal arrhythmia by color coded M-mode Doppler echocardiography.
Geburtshilfe Frauenheilkd. 50, 286-290.
- Gembruch U., Chatterjee M., Bald R., Eldering G., Gocke H., Urban A. E., Hansmann M. (1990)**
Prenatal diagnosis of aortic atresia by color Doppler flow mapping.
Prenat. Diagn. 19, 211-217.
- Gembruch U., Knopfle G., Chatterjee M. S., Bald R., Hansmann M. (1990)**
1st-trimester diagnosis of fetal congenital heart disease by transvaginal 2-dimensional and Doppler echocardiography.
Obstet. Gynecol. 75, 496-498.
- Gilbert W. M., Nicolaides K. H. (1987)**
Fetal omphalocele: Associated malformations and chromosomal defects.
Obstet. Gynecol. 70, 633-635.

- Giorlandino C., Rivosecchi M., Bilancioni E., Bagolan P., Zaccara A., Taramanni C., Vizzione A. (1990)**
Successful intrauterine therapy of a large fetal ovarian cyst.
Prenat. Diagn. 10, 473-475.
- Glaves J., Baker J. L. (1983)**
Spontaneous resolution of maternal hydramnios in congenital cystic adenomatoid malformation of the lung. Antenatal ultrasound features. Case report.
Br. J. Obstet. Gynaecol. 90, 1065-1068.
- Glick P. L., Siebert J. R., Benjamin D. R. (1990)**
Pathophysiology of congenital diaphragmatic hernia.
J. Pediatr. Surg. 25, 492-495.
- Goldstein I., Lockwood C., Hobbins J. C. (1987)**
Ultrasound assessment of fetal intestinal development in the evaluation of gestational age.
Obstet. Gynecol. 70, 682-686.
- Goldstein R. B., Filly R. A., Callen P. W. (1987)**
Sonographic diagnosis of meconium ileus in utero.
J. Ultrasound Med. 6, 663-666.
- Gorczyca D. P., Lindfors K. K., Giles K. A., McGahan J. P., Hanson F. W., Tennant F. P. (1989)**
Prenatally diagnosed gastroschisis in monozygotic twins.
J. Clin. Ultrasound 17, 216-218.
- Graham D., Winn K., Dex W., Sanders R. C. (1982)**
Prenatal diagnosis of cystic adenomatoid malformation of the lung.
J. Ultrasound Med. 1, 9-12.
- Guzman E. R. (1990)**
Early prenatal diagnosis of gastroschisis with transvaginal ultrasonography.
Am. J. Obstet. Gynecol. 162, 1253-1254.
- Haeusler M. C., Hofmann H. M. H., Hoenigl W., Karpf E. F., Rosenkranz W. (1990)**
Congenital generalized cystic lymphangiomatosis diagnosed by prenatal ultrasound.
Prenat. Diagn. 10, 617-621.
- Hancock B. J., Wiseman N. E. (1989)**
Congenital duodenal obstruction. The impact of an antenatal diagnosis.
J. Pediatr. Surg. 24, 1027-1031.
- Hanretty K. P., Rubin P. C. (1990)**
The use of Doppler ultrasound in the study of fetal cardiovascular physiology.
J. Neurosc. M. 34, 159-167.
- Hansen L. K., Pedersen S. A., Kristoffersen K. (1987)**
Prenatal rupture of omphalocele. Case report.
J. Clin. Ultrasound 15, 191-193.
- Harris R. D., Nyberg D. A., Mack L. A., Weinberger E. (1987)**
Anorectal atresia. Prenatal sonographic diagnosis.
A. J. R. 149, 395-400.
- Harrison M. R., Adzick N. S., Jennings R. W., Duncan B. W., Rosen M. A., Filly R. A., Goldberg J. D., DeLorimier A. A., Golbus M. S. (1990)**
Antenatal intervention for congenital cystic adenomatoid malformation.
Lancet 336, 965-967.
- Harrison M. R., Filly R. A., Stanger P., DeLorimier A. A. (1982)**
Prenatal diagnosis and management of omphalocele and ectopia cordis.
J. Pediatr. Surg. 17, 64-66.
- Harrison M. R., Langer J. C., Adzick N. S., Golbus M. S., Filly R. A., Anderson R. L., Rosen M. A., Callen P. W., Goldstein R. B., DeLorimier A. A. (1990)**
Correction of congenital diaphragmatic hernia in utero. Initial clinical experience.
J. Pediatr. Surg. 25, 47-57.
- Hasan S., Hermansen M. C. (1986)**
The prenatal diagnosis of ventral abdominal wall defects.
Am. J. Obstet. Gynecol. 155, 842-845.
- Hata T., Takamori H., Hata K., Takamiya D., Murao F., Kitao M. (1988)**
Antenatal diagnosis of congenital heart disease and fetal arrhythmia by ultrasound. Prospective study.
Gynecol. Obstet. Invest. 26, 118-125.
- Hayden C. K., Schwartz M. Z., Davis M., Swischuk L. E. (1983)**
Combined esophageal and duodenal atresia: Sonographic findings.
A. J. R. 140, 225-226.
- Hertzberg B. S., Bowie J. D. (1990)**
Fetal gastrointestinal abnormalities.
Radiol. Clin. North Am. 28, 101-114.
- Hesseldahl H., Als O., Dorph S., Kjer J. J., Strom K. V. (1980)**
Prenatal diagnosis of omphalocele by ultrasound and amniography.
Acta Obstet. Gynecol. Scand. 59, 83-86.
- Hirata G. I., Medearis A. L., Platt L. D. (1990)**
Fetal abdominal abnormalities associated with genetic syndromes.
Clin. Perinatol. 17, 675-702.
- Holzgrevé W. (1990)**
Sonographic screening for anatomic defects.
Semin. Perinatol. 14, 504-513.
- Hughes H. A., Feinstein S. J., Lodeiro J. G., Byers J. W., Srinivas J., Sunderji S., Aubry R. H. (1990)**
Umbilical cord cyst presenting as an omphalocele at 15 weeks gestation.
J. Reprod. Med. 35, 658-660.
- Hughes M. D., Nyberg D. A., Mack L. A., Pretorius D. H. (1989)**
Fetal omphalocele. Prenatal ultrasound detection of concurrent anomalies and other predictors of outcome.
Radiology 173, 371-380.

- Huhta J. C., Carpenter R. J., Moise K. J., Deter R. L., Ott D. A., McNamara D. G. (1987)**
Prenatal diagnosis and postnatal management of critical aortic stenosis.
Circulation 75, 573-576.
- Jackson G. H., Yiuchiu V. S., Smith W. L., Chiu L. C. (1983)**
Sonography of combined oesophageal and duodenal atresia.
J. Ultrasound Med. 2, 473-474.
- Jassani M. N., Gauderer M. W. L., Fanaroff A. A., Fletcher B., Merkatz I. R. (1982)**
A perinatal approach to the diagnosis and management of gastrointestinal malformations.
Obstet. Gynecol. 59, 33-39.
- Jeffrey R. B., Laing F. C. (1982)**
High-resolution real-time sonography of fetal cardiovascular anatomy.
J. Ultrasound Med. 1, 249-251.
- Jouppila P. (1984)**
Ultrasonic and clinical aspects in the diagnosis and prognosis of congenital gastrointestinal anomalies.
- Jouppila P., Kirkinen P., Tuononen S. (1982)**
Ultrasonic detection of bilateral ovarian cysts in the fetus.
Eur. J. Obstet. Gynecol. Reprod. Biol. 13, 87-92.
- Journel H., Roussey M., Plais M. H., Milon J., Almange C., LeMarec B. (1986)**
Prenatal diagnosis of familial tuberous sclerosis following detection of cardiac rhabdomyoma by ultrasound.
Prenat. Diagn. 6, 283-289.
- Kagan A. R., Steckel R. J. (1983)**
Cervical mass in a fetus associated with maternal hydramnios.
A. J. R. 140, 507-509.
- Kelly D. R., Grant E. G., Zeman R. K., Choyke P. L., Bolan J. C., Warsof S. L. (1986)**
In utero diagnosis of congenital diaphragmatic hernia by CT amniography.
J. Comput. Assist. Tomogr. 10, 500-502.
- Klingensmith W. C., Cioffi-Ragan D. T., Harvey D. E. (1988)**
Diagnosis of ectopia cordis in the second trimester.
J. Clin. Ultrasound 16, 204-206.
- Knott P. D., Colley N. V. (1987)**
Can fetal gastroschisis always be diagnosed prenatally?
Prenat. Diagn. 7, 607-610.
- Koontz W. L., Shaw L. A., Lavery J. P. (1986)**
Antenatal sonographic appearance of Beckwith-Wiedemann syndrome.
J. Clin. Ultrasound 14, 57-59.
- Kragt H., Thomas S. M., Meyboom E. J., Laurini J. L. (1985)**
Prenatal ultrasonic diagnosis and management of ectopia cordis.
Eur. J. Obstet. Gynecol. 20, 177-180.
- Kronich W., Salzer-Muhar U., Strigl E., Gerstner G. J. (1990)**
Antenatal diagnosis of multiple cardiac malformations by routine ultrasound scanning.
Ultrasch. Med. 11, 48-50.
- Kurjak A., Zalud I., Jurkovic D., Alfircic Z., Tomic K. (1989)**
Ultrasound diagnosis and evaluation of fetal tumors.
J. Perinat. Med. 17, 173-193.
- Kushnir O., Izquierdo L., Vigil D., Curet L. B. (1990)**
Early transvaginal sonographic diagnosis of gastroschisis.
J. Clin. Ultrasound 18, 194-197.
- Lange I. R. (1985)**
Congenital anomalies. Detection and strategies for management.
Semin. Perinatol. 9, 151-162.
- Langer J. C., Adzick N. S., Filly R. A., Golbus M. S., DeLorimier A. A., Harrison M. R. (1989)**
Gastrointestinal-tract obstruction in the fetus.
Arch. Surg. 124, 1183-1187.
- Lewis D. F., Towers C. V., Garite T. J., Jackson D. N., Nageotte M. P., Major C. A. (1990)**
Fetal gastroschisis and omphalocele. Is Cesarean section the best mode of delivery?
Am. J. Obstet. Gynecol. 163, 773-775.
- Lindfors K. K., McGahan J. P., Walter J. P. (1986)**
Fetal omphalocele and gastroschisis. Pitfalls in sonographic diagnosis.
A. J. R. 147, 797-800.
- Lindham S., Ramel S. (1987)**
A retrospective study of 91 cases with gastroschisis or omphalocele 1956-1985.
Z. Kinderchir. 42, 366-370.
- Lowry R. B., Baird P. A. (1982)**
Familial gastroschisis and omphalocele.
Am. J. Hum. Genet. 34, 517-518.
- Lyngbye T., Haugaard L., Klebe J. G. (1986)**
Antenatal sonographic diagnoses of giant cystic hygroma of the neck.
Acta Obstet. Gynecol. Scand. 65, 873-875.
- Lys F., De Wals P., Borlee-Grimee L., Billiet A., Vincotte-Mols M., Levi S. (1989)**
Evaluation of routine ultrasound examination for the prenatal diagnosis of malformation.
Eur. J. Obstet. Gynecol. Reprod. Biol. 30, 101-109.
- Macchiella D., Merz E. (1990)**
Prenatal diagnosis of congenital adenomatoid malformation of the lung type II by ultrasound.
Geburtshilfe Frauenheilkd. 50, 495-498.
- Machado M. V., Crawford D. C., Anderson R. H., Allan L. D. (1988)**
Atrioventricular septal defect in prenatal life.
Br. Heart J. 59, 352-355.
- Mann L., Ferguson-Smith M. A. (1984)**
Prenatal assessment of anterior abdominal wall defects and their prognosis.
Prenat. Diagn. 4, 427-435.
- Marasini M., Cordone M., Pongiglione G., Lituania M., Berolini A., Ribaldone D. (1988)**
In utero ultrasound diagnosis of congenital heart disease.
J. Clin. Ultrasound 16, 103-107.

- Marks F., Thomas P., Lusting I., Greco M. A., Raghavendra B. N., Wasserman R.** (1990)
In utero sonographic description of a fetal liver adenoma.
J. Ultrasound Med. 9, 119-122.
- Martin L. W., Torres A. M.** (1985)
Omphalocele and gastroschisis.
Surg. Clin. North Am. 65, 1238-1244.
- Marwood R. P., Davison O. W.** (1981)
Antenatal diagnosis of diaphragmatic hernia.
Br. J. Obstet. Gynaecol. 88, 71-72.
- Mayden K. L., Tortora M., Chervenak F. A., Hobbins J. C.** (1984)
The antenatal sonographic detection of lung masses.
Am. J. Obstet. Gynecol. 148, 349-351.
- McGahan J. P.** (1991)
Sonography of the fetal heart. Findings on the 4-chamber view.
A. J. R. 156, 547-553.
- Meizner I., Barziv J.** (1986)
Prenatal ultrasonic diagnosis of anterior abdominal wall defects.
Eur. J. Obstet. Gynecol. Reprod. Biol. 22, 217-224.
- Meizner I., Barziv J., Insler V.** (1986)
Prenatal ultrasonic diagnosis of fetal thoracic and intrathoracic abnormalities.
Isr. J. Med. Sci. 22, 350-354.
- Meizner I., Carmi R., Katz M., Insler V.** (1989)
In utero prenatal diagnosis of Beckwith-Wiedemann syndrome. A case report.
Eur. J. Obstet. Gynecol. 32, 259-264.
- Meizner I., Levy A., Maresh A., Katz M., Maresh A. J., Kata M.** (1991)
Fetal ovarian cysts. Prenatal ultrasonographic detection and postnatal evaluation and treatment.
Am. J. Obstet. Gynecol. 164, 874-878.
- Meller J. L., Reyes H. M., Loeff D. S.** (1989)
Gastroschisis and omphalocele.
Clin. Perinatol. 16, 113-122.
- Mendoza A., SoWolf P., Edwards D. K., Lepoold G. R., Volland J. R., Benirschke K.** (1986)
Prenatal ultrasonographic diagnosis of congenital adenomatoid malformation of the lung. Correlation with pathology and implications for pregnancy management.
Arch. Pathol. Lab. Med. 110, 402-404.
- Mercer S., Mercer B., Dalton M. E. G., Soucy P.** (1988)
Gastroschisis. Ultrasonographic diagnosis, perinatal embryology, surgical and obstetric treatment and outcomes.
Can. J. Surg. 31, 25-26.
- Miro J., Bard H.** (1988)
Congenital atresia and stenosis of the duodenum: The impact of a prenatal diagnosis.
Am. J. Obstet. Gynecol. 158, 555-559.
- Morcos S. F., Lobb M. O.** (1986)
The antenatal diagnosis by ultrasonography of type-III congenital cystic adenomatoid malformation of the lung.
Br. J. Obstet. Gynaecol. 93, 1002-1005.
- Mornet E., Serre J. R., Farrall M., Boué J., Somon-Bouy B., Estivill X., Boué A.** (1988)
Genetic differences between cystic fibrosis with and without meconium ileus.
Lancet 1, 376-378.
- Morville P., Planche C., Mauran P., Santerne B.** (1986)
Endocardial fibroelastosis. prenatal manifestation of stenosis of the aortic aperture. Echographic diagnosis.
Helv. Paediatr. Acta 41, 69-75.
- Muller F., Aubry M. C., Gasser B., Duchatel F., Boué J., Boué A.** (1985)
Prenatal diagnosis of cystic fibrosis. Meconium ileus in affected fetuses.
Prenat. Diagn. 5, 109-117.
- Nagata S., Koyanagi T., Horimoto N., Satoh S., Nakano H.** (1990)
Chronological development of the fetal stomach assessed using real-time ultrasound.
Early Hum. Dev. 22, 15-22.
- Nakayama D. K., Harrison M. R., Chinn D. H., Callen P. W., Filly R. A., Golbus M. S., DeLorimier A. A.** (1985)
Prenatal diagnosis and natural history of the fetus with a congenital diaphragmatic hernia. Initial clinical experience.
J. Pediatr. Surg. 20, 118-124.
- Nelson L. H., Clark C. E., Fishburne J. I., Urban R. B., Penry M. F.** (1982)
Value of serial sonography in the in utero detection of duodenal atresia.
Obstet. Gynecol. 59, 657-660.
- Nelson P. A., Bowie J. D., Filston H. C., Crane L. M.** (1982)
Sonographic diagnosis of omphalocele in utero.
A. J. R. 138, 1178-1180.
- Nicolaides K. H., Campbell S.** (1987)
Diagnosis and management of fetal malformations.
Baill. Clin. Obstet. Gynaec. 1, 591-622.
- Norio R., Kääriäinen H., Rapola J., Herva R., Kekomäki M.** (1984)
Familial congenital diaphragmatic defects: Aspects of etiology, prenatal diagnosis, and treatment.
Am. J. Med. Genet. 17, 471-483.
- Nugent C. E., Hayashi R. H., Rubin J.** (1989)
Prenatal treatment of type I congenital cystic adenomatoid malformation by intrauterine fetal thoracocentesis.
J. Clin. Ultrasound 17, 675-677.
- Nyberg D. A., Hastrup W., Watts H., Mack L. A.** (1987)
Dilated fetal bowel. A sonographic sign of cystic fibrosis.
J. Ultrasound Med. 6, 257-260.
- Opitz J. M., Gilbert E. F.** (1982)
Pathogenetic analysis of congenital anomalies in humans.
Pathol. Annu. 12, 301-349.

- Ornoy A., Arnon J., Katznelson D., Granat M., Caspi B., Chemke J.** (1987)
Pathological confirmation of cystic fibrosis in the fetus following prenatal diagnosis.
Am. J. Med. Genet. 28, 935-947.
- Pagliano M., Mossetti M., Ragno P.** (1990)
Echographic diagnosis of omphalocele in the 1st trimester of pregnancy.
J. Clin. Ultrasound 18, 658-660.
- Paladini D., Chita S. K., Allan L. D.** (1990)
Prenatal measurement of cardiothoracic ratio in evaluation of heart disease.
Arch. Dis. Child. 65, 20-23.
- Papp Z., Tóth Z., Szabó M., Szeifert G. T.** (1985)
Early prenatal diagnosis of cystic fibrosis by ultrasound.
Clin. Genet. 28, 356-358.
- Patel P. J., Kalowole T. M., Baaqueel H. S., Aljisi N.** (1989)
Antenatal sonographic findings of congenital chloride diarrhea.
J. Clin. Ultrasound 17, 115-118.
- Perrelli L., Calisti A., Romagnoli C., Nola G.** (1983)
Antenatal ultrasonic demonstration of congenital diaphragmatic hernia.
Z. Kinderchir. 38, 108-109.
- Persutte W. H., Yeasting R. A., Lenke R. R., Levine M. M.** (1990)
Prenatal ultrasonographic appearance of agenesis of the ductus arteriosus and pulmonic valve hypoplasia. A case report and review of the embryogenesis.
J. Ultrasound Med. 9, 541-545.
- Petit P., Bossens M., Thomas D., Moerman P., Fryns J. P., Van den Berghe H.** (1987)
Type-III congenital cystic adenomatoid malformation of the lung. Another cause of elevated alpha-fetoprotein.
Clin. Genet. 32, 172-174.
- Pezzuti R. T., Isler R. J.** (1983)
Antenatal ultrasound detection of cystic adenomatoid malformation of lung: Report of a case and review of the recent literature.
J. Clin. Ultrasound 11, 342-346.
- Pijpers L., Reuss A., Stewart P. A., Wladimiroff J. W., Sachs E. S.** (1988)
Fetal cystic hygroma. Prenatal diagnosis and management.
Obstet. Gynecol. 72, 223-224.
- Preziosi P., Fariello G., Maiorana A., Malena S., Ferro F.** (1986)
Antenatal sonographic diagnosis of complicated ovarian cysts.
J. Clin. Ultrasound 14, 196-198.
- Rahmani M. R., Zalev A. H.** (1986)
Antenatal detection of esophageal atresia with distal tracheoesophageal fistula.
J. Clin. Ultrasound 14, 143-145.
- Randolph J.** (1982)
Omphalocele and gastroschisis.
J. S. C. Med. Assoc. 75, 1517-1519.
- Reed K. L.** (1989)
Fetal arrhythmias. Etiology, diagnosis, pathophysiology, and treatment.
Semin. Perinatol. 13, 294-304.
- Rempen A., Feige A.** (1985)
Differential diagnosis of sonographically detected tumors in the fetal cervical region.
Eur. J. Obstet. Gynecol. 20, 89-105.
- Rempen A., Feige A., Wunsch P.** (1987)
Prenatal diagnosis of bilateral cystic adenomatoid malformation of the lung.
J. Clin. Ultrasound 15, 3-8.
- Rempen A., Kaesemann H., Feige A., Fiedler K.** (1986)
Sonographic prenatal diagnosis and clinical management in intestinal obstructions.
Z. Geburtshilfe Perinatol. 190, 73-82.
- Reuss A., Pijpers L., Van Swaaij E., Jahoda M. G. J., Wladimiroff J. W.** (1987)
First-trimester diagnosis of recurrence of cystic hygroma using a vaginal ultrasound transducer.
Eur. J. Obstet. Gynecol. Reprod. Biol. 26, 271-273.
- Rizzo N., Gabrielli S., Perolo A., Pilu G., Cacciari A., Domini R., Bovicelli L.** (1989)
Prenatal diagnosis and management of fetal ovarian cysts.
Prenat. Diagn. 9, 97-103.
- Roberson D. A., Silverman N. H.** (1989)
Ebstein anomaly. Echocardiographic and clinical features in the fetus and neonate.
J. Am. Col. C. 14, 1300-1307.
- Roberts J. P., Burge D. M.** (1990)
Antenatal diagnosis of abdominal wall defects. A missed opportunity.
Arch. Dis. Child. 65, 687-689.
- Romero R., Ghidini A., Costigan K., Touloukian R. L., Hobbins J. C.** (1988)
Prenatal diagnosis of duodenal atresia. Does it make any difference?
Obstet. Gynecol. 7, 139-741.
- Romero R., Oyarzun E., Sirtori M., Hobbins J. C.** (1988)
Detection and management of anatomic congenital anomalies. A new obstetric challenge.
Obstet. Gynecol. Clin. 15, 215-236.
- Rosendahl H., Kivinen S.** (1989)
Antenatal detection of congenital malformations by routine ultrasonography.
Obstet. Gynecol. 73, 947-951.
- Roskes E. J., Boughman J. A., Schwartz S., Cohen M. M.** (1990)
Congenital cardiovascular malformations (CCVM) and structural chromosome abnormalities. A report of 9 cases and literature review.
Clin. Genet. 38, 198-210.

- Rutledge J. C., Winberg A. G., Friedman J. M., Harrod M. J., Santos-Ramos R.** (1986)
Anatomic correlates of ultrasonographic prenatal diagnosis.
Prenat. Diagn. 6, 51-61.
- Saltzman D. H., Adzick N. S., Benacerraf B. B.** (1988)
Fetal cystic adenomatoid malformation of the lung. Apparent improvement in utero.
Obstet. Gynecol. 71, 1000-1002.
- Salzman L., Kuligowska E., Semine A.** (1986)
Pseudoomphalocele. Pitfall in fetal sonography.
A. J. R. 146, 1283-1285.
- Sarda P., Bard H., Teasdale F., Grignon A.** (1983)
The importance of an antenatal ultrasonographic diagnosis of correctable fetal malformations.
Am. J. Obstet. Gynecol. 147, 443-445.
- Schroder W.** (1990)
Hygroma colli in ultrasound as an early sign of fetal Ullrich-Turner syndrome.
Z. Geburtshilfe Perinatol. 194, 283-285.
- Sermer M., Benzie R. J., Pitson L., Carr M., Skidmore M.** (1987)
Prenatal diagnosis and management of congenital defects of the anterior abdominal wall.
Am. J. Obstet. Gynecol. 156, 308-312.
- Shah Y. G., Metlay L.** (1990)
Prenatal ultrasound diagnosis of Beckwith-Wiedemann syndrome.
J. Clin. Ultrasound 18, 597-600.
- Simon-Bouy B., Serre J. L., Mornet E., Tallandier A., Boué J., Boué A.** (1989)
Genetic differences between cystic fibrosis with and without meconium ileus.
Lancet 2, 102-102.
- Sipes S. L., Weiner C. P., Sipes D. R., Grant S. S., Williamson R. A.** (1990)
Gastroschisis and omphalocele. Does either antenatal diagnosis or route of delivery make a difference in perinatal outcome?
Obstet. Gynecol. 76, 195-199.
- Skoll M. A., Marquette G. P., Hamilton E. F.** (1987)
Prenatal ultrasonic diagnosis of multiple bowel atresias.
Am. J. Obstet. Gynecol. 156, 472-473.
- Smith L. G., Carpenter R. J., Gonsoulin W., Mari G., Reiter A. A., Geenberg F., Powell C.** (1990)
Prenatal diagnosis of a chest-wall mass with ultrasonography and Doppler velocimetry.
Am. J. Obstet. Gynecol. 163, 567-569.
- Stillier R. J., Roberts N. S., Winer S., Vaughn B.** (1985)
Congenital diaphragmatic hernia. Antenatal diagnosis and obstetrical management.
J. Clin. Ultrasound 13, 212-215.
- Stringel G., Gillieson M., Muram D., Mercer S.** (1983)
Perinatal management of major gastrointestinal anomalies diagnosed by maternal ultrasound.
Clin. Pediatr. 22, 564-566.
- Suita S., Ikeda K., Koyanagi T., Nakano H.** (1984)
Neonatal ovarian cyst diagnosed antenatally: Report of two patients.
J. Clin. Ultrasound 12, 517-519.
- Szabó M., Münnich Á., Teichmann F., Huszka M., Veress L., Papp Z.** (1990)
Discriminant analysis for assessing the value of amniotic fluid microvillar enzymes in the prenatal diagnosis of cystic fibrosis.
Prenat. Diagn. 10, 761-769.
- Szabó M., Teichmann F., Szeifert G. T., Tóth M., Tóth Z., Török O., Papp Z.** (1985)
Prenatal diagnosis of cystic fibrosis by trehalase enzyme assay in amniotic fluid.
Clin. Genet. 28, 16-22.
- Szabó M., Teichmann F., Huszka M., Münnich Á., Veress L., Papp Z.** (1991)
Prenatal diagnosis of cystic fibrosis by microvillar membrane enzyme analysis in amniotic fluid.
Acta Paediatr. Hung. 31, 263-274.
- Szeifert G. T., Szabó M., Papp Z.** (1985)
Morphology of cystic fibrosis at 17 weeks of gestation.
Clin. Genet. 28, 561-565.
- Tabsh K. M. A.** (1982)
Antenatal sonographic appearance of a fetal ovarian cyst.
J. Clin. Ultrasound 1, 329-331.
- Thurkow A. L., Visser G. H. A., Oosterhuis J. W., De Vries J. A.** (1983)
Ultrasound observations of a malignant cervical teratoma of the fetus in a case of polyhydramnios: Case history and review.
Eur. J. Obstet. Gynecol. Reprod. Biol. 14, 375-384.
- Tóth Z., Kóródi I., Vachter J., Dezső B., Papp Z.** (1984)
Antenatally diagnosed hygroma colli.
Acta Paediatr. Hung. 25, 333-338.
- Török O., Tóth Z., Szabó M., Papp Z.** (1990)
Ultrasound diagnosis and screening of fetal cystic fibrosis.
Acta Univ. Carol. Med. 36, 139-141.
- Trecet J. C., Claramunt V., Larraz J., Ruiz E., Zuzuarregui M., Ugalde F. J.** (1984)
Prenatal ultrasound diagnosis of fetal teratoma of the neck.
J. Clin. Ultrasound 12, 509-511.
- Tucci M., Bard H.** (1990)
The associated anomalies that determine prognosis in congenital omphaloceles.
Am. J. Obstet. Gynecol. 163, 1646-1649.

- Ursell P. C., Byrne J. M., Strobino B. A., Gersony W. M., Blanck W. A. (1984)**
Congenital heart disease among spontaneously aborted fetuses. *Circulation* 70, 426-426.
- Van den Born M. E., Bax N. M. A., Van de Vange N., Gerards L. J., Christiaens G. C. (1987)**
Antenatal ultrasonographic diagnosis of a congenital posterolateral diaphragmatic defect. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 25, 139-144.
- Vermesh M., Mayden K. L., Confinio E., Giglia R. V., Gleicher N. (1986)**
Prenatal sonographic diagnosis of Hirschsprung's disease. *J. Ultrasound Med.* 5, 37-39.
- Vincent R. N., Menticoglou S., Chanas D., Manning F., Collins G. F., Smallhorn J. (1987)**
Prenatal diagnosis of an unusual form of hypoplastic left heart syndrome. *J. Ultrasound Med.* 6, 261-264.
- Vintzileos A. M., Campbell W. A., Nochimson D. J., Weinbaum P. J. (1987)**
Antenatal evaluation and management of ultrasonically detected fetal anomalies. *Obstet. Gynecol.* 69, 640-660.
- Weinberg B., Diakoumakis E. E. (1985)**
Three complex cases of foregut atresia: Prenatal sonographic diagnosis with radiographic correlation. *J. Clin. Ultrasound* 13, 481-484.
- Wilhelm C., Klosa W., Müller M., Schillinger H. (1988)**
Prenatal sonography of abdominal wall defects and stenoses of the intestinal tract. *Geburtshilfe Frauenheilkd.* 48, 240-245.
- Winter R. M., Knowles S. A. S., Bieber F. R., Baraitser M. (1988)**
The Malformed Fetus and Stillbirth. A Diagnostic Approach. John Wiley and Sons, Chichester-New York
- Wladimiroff J. W., Molenaar J. C., Niermeijer M. F., Stewart P. A., Van Eyck J. (1983)**
Prenatal diagnosis and management of omphalocele. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 16, 19-23.
- Wladimiroff J. W., Stewart P. A., Sachs E. S., Niermeijer M. F. (1985)**
Prenatal diagnosis and management of congenital heart defect. Significance of associated fetal anomalies and prenatal chromosome studies. *Am. J. Med. Genet.* 21, 285-290.
- Worthen N. J., Worthen W. F. (1982)**
Disruption of the diaphragmatic echoes: A sonographic sign of diaphragmatic disease. *J. Clin. Ultrasound* 10, 43-45.
- Yagel S., Sherer D., Hurwitz A. (1985)**
Significance of ultrasonic prenatal diagnosis of ventricular septal defect. *J. Clin. Ultrasound* 13, 588-590.
- Yagel S., Zlotogora J., Kanetti H., Voss R. (1988)**
Fetal duodenal obstruction. *Acta Obstet. Gynecol. Scand.* 67, 465-466.
- Yankes J. R., Bowie J. D., Effmann E. L., Marshburn P. B., Carroll B. A., Filston H. C. (1988)**
Antenatal diagnosis of meconium peritonitis with inguinal hernias by ultrasonography. Therapeutic implications. *J. Ultrasound Med.* 7, 221-223.
- Young G., Lheureux P. R., Kruckeberg S. T., Swanson D. A. (1989)**
Mediastinal bronchogenic cyst. Prenatal sonographic diagnosis. *A. J. R.* 152, 125-127.
- Zerres K., Gembruch U., Schwannitz G., Redel D. A., Bald R., Gottschl. A., Hansmann M. (1990)**
Fetal echocardiography and clinical genetics. A close relationship. *Z. Kardiol.* 79, 96-106.

Renal and Urinary Tract Abnormalities

Advances in ultrasound have led to improved diagnosis of cystic renal disease and better knowledge of the pathological mechanisms.

Potter recognized four forms of congenital cystic kidney.

Infantile Polycystic Kidney

The collecting tubules develop cystic dilatations, 1-2 mm in diameter, with oliguria/anuria and oligohydramnios. The process is usually bilateral, and incompatible with survival after birth (also on account of the severe associated pulmonary hypoplasia). There is cystic degeneration and periportal fibrosis in the liver, with an inverse relationship between the severity of changes in the kidney and in the liver. Cystic changes may occur in the lungs and other organs.

Inheritance is autosomal recessive. The disease is found twice as frequently in girls as in boys.

Prenatal ultrasound diagnosis is possible before the 20th week. There is oligohydramnios, and the kidneys are enlarged and filled with innumerable small cysts; they are conspicuously echogenic. No isolated renal cysts are seen. The urinary bladder cannot be identified.

Multicystic Dysplastic Kidney

Large cysts, 10-20 mm in diameter, develop in the nephrons (thin-walled) and in the collecting tubules (thick-walled). There is little communication between the cysts, which are separated by loose connective

tissue. Affected kidneys lack normal parenchyma and do not produce urine. Cysts are not found in other organs.

Sometimes the contralateral kidney is absent, or hypoplastic. Severe bilateral problems are incompatible with survival. About two-thirds of cases are unilateral.

The disorder is found more often in boys. The cause is, in general, unknown; it might sometimes be a sequel to occlusion of a ureter (vascular compression? infection?) early in pregnancy. Some multiple malformation syndromes, e.g., the Meckel syndrome (autosomal recessive inheritance), may be associated with multicystic dysplastic kidneys.

On ultrasound the kidneys are irregular, distorted by grape-like clusters of cysts of variable size.

When the malformation is unilateral, the amniotic fluid volume is normal and the bladder fills well, and one may safely wait to deliver the baby at term. Very often polyhydramnios occurs. Bilateral disease is usually associated with oligohydramnios; in such cases, if the fetus does not produce urine in response to 10 mg Furosemide given i.v. to the mother, the prognosis is hopeless and termination may be discussed.

Adult Polycystic Kidney (ADPKD)

Some nephrons and tubules develop into cysts, thin-walled and thick-walled, respectively. Cysts of variable diameter are dispersed on a

background of normal nephrons and tubules. With advancing age the size and number of the cysts increases, renal function begins to fail, and hypertension and occasional haematuria develop. Cysts may be found in other organs (liver, lungs and pancreas). Subarachnoid haemorrhage, from ruptured aneurysm, occurs quite frequently.

Inheritance is autosomal dominant. Fifty per cent of children of an affected parent will be affected. The disease locus has been mapped to the short arm of chromosome 16 and diagnosis at the molecular level is possible, using linked RFLPs. However, some families which do not show linkage to 16p have recently been described.

The adult-type of polycystic kidney disease can already be diagnosed with ultrasound in the presymptomatic stages; sometimes it is recognizable even prenatally. The image then is similar to that seen in the infantile type of polycystic kidney disease, but in the adult type there is always filling of the bladder and a normal amniotic fluid volume.

Hydronephrotic Kidney

Urethral obstruction or, in the second half of gestation, ureteral obstruction, leads to the development of a hydronephrotic kidney. In mild cases only the pelves and the calices are dilated (pyelectasis), and the renal parenchyma is of normal thickness. The dilatations are regularly formed, filled with urine, and maintain the regular anatomical pattern of the caliceal system. If the

obstruction persists, the parenchyma grows thinner, and in the most severe cases a grossly hydronephrotic kidney develops, looking on ultrasound like a solitary cyst (perirenal urinoma). In severe bilateral cases urine production ceases and oligohydramnios is found. Most unilateral cases are accompanied by increased amniotic fluid volume. The histological picture of the hydronephrotic kidney is characterized by subcapsular cysts developing from both tubules and nephrons.

The hydronephrotic kidney can be diagnosed with prenatal ultrasound. In severe cases three other possibilities must be excluded: these are hydrometrocolpos, ovarian cyst and teratoma.

Hydronephrosis develops as a sequel to urethral obstruction or, in the second half of pregnancy, to obstruction of the ureter. The obstruction can be located on ultrasound. Amniotography may help establish the diagnosis.

In some cases, fetal pyelectasis ceases to progress after birth. Polyhydramnios may contribute to the development of pyelectasis, or be a consequence of it.

Permanent renal damage may develop in a number of ways.

Obstruction at the Ureteropelvic Junction

This is the most frequent site of obstruction. The cause of the anatomical obstruction is unknown. Familial cases are seldom seen. The

malformation is unilateral in 70%. In these cases the contralateral kidney is intact, the urinary bladder fills, the amniotic fluid is normal in volume, and polyhydramnios develops in step with the hydronephrosis. Changes are bilateral in 30%, and in these the kidneys are asymmetrically affected.

In unilateral cases, and in bilateral ones with adequate renal function, the fetus may be delivered at term. Sometimes, to preserve the renal parenchyma, repeated renocentesis, or establishment of a renoamniotic shunt, may be justified.

In bilateral hydronephrosis with poor renal function, induction of premature labour should be considered; the timing of induction should be discussed with the urologists and the paediatricians.

One must remember that some cases of pyelectasis (e.g., those due to vesicoureteral reflux) may regress prenatally. Intrauterine procedures, or induction of premature labour, should be employed only in severe cases of hydronephrosis.

Obstruction Due to Posterior Urethral Valves

The whole urinary tract above the obstruction is affected (hydrourethra, dilated, thick-walled urinary bladder, hydroureter, hydronephrosis, abdominal wall distension, ascites), and as a consequence of the oligohydramnios, there is pulmonary hypoplasia, and deformities of face and limbs, etc. It seems likely

that this malformation sequence is identical with the prune-belly syndrome claimed by neonatologists: diastasis of the abdominal wall muscles, characteristically wrinkled abdominal skin and megaureter. The genital tract is almost always involved: cryptorchidism in boys, müllerian duct anomalies in girls.

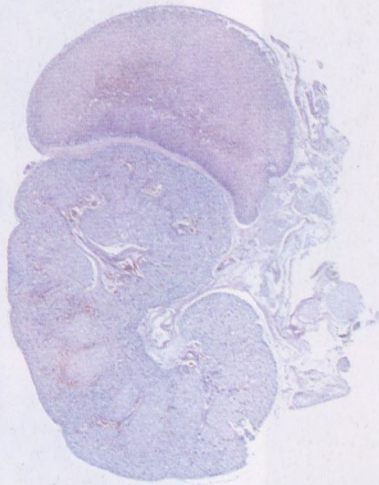
Megacystis-Microcolon-Hypperistalsis Syndrome

Other causes of obstructive uropathy include urethral stricture and aplasia, and a lethal syndrome of which megacystis (despite an intact urethra) and a very narrow immotile colon (microcolon, hypoperistalsis) are characteristic. This latter condition is virtually untreatable surgically or by medication. The causes of its development are little known, but there is neuronal dysplasia in the affected structures.

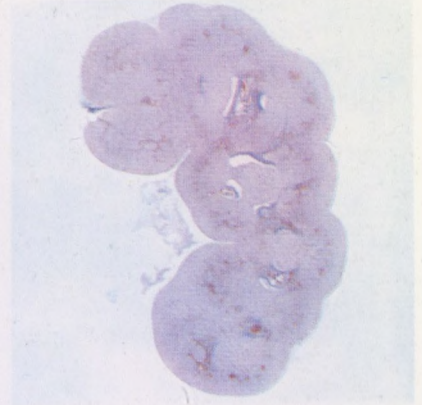
Exstrophy of the Bladder

Exposure and protrusion of the posterior wall of the urinary bladder characterize this congenital anomaly, which occurs chiefly in males. The trigone of the bladder and the ureteric orifices are exposed, and urine dribbles intermittently on the mucous membrane of the everted bladder. Exstrophy results from incomplete midline closure of the inferior part of the anterior abdominal wall. Fortunately, this severe malformation is rare.

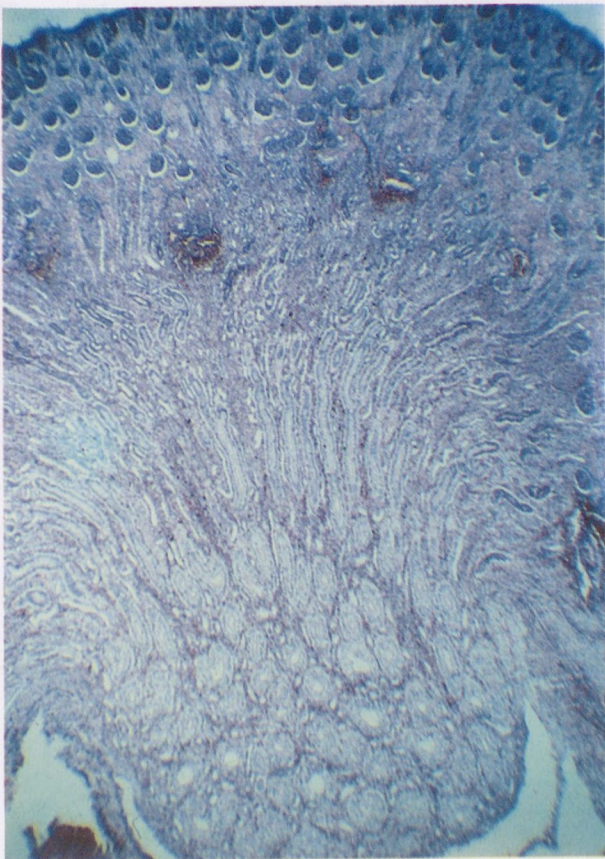
a



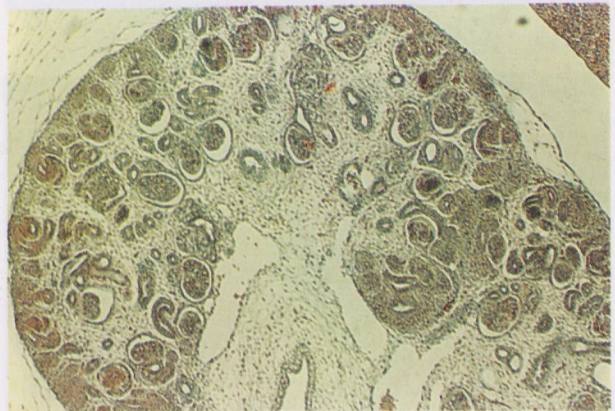
b



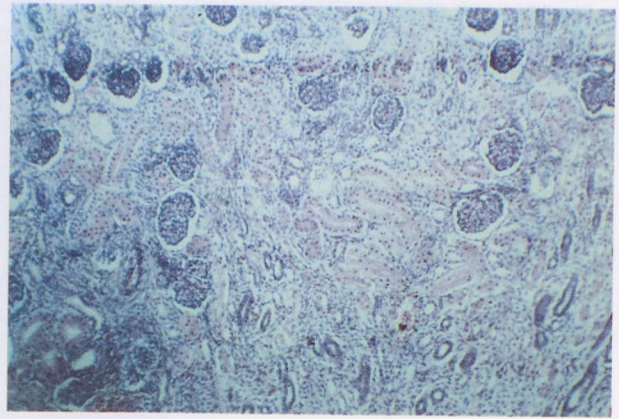
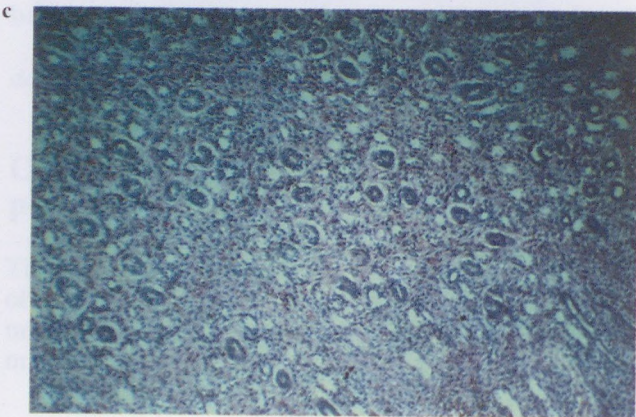
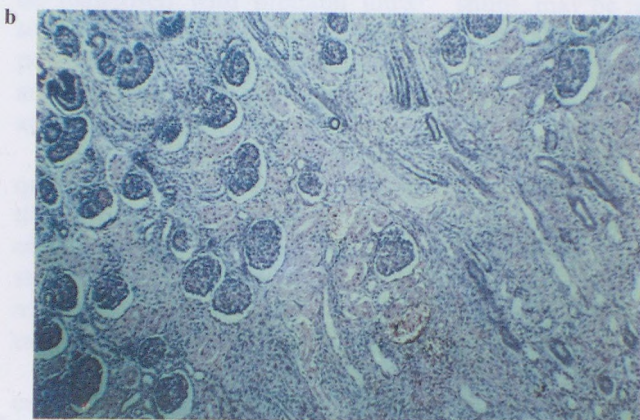
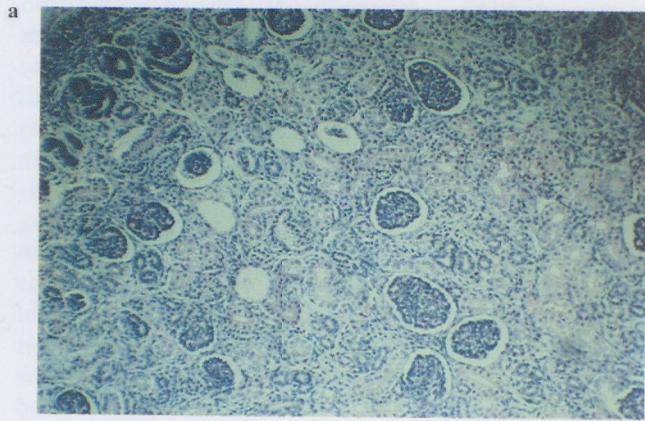
c



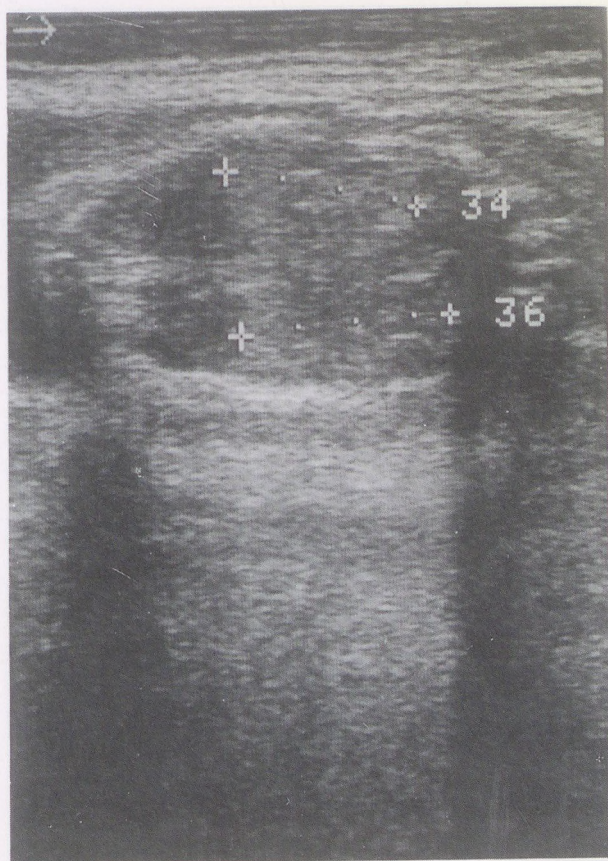
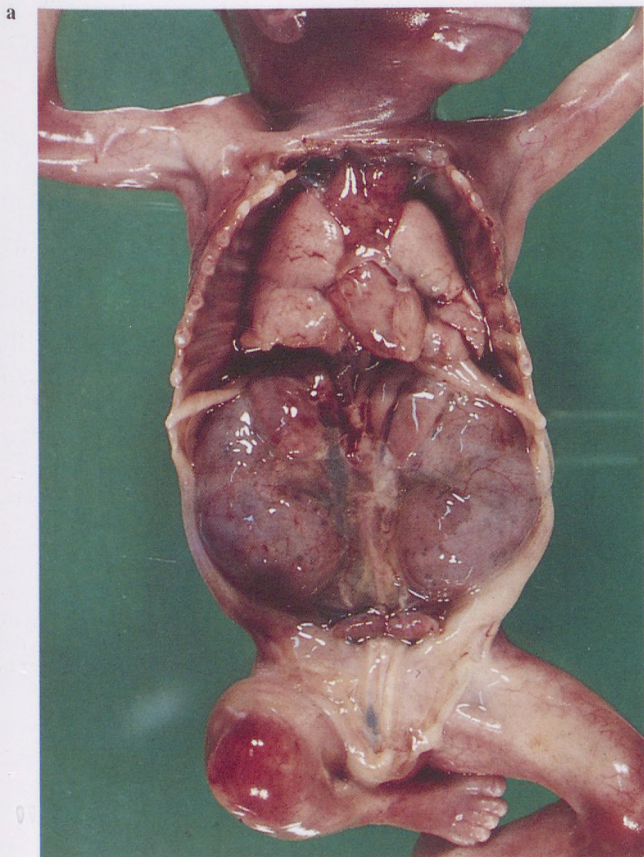
d



Figures 8-1a, b, c and d. Longitudinal section of a normal mid-trimester fetal kidney and adrenal gland (a); note the embryonic lobulation (b); the cortex, medullary pyramid and papilla are all clearly defined (HE, x40) (c and d).



Figures 8-2a, b, c and d. Normal kidney from a 24-week-old fetus: (a) nephrogenic zone, outer cortex (HE, x100); (b) cortex with a regular pattern of glomeruli and tubules (HE, x100); (c) medulla, loops of Henle and collecting tubules (HE, x100); (d) corticomedullary junction, regular pattern of normally developed glomeruli, tubules and loops of Henle.



Figures 8-3a, b and c. Infantile polycystic kidney (Potter type I): (a) macroscopic view of a bilateral form; (b) ultrasound view of infantile polycystic kidneys: they are large and display a "spongy" appearance. The cysts cannot be separated by ultrasound; their small diameter is below the resolving power of ultrasound equipment; (c) longitudinal section; cortex and medulla have a sponge-like appearance, and contain innumerable small cysts.



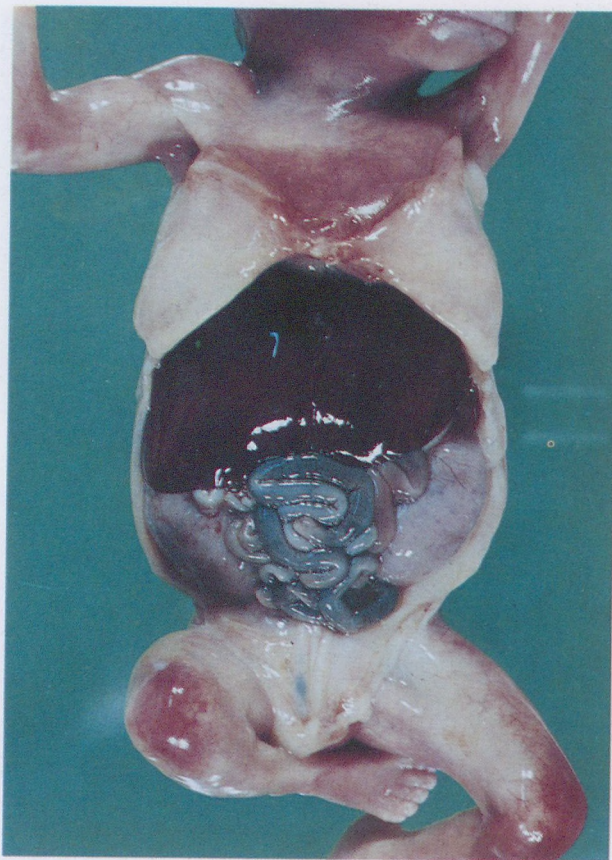
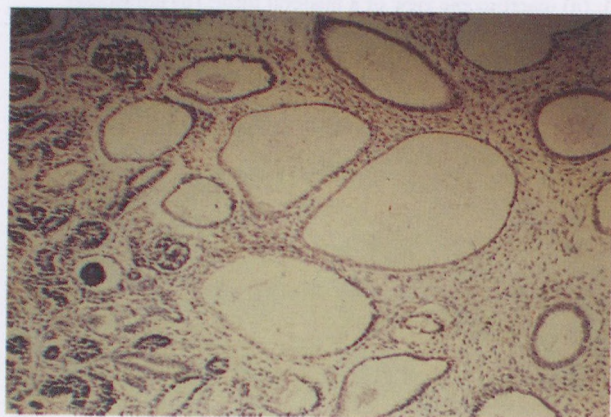
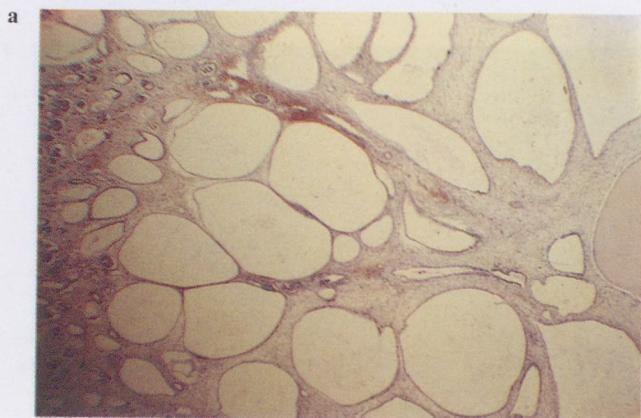


Figure 8-4. Bilateral polycystic kidney disease of infantile type in a 19-week-old fetus.



Figures 8-5a and b. Infantile polycystic kidney: (a) multiple cysts are seen in the medulla, with increased peritubular connective tissue; rather few glomeruli are seen in the cortex (HE, x40); (b) normal appearance of glomeruli, with adjacent cystically dilated tubules within the renal medulla.



Figure 8-6. Bilateral polycystic kidneys of infantile type in a male mid-trimester fetus.

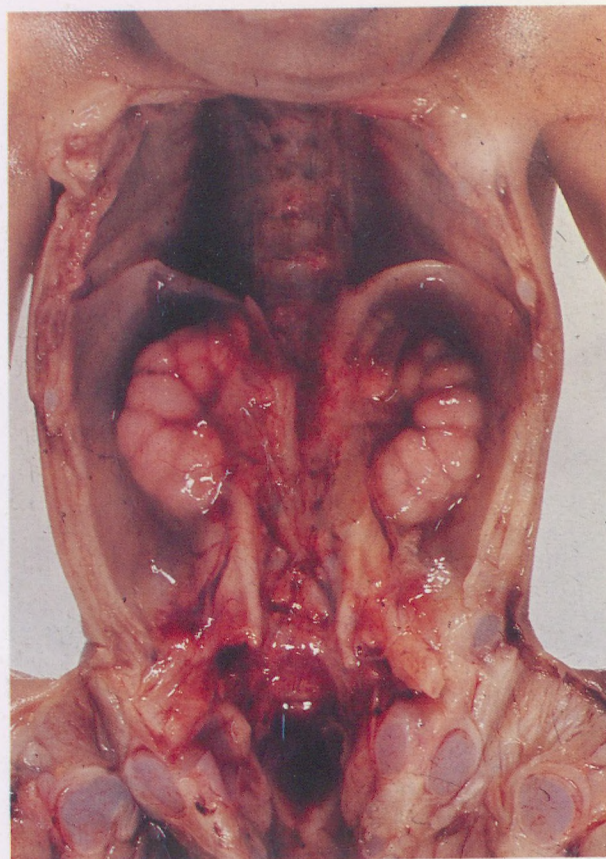


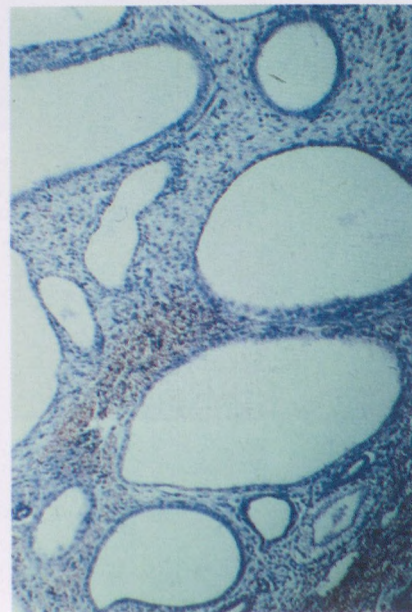
Figure 8-7. Kidneys showing normal lobulation in a mid-trimester anencephalic fetus. (Anencephaly associated with suprarenal gland hypoplasia.)

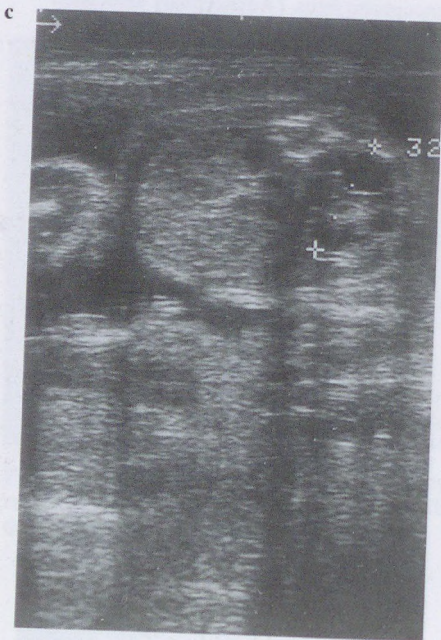
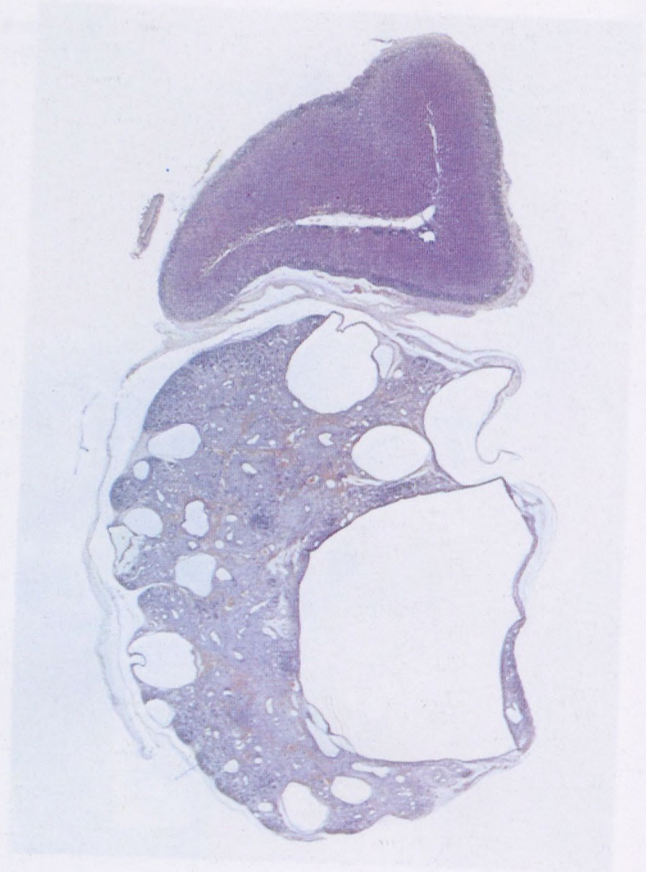
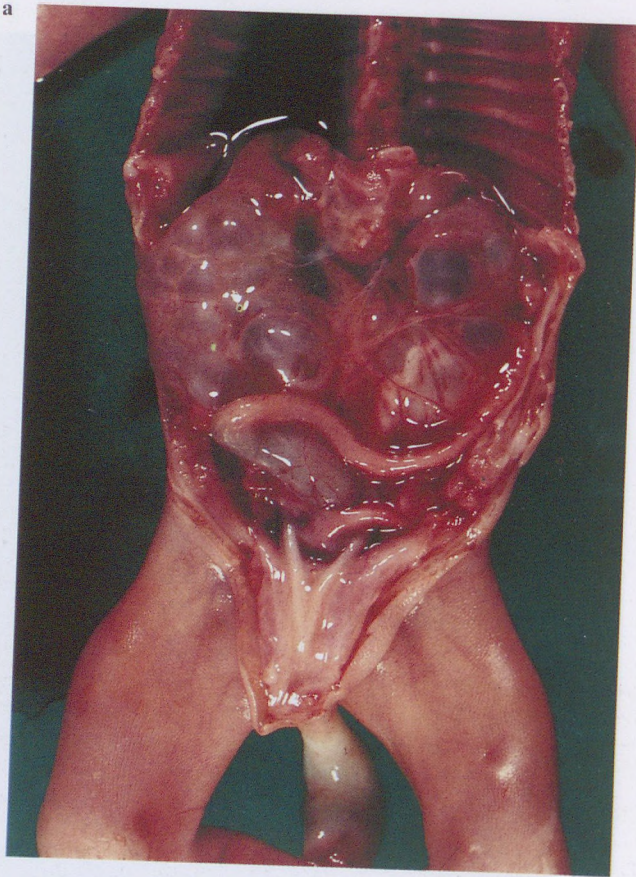
a



Figures 8-8a and b. Infantile type polycystic kidney: (a) horizontal section; (b) small cysts without connective tissue proliferation (HE, x100).

b





Figures 8-9a, b, c and d. Enlarged multicystic kidneys: (a) *in situ*; (b) longitudinal section of kidney and adrenal gland. Many cystic spaces are seen. The corticomedullary junction is not clearly demarcated; (c) a case of unilateral multicystic kidney detected by ultrasound at 24 weeks of gestation; (d) multiple cysts separated by distinct septa; ultrasound in a case of unilateral multicystic kidney (22 weeks of age).

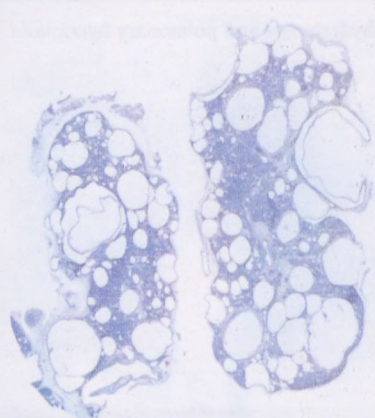
d



a



b

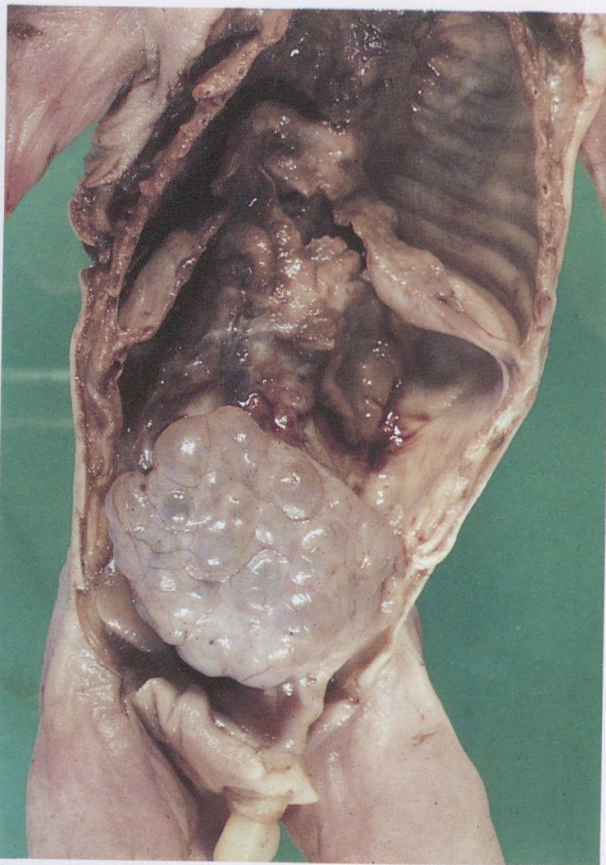


Figures 8-10a, b and c. Multicystic dysplastic kidneys (Potter type II): (a) moderate cystic enlargement of both kidneys, with loss of the normal embryonic lobulation; (b) cut surface: the cysts are greatly variable in size, and no renal parenchyma can be distinguished; (c) longitudinal section of fetal kidney showing numerous cystic spaces of varying diameter in both cortex and medulla.

a

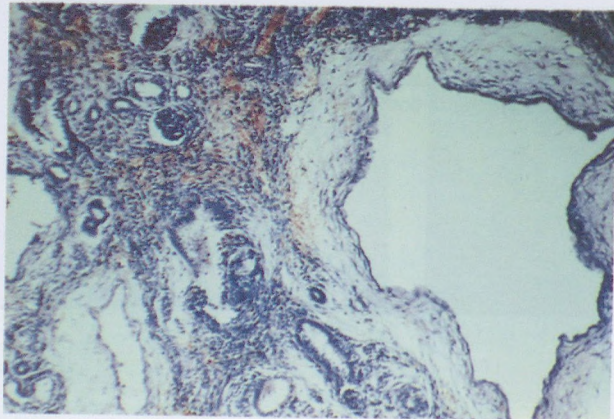


b

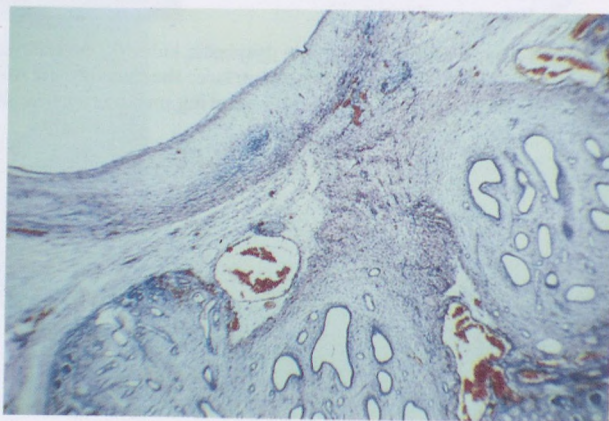


Figures 8-11a and b. Extreme unilateral enlargement of multicystic kidney, associated with oligohydramnios and pulmonary hypoplasia. The other kidney was absent.

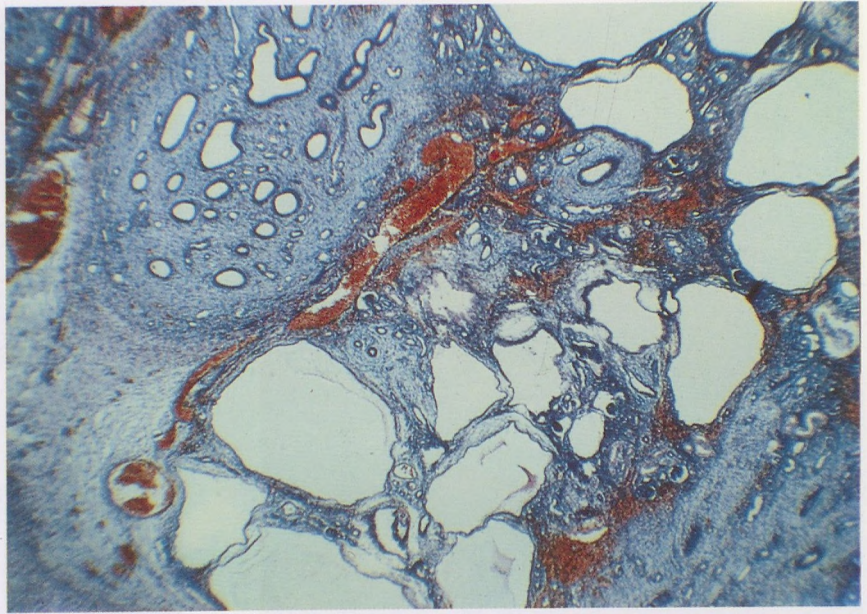
a



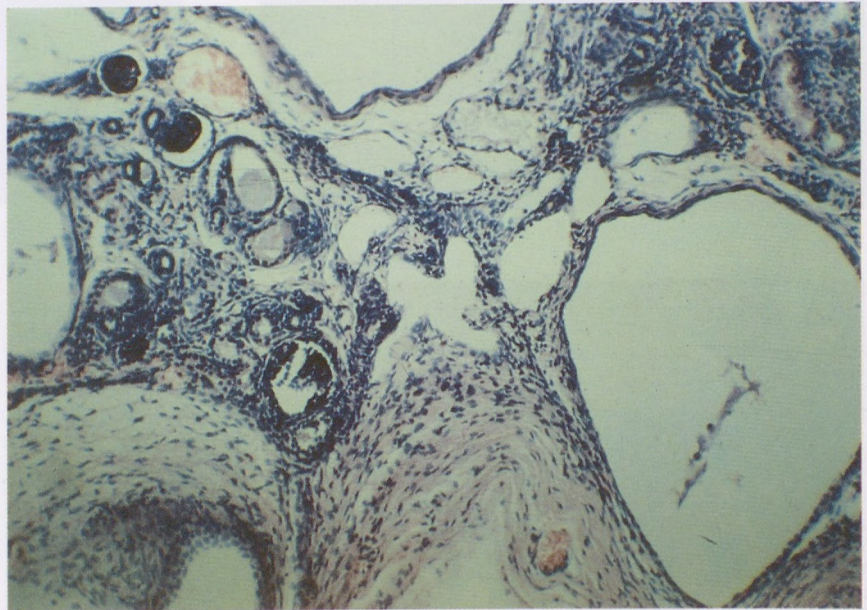
b



Figures 8-12a and b. Type II cystic kidney: (a) to show cysts lined by thickened connective tissue, and scattered glomeruli (HE, x200); (b) part of a giant cyst with dysplastic tubules (HE, x200).

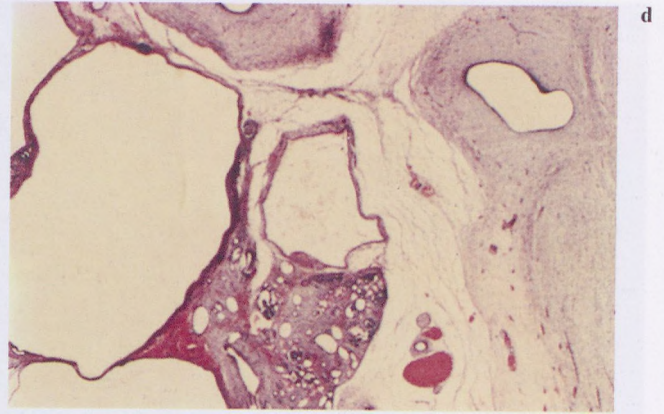
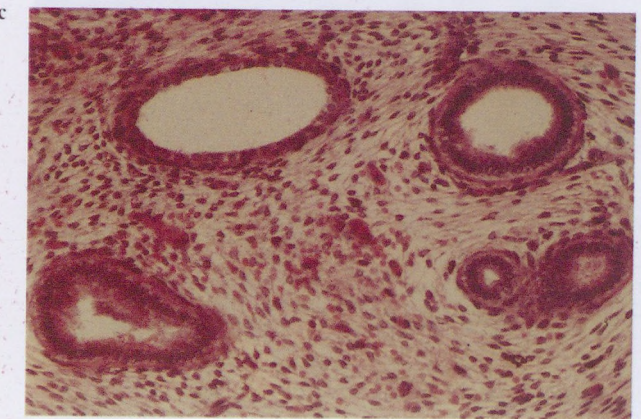
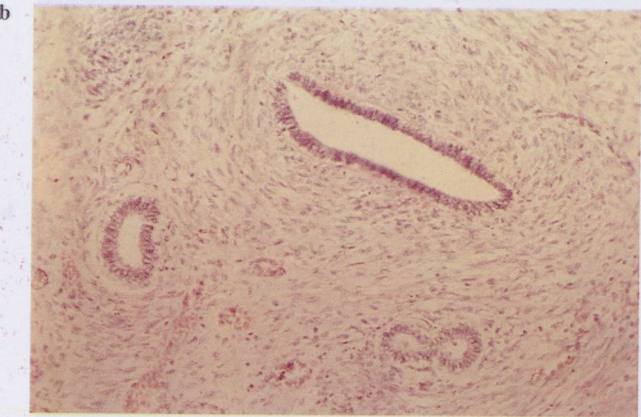
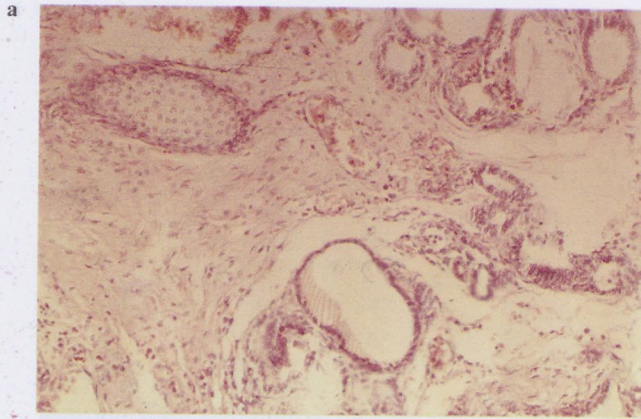


a



b

Figures 8-13a and b. Type II cystic kidney at a higher magnification: between the cysts there are groups of small dysplastic tubules, and glomeruli at different stages of development (HE, x200).

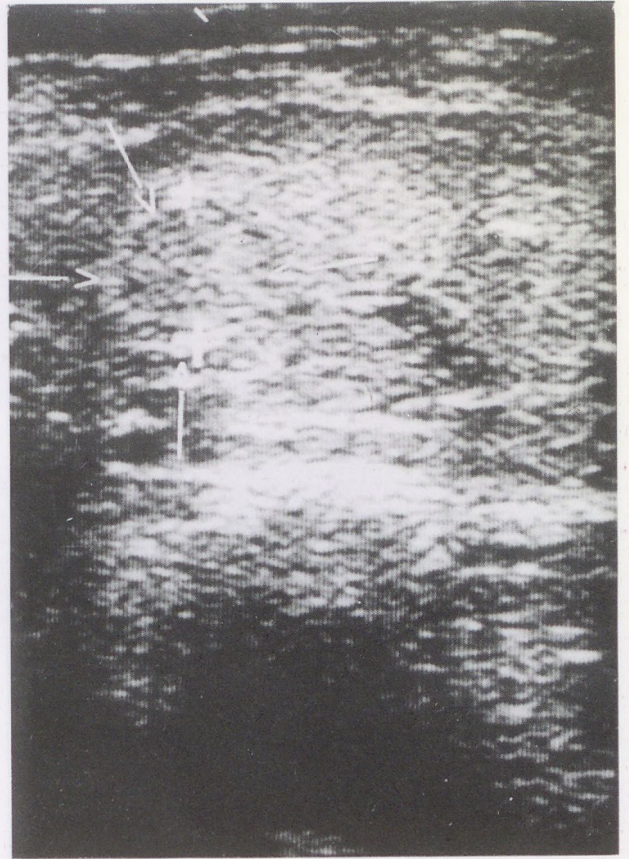


Figures 8-14a, b, c and d. Type II dysplastic kidney: (a and b) primitive ducts lined with columnar epithelium and surrounded by mesenchyma (HE, x200); (c) at higher magnification (HE, x300); (d) dilated tubules, surrounded by connective tissue (Endes trichrome, x200).

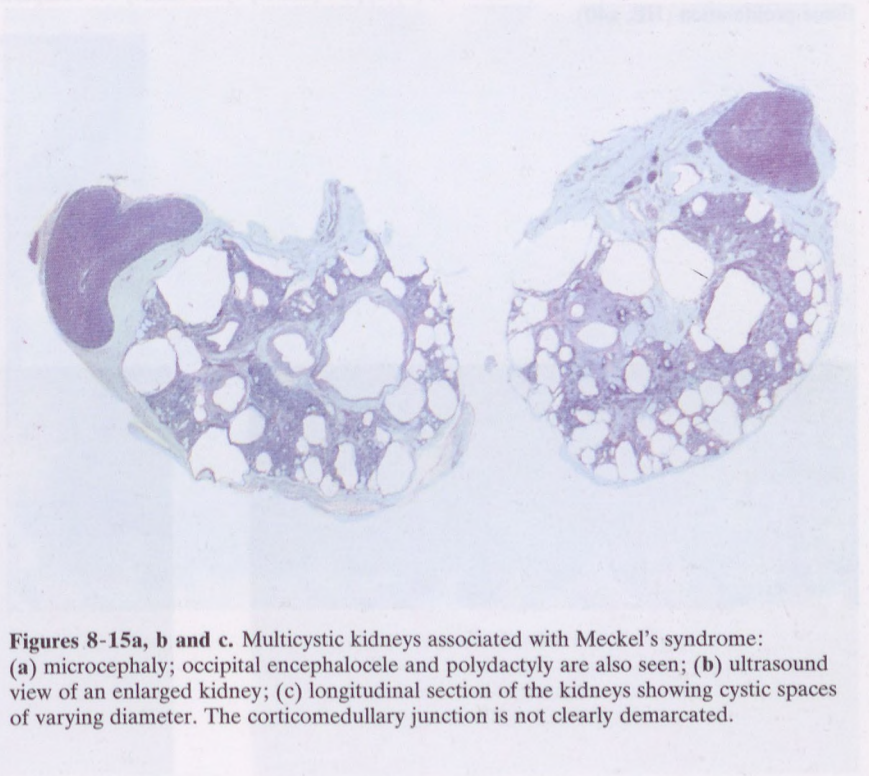
a



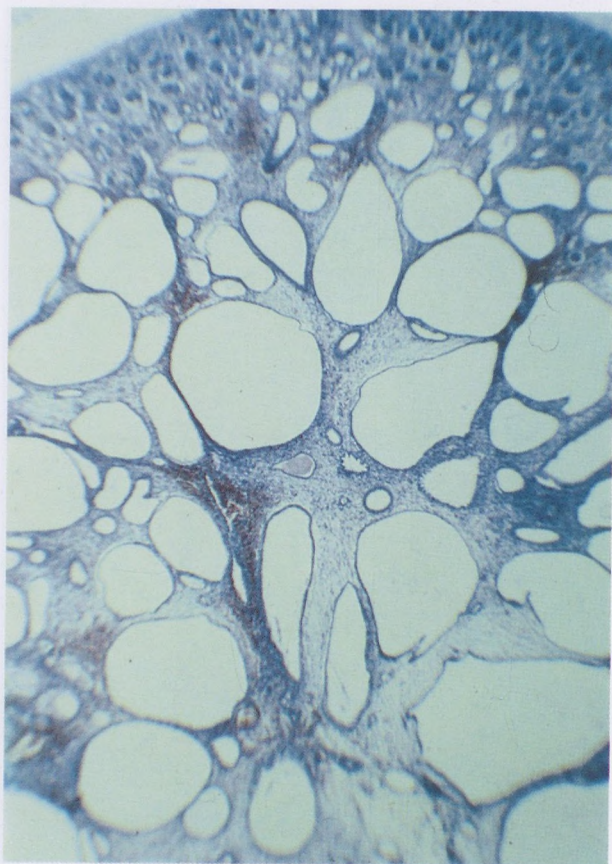
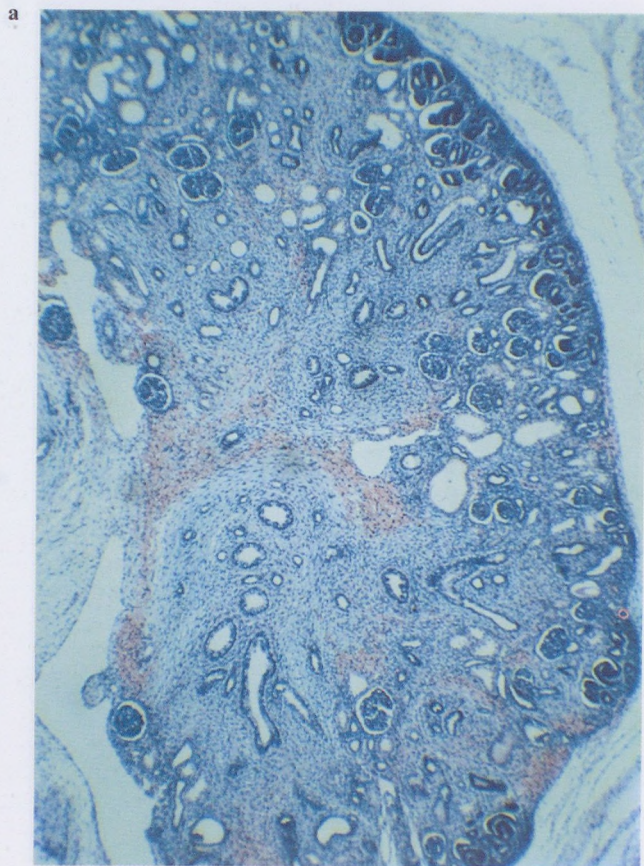
b



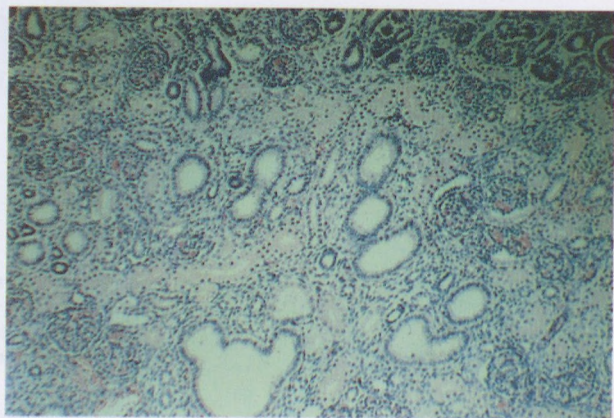
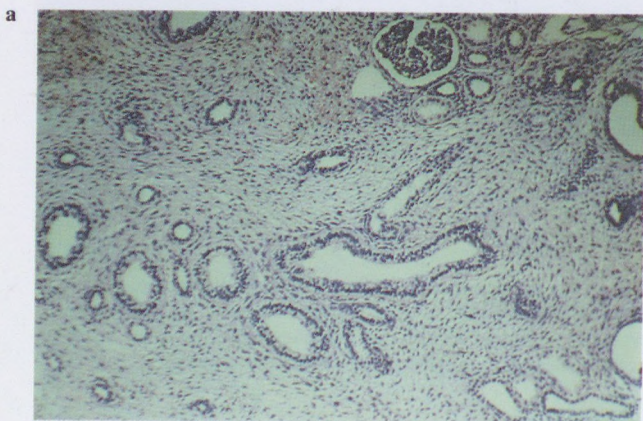
c



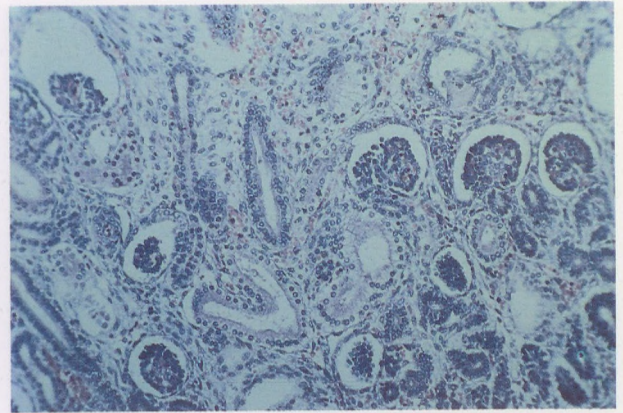
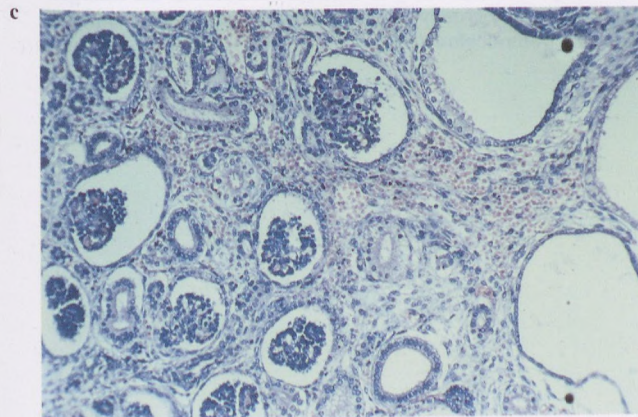
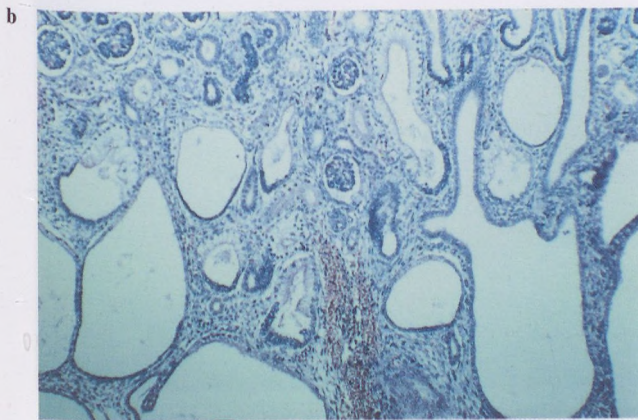
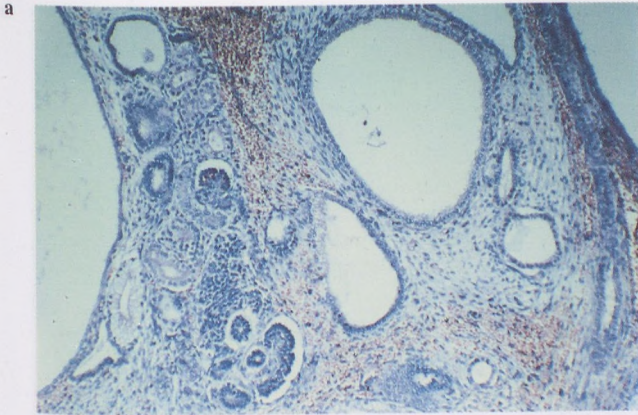
Figures 8-15a, b and c. Multicystic kidneys associated with Meckel's syndrome: (a) microcephaly; occipital encephalocele and polydactyly are also seen; (b) ultrasound view of an enlarged kidney; (c) longitudinal section of the kidneys showing cystic spaces of varying diameter. The corticomedullary junction is not clearly demarcated.



Figures 8-16a and b. Type III (adult) cystic kidney: (a) slightly dilated tubules are scattered throughout the cortex and medulla, intermixed with normal nephrons (HE, x40); (b) Type I (infant) cystic kidney for comparison: numerous small cysts without connective tissue proliferation (HE, x40).



Figures 8-17a and b. Type III cystic kidney: tubular dilatation, early changes (HE, x100).

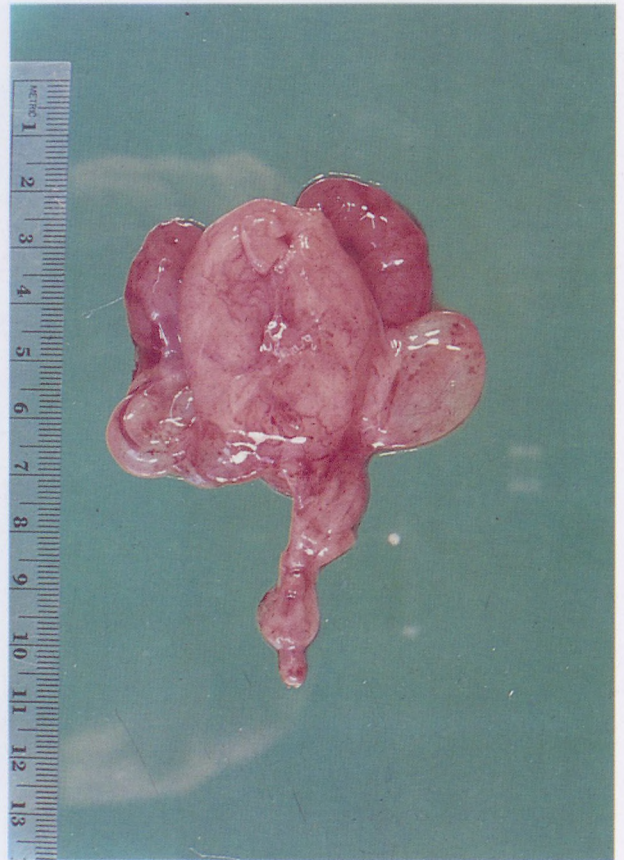


Figures 8-18a, b, c and d. Type III cystic kidney: (a and b) a few glomeruli and some moderately dilated tubules, surrounded by proliferating connective tissue are scattered between the cysts (HE, x100); (c and d) moderately dilated Bowman's capsules, containing glomeruli and a few cystically dilated tubules (HE, x200).

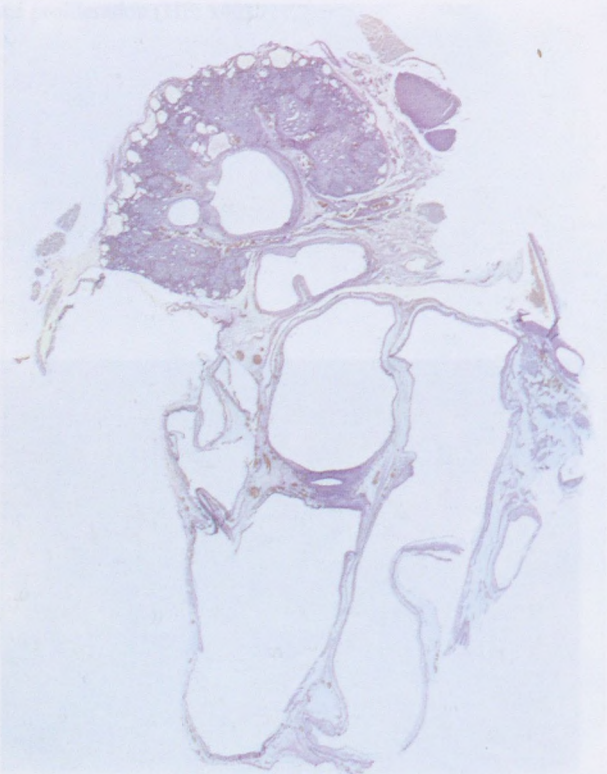
a



b

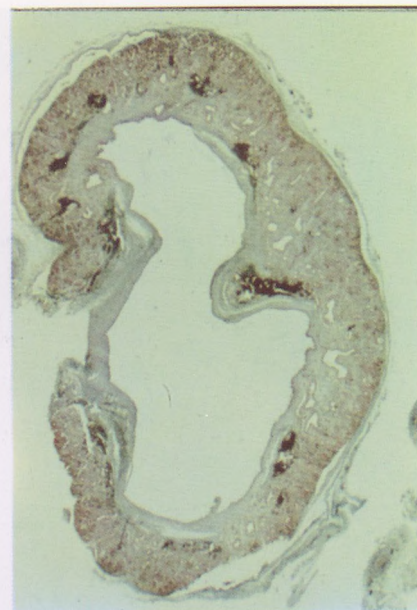
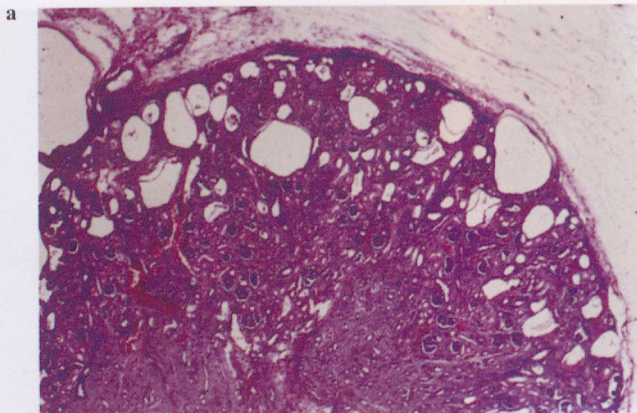


c

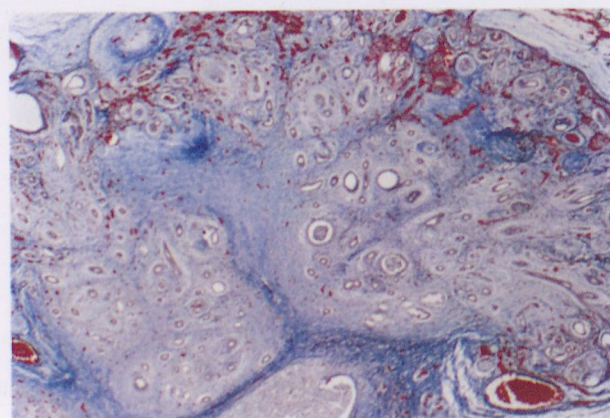
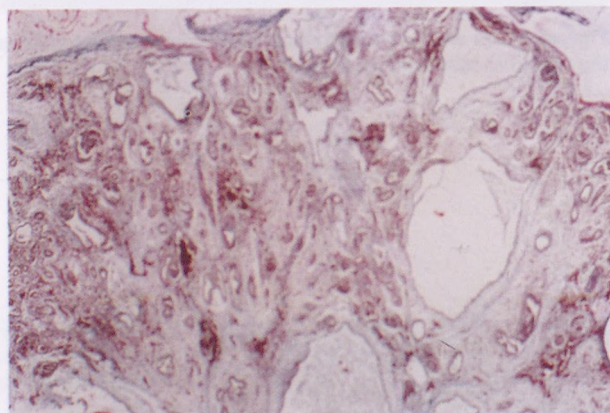


Figures 8-19a and b. Megacystis in mid-trimester fetus with enormously distended abdomen and with bilateral talipes (**a**); hydronephrosis secondary to urethral obstruction: the enlarged bladder and the grossly dilated ureters lie between the kidneys, and the urethra below (**b**).

Figure 8-19c. Transverse section of hydronephrotic kidney showing subcapsular cysts and dilated ureter (Potter type IV).

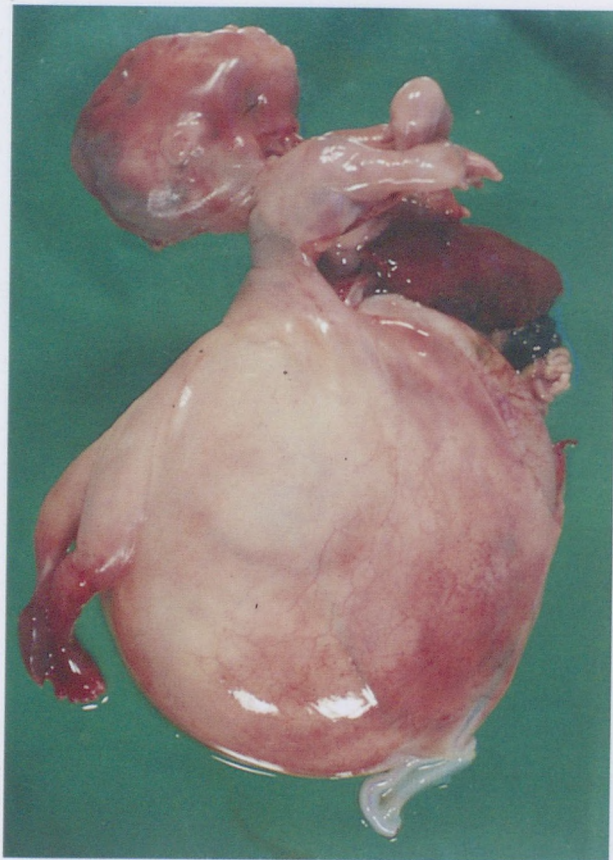


Figures 8-20a and b. Type IV dysplastic kidney: scattered small cysts in the subcapsular layer, and normal nephrons (HE, x40) (a); hydronephrosis, original magnification: dilated renal pelvis and atrophied parenchyma (b).

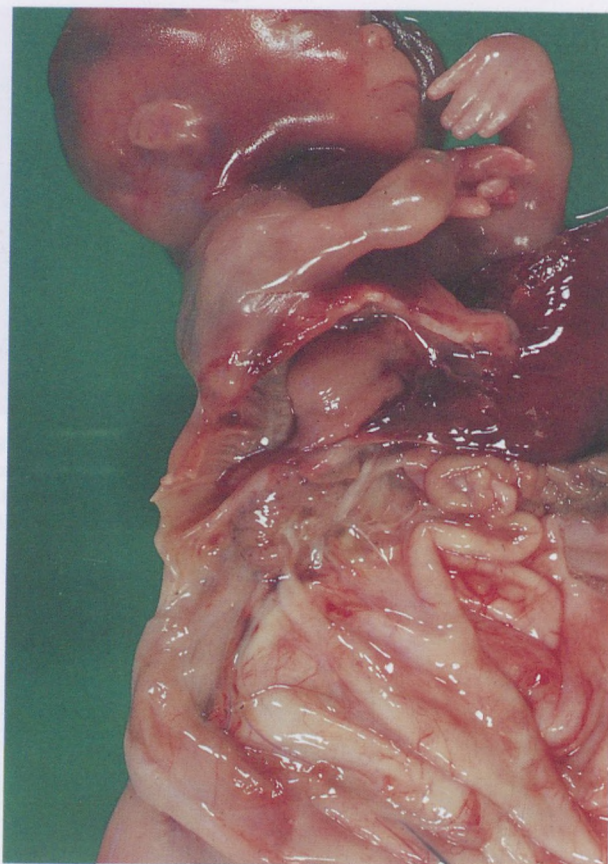


Figures 8-21a and b. Type IV dysplastic kidney: small subcapsular cysts with thickened connective tissue wall (Endes trichrome, x100).

a



b



Figures 8-22a and b. Grossly enlarged bladder associated with urethral atresia (a); internal surface of the grossly enlarged bladder: the rugosities mimic cerebral gyri (b).

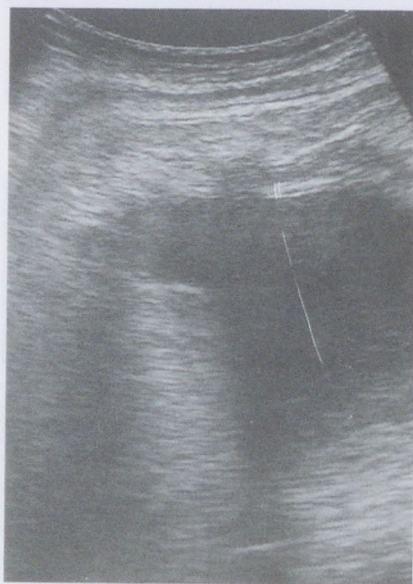


Figure 8-23a. The fetal bladder is markedly enlarged in a case of urethral obstruction (ultrasound view).

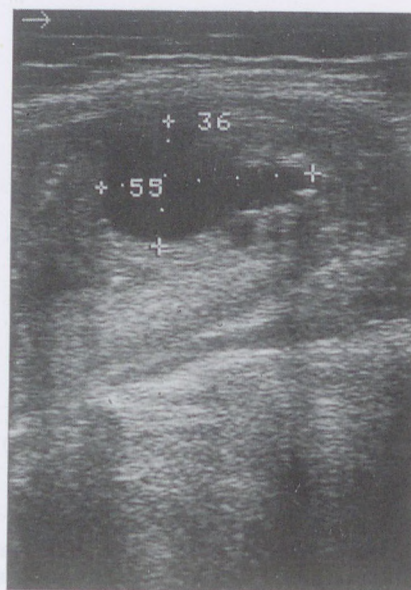
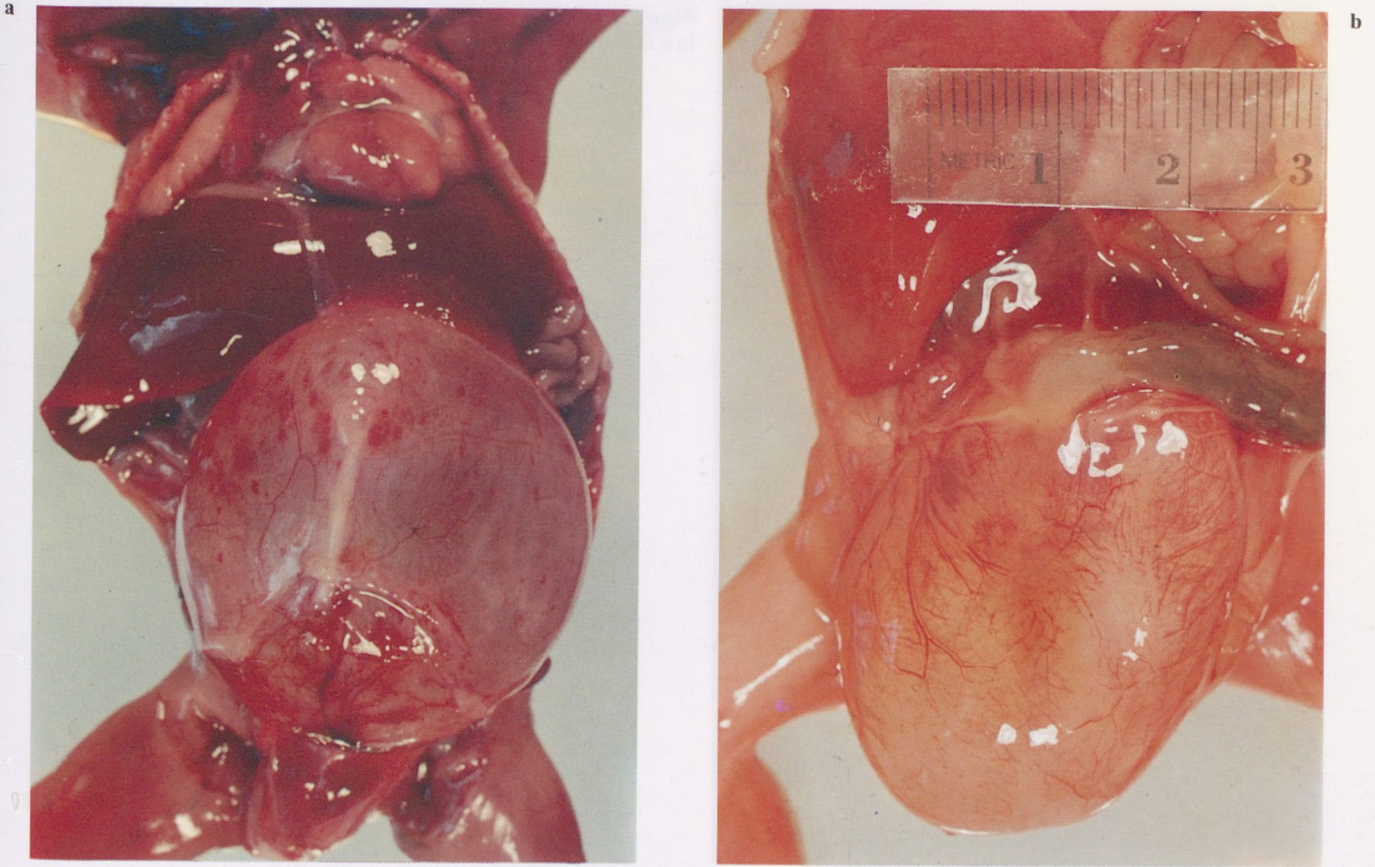
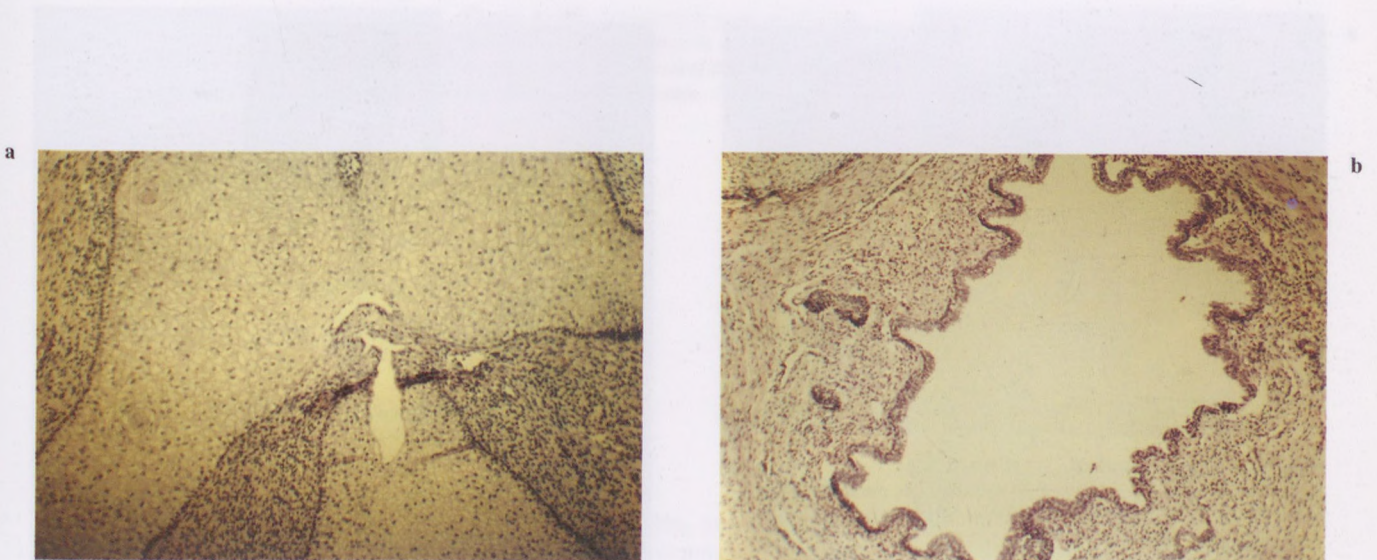


Figure 8-23b. Extreme dilatation of the bladder and complete absence of amniotic fluid in urethral obstruction (ultrasound view).



Figures 8-24a and b. Grossly enlarged bladder associated with urethral stenosis in mid-trimester fetus.



Figures 8-25a and b. Urethral stenosis: (a) irregular narrowing of the urethra (HE, x100); (b) dilated section of urethra from above the obstruction (HE, x100).



Figure 8-26. Urethral obstruction due to posterior urethral valve in a mid-trimester fetus.



Figures 8-27a and b. Prune-belly syndrome: (a) with associated renal tract malformations; neonatal death; (b) with characteristic asymmetrical protrusion of the lower abdominal wall and cryptorchidism.

Figure 8-28. Grossly dilated bladder in an 18-week-old fetus with megacystis, microcolon and intestinal hypoperistalsis syndrome.

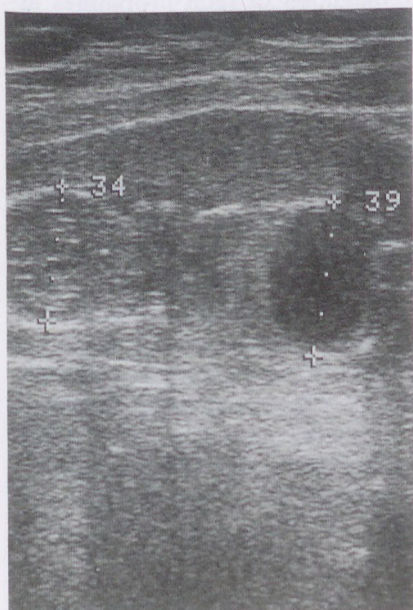


Figure 8-29a. Ultrasound view of extreme dilatation of the bladder in a case of megacystis, microcolon and intestinal hypoperistalsis syndrome.

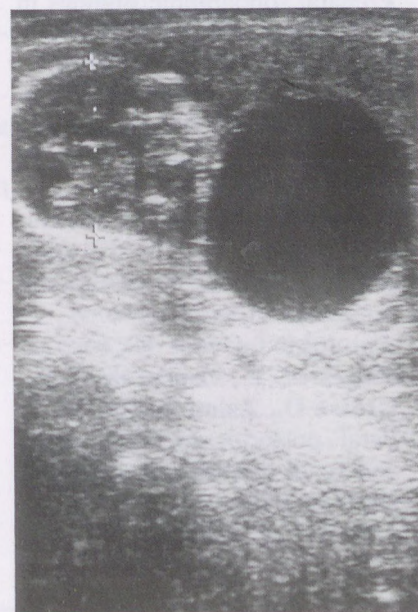


Figure 8-29b. Megacyst occupying the whole fetal abdomen. The fetal head is also visible on the right side (ultrasound view).

References

- Ahmed S., Lequesne G. W.** (1988)
Urological anomalies detected on antenatal ultrasound. A 9-year review.
Aust. Paediatr. J. 24, 178-183.
- Avni E. F., Rodesch F., Schulman C. C.** (1985)
Fetal uropathies. Diagnostic pitfalls and management.
J. Urol. 134, 921-925.
- Avni E. F., Thoua Y., Lalmand B., Didier F., Droulle P., Schulman C. C.** (1987)
Multicystic dysplastic kidney. Natural history from in utero diagnosis and postnatal follow-up.
J. Urol. 138, 1420-1424.
- Barakat A. Y., Awazu M., Fleischer A. C.** (1989)
Antenatal diagnosis of renal abnormalities. A review of the state of the art.
South. Med. J. 82, 229-234.
- Barth R. A., Filly R. A., Sondheim R. F. K.** (1990)
Prenatal sonographic findings in bladder exstrophy.
J. Ultrasound Med. 9, 359-361.
- Bear C. J., McManamon P., Morgan J., Payne R. H., Lewis H., Gault M. H., Churchill D. N.** (1984)
Age at clinical onset and at ultrasonographic detection of adult polycystic kidney disease: Data for genetic counseling.
Am. J. Med. Genet. 18, 45-53.
- Bellinger M. F., Comstock C. H., Grosso D., Zaino R.** (1983)
Fetal posterior urethral valves and renal dysplasia at 15 weeks gestational age.
J. Urol. 129, 1238-1239.
- Bernaschek G., Schaller A.** (1987)
On the prenatal diagnosis of the sequelae of supraventricular stenoses. Hydronephrosis and hydroureter.
Z. Geburtshilfe Perinatol. 19, 15-20.
- Bowie J. D., Rosenberg E. R., Andreotti R. F., Fields S. I.** (1983)
The changing sonographic appearance of fetal kidneys during pregnancy.
J. Ultrasound Med. 2, 505-507.
- Bronshtein M., Kushnir O., Benrafael Z., Shalev E., Nebel L., Mashiach S., Shalev J.** (1990)
Transvaginal sonographic measurement of fetal kidneys in the 1st trimester of pregnancy.
J. Clin. Ultrasound 18, 302-306.
- Bronshtein M., Yoffe N., Brandes J. M., Blumenfeld Z.** (1990)
1st and early 2nd trimester diagnosis of fetal urinary-tract anomalies using transvaginal sonography.
Prenat. Diagn. 10, 653-666.
- Bulic M., Podobnik M., Korenec B., Bistricki J.** (1987)
First-trimester diagnosis of low obstructive uropathy: An indicator of initial renal function in the fetus.
J. Clin. Ultrasound 15, 537-541.
- Campbell A. F.** (1988)
Multicystic dysplastic kidney and contralateral renal aplasia in a twin. Diagnosis by prenatal sonography.
A. J. R. 151, 145-146.
- Cass A., Smith S., Godec C., Veeraghavan K., Tsai S., Bendel R.** (1981)
Prenatal diagnosis of fetal urinary tract abnormalities by ultrasound.
Urology 18, 197-202.
- Colodny A. H.** (1987)
Antenatal diagnosis and management of urinary abnormalities.
Pediatr. Clin. North Am. 34, 1365-1381.
- Dalton M., Romero R., Grannum P., Depalma L., Jeanty P., Hobbins J. C.** (1986)
Antenatal diagnosis of renal anomalies with ultrasound. 4. Bilateral multicystic kidney disease.
Am. J. Obstet. Gynecol. 154, 532-537.
- Deutinger J., Bernaschek G., Gherardini G., Schatten Ch.** (1986)
Fetal megacystis. Prenatal diagnosis and attempt at treatment.
Z. Geburtshilfe Perinatol. 190, 168-171.
- DeWolf D., Keuppens F., Temmerman M., Verboven M., DeNeyer M., Delree M., Sacre-Smits L.** (1989)
Antenatal diagnosis of urological disorders by ultrasound. A critical review.
Eur. J. Pediatr. 149, 62-64.
- Drugan A., Zador I. E., Bhatia R. K., Sacks A. J., Evans M. I.** (1989)
1st trimester diagnosis and early in utero treatment of obstructive uropathy.
Acta Obstet. Gynecol. Scand. 68, 645-649.
- Duval J. M., Milon J., Coadou Y., Blouet J. M., Langella B., Bourgin T., Nicolas J. C., Fremont B., Duval J. C., Jouan H.** (1985)
Ultrasonographic anatomy and diagnosis of fetal uropathies affecting the upper urinary tract. 1. Obstructive uropathies.
Anat. Clin. 7, 301-332.
- Duval J. M., Milon J., Coadou Y., Blouet J. M., Langella B., Bourgin T., Nicolas J. C., Fremont B., Duval J. C., Jouan H.** (1986)
Ultrasonographic anatomy and diagnosis of fetal uropathies affecting the upper urinary tract. 2. Non-obstructive uropathies.
Surg. Radiol. Anat. 8, 131-145.
- Edwards O. P., Baldinger S.** (1989)
Prenatal onset autosomal dominant polycystic kidney disease.
Urology 34, 265-270.

- Farrel S. A.** (1988)
Intrauterine death in megacystis-microcolon-intestinal hypoperistalsis syndrome.
J. Med. Genet. 25, 350-351.
- Feige A., Fiedler K., Rempen A., Osterhage H. R.** (1984)
Prenatal diagnosis of prune-belly syndrome in siblings in 2 consecutive pregnancies.
Z. Geburtshilfe Perinatol. 188, 239-243.
- Fisk N. M., Dhillon H. K., Ellis C. E., Nicolini U., Tannirandorn Y., Rodeck C. H.** (1990)
Antenatal diagnosis of megalourethra in a fetus with the prune belly syndrome.
J. Clin. Ultrasound 18, 124-128.
- Fitzsimons R. B., Keohane C., Galvin J.** (1985)
Prune belly syndrome with ultrasound demonstration of reduction of megacystis in utero.
Br. J. Radiol. 58, 374-376.
- Fong K. W., Rahmani M. R., Rose T. H., Skidmore M. B., Connor T. P.** (1986)
Fetal renal cystic disease. Sonographic-pathologic correlation.
A. J. R. 146, 767-773.
- Fourcroy J. L., Blei C. L., Glassman L. M., White R.** (1983)
Prenatal diagnosis by ultrasonography of genitourinary abnormalities.
Urology 22, 223-229.
- Fryns J. P., Van der Berghe K., Moerman F.** (1986)
Mid-trimester ultrasonographic diagnosis of early manifesting adult form of polycystic kidney disease.
Hum. Genet. 74, 461-461.
- Garrett W. J., Warren P. S., Fisher C. C.** (1984)
Ultrasound in the diagnosis and management of urinary tract disorders in the fetus.
Ultrasound Med. Biol. 10, 473-483.
- Glazer G. M., Filly R. A., Callen P. W.** (1982)
The varied sonographic appearance of the urinary tract in the fetus and newborn with urethral obstruction.
Radiology 144, 563-568.
- Gnirs J., Boos R., Waldherr R., Schmidt W.** (1988)
Prune-belly syndrome: Prenatal diagnosis and obstetric procedure.
Z. Geburtshilfe Perinatol. 192, 114-121.
- Golbus M. S., Harrison M. R., Filly R. A.** (1983)
Prenatal diagnosis and treatment of fetal hydronephrosis.
Semin. Perinatol. 7, 102-108.
- Gruenewald S. M., Cohen R. C., Antico V. F., Farlow D. C., Cass D. T.** (1990)
Diagnosis and treatment of antenatal uropathies.
J. Paediat. C. 26, 142-147.
- Gruenewald S. M., Crocker E. F., Walker A. G., Trudinger B. J.** (1984)
Antenatal diagnosis of urinary tract abnormalities: Correlation of ultrasound appearance with postnatal diagnosis.
Am. J. Obstet. Gynecol. 148, 278-283.
- Grupe W. E.** (1987)
The dilemma of intrauterine diagnosis of congenital renal disease.
Pediatr. Clin. North Am. 34, 629-638.
- Hadlock F. P., Deter R. L., Carpenter R., Gonzalez E. T., Park S. K.** (1981)
Sonography of fetal urinary tract anomalies.
A. J. R. 137, 261-267.
- Hadlock F. P., Deter R. L., Carpenter R. J.** (1984)
Sonography of the fetal genitourinary tract.
Semin. Ultrasound 5, 213-228.
- Hanbury D. C., Whitaker R. H., Tudor J., Dixon A. K., Wraight E. P.** (1989)
Maps for diagnosis and management of antenatal urinary tract dilatation.
Br. J. Urol. 64, 221-226.
- Harrison M. R., Golbus M. S., Filly R. A.** (1991)
The unborn patient.
W. B. Saunders, Philadelphia.
- Hausler M., Hofmann H. M. H., Schaffer M., Hofer P., Rollett H., Ring E., Ipsiroglu O. S.** (1989)
The value of prenatal ultrasound screening as exemplified by urinary tract malformations. Data of the Styrian Malformation Register 1985 to 1987.
Wien. Klin. Wochenschr. 101, 346-350.
- Hayden S. A., Russ P. D., Pretorius D. H., Manco-Johnson M. L., Clewell W. H.** (1988)
Posterior urethral obstruction. Prenatal sonographic findings and clinical outcome in 14 cases.
J. Ultrasound Med. 7, 371-375.
- Helin I., Persson P. H.** (1983)
Prenatal diagnosis of urinary tract abnormalities by ultrasound.
Eur. J. Pediatr. 140, 175-175.
- Hobbins J. C., Romero R., Granum P. A. T., Berkowitz R. L., Cullen M., Mahoney M. J.** (1984)
Antenatal diagnosis of renal anomalies with ultrasound. I. Obstructive uropathy.
Am. J. Obstet. Gynecol. 148, 868-877.
- Hodgkinson K. A., Kerzinstomar L., Watters E. A., Harris R.** (1990)
Adult polycystic kidney disease. Knowledge, experience, and attitudes to prenatal diagnosis.
J. Med. Genet. 27, 552-558.

- Hoffmann H., Chaoui R., Bollmann R., Halle Von H., Zeinert A.** (1990)
Prenatal application of pulsed Doppler ultrasonography in differential diagnosis of bilateral fetal kidney malformations. *Geburtshilfe Frauenheilkd.* 50, 203-206.
- Hunt G. M., Whitaker R. H.** (1987)
The pattern of congenital renal anomalies associated with neural tube defects. *Dev. Med. Child Neurol.* 29, 91-95.
- Hurwitz A., Yagel S., Rabinovitz R., Mogle P.** (1984)
Hydramnios caused by pure megacystis. *J. Clin. Ultrasound* 12, 110-111.
- Journel H., Guyot C., Barc R. M., Belbeoch P., Quemener A., Jouan H.** (1989)
Unexpected ultrasonographic prenatal diagnosis of autosomal dominant polycystic kidney disease. *Prenat. Diagn.* 9, 663-671.
- Kangarloo H., Fine R. N.** (1983)
Ultrasonography of cystic renal dysplasia. *Int. J. Pediatr. Nephrol.* 4, 205-209.
- Kaplan P., Jaffe R., Schoenfeld A., Ovadia J.** (1990)
Sonographic findings in the prenatal diagnosis of bladder exstrophy. *Am. J. Obstet. Gynecol.* 162, 675-678.
- King L. R., Hatcher P. A.** (1990)
Natural history of fetal and neonatal hydronephrosis. *Urology* 35, 433-438.
- Kleiner B., Callen P. W., Filly R. A.** (1987)
Sonographic analysis of the fetus with ureteropelvic junction obstruction. *A. J. R.* 148, 359-363.
- Kleiner B., Filly R. A., Mack L., Callen P. W.** (1986)
Multicystic dysplastic kidney. Observations of contralateral disease in the fetal population. *Radiology* 161, 27-29.
- Main D., Mennuti M. T., Cornfeld D., Coleman B.** (1983)
Prenatal diagnosis of adult polycystic kidney disease. *Lancet* 2, 337-338.
- Maizels M., Zaontz M. R., Firlit C. F.** (1990)
Role of in-office ultrasonography in screening infants and children for urinary obstruction. *Urol. Clin. North Am.* 17, 429-435.
- Mandell J., Peters C. A., Retik A. B.** (1990)
Current concepts in the perinatal diagnosis and management of hydronephrosis. *Urol. Clin. North Am.* 17, 247-262.
- Martin J. J., Taylor E. S.** (1981)
Diagnosis of bilateral hydronephrosis in utero by ultrasonography. *Urology* 17, 272-273.
- McHugo J. M., Shafi M. I., Rowlands D., Weaver J. B.** (1988)
Prenatal diagnosis of adult polycystic kidney disease. *Br. J. Radiol.* 61, 1072-1074.
- Meizner I., Barziv J.** (1985)
Prenatal ultrasonic diagnosis of cloacal exstrophy. *Am. J. Obstet. Gynecol.* 153, 802-803.
- Meizner I., Barziv J., Katz M.** (1985)
Prenatal ultrasonic diagnosis of the extreme form of prune belly syndrome. *J. Clin. Ultrasound* 13, 581-583.
- Melson G. L., Shackelford G. D., Cole B. R., McClennan B. L.** (1985)
The spectrum of sonographic findings in infantile polycystic kidney disease with urographic and clinical correlations. *J. Clin. Ultrasound* 13, 113-119.
- Mirk P., Calisti A., Fileni A.** (1986)
Prenatal sonographic diagnosis of bladder exstrophy. *J. Ultrasound Med.* 5, 291-293.
- Murphy J. L., Mendoza S. A., Griswold W. R., Reznik V. M.** (1989)
Severe bilateral renal disease. Correlation of antenatal and autopsy findings. *Prenat. Diagn.* 9, 119-125.
- Murugasu B., Yip W. C. L., Tay J. S. H., Kit-Yee C., Hui-Kim Y., Hock-Boon W.** (1990)
Sonographic screening for renal tract anomalies associated with congenital heart disease. *J. Clin. Ultrasound* 18, 79-83.
- Oesch I., Jann X., Bettex M.** (1982)
Ultrasonographic antenatal detection of obstructed bladder. *Eur. Urol.* 8, 78-81.
- Orvis B. R., Bottles K., Kogan B. A.** (1988)
Testicular histology in fetuses with the prune belly syndrome and posterior urethral valves. *J. Urol.* 139, 335-337.
- Patten R. M., Mack L. A., Wang K. Y., Cyr D. R.** (1990)
The fetal genitourinary tract. *Radiol. Clin. North Am.* 28, 115-130.
- Petrikovsky B. M., Walzak M. P., Daddario P. F.** (1988)
Fetal cloacal anomalies. Prenatal sonographic findings and differential diagnosis. *Obstet. Gynecol.* 72, 464-469.
- Potter E. L., Craig J. M.** (1976)
Pathology of the Fetus. Year Book Medical Publ. Inc. Lloyd Luke (Medical Books), London
- Pretorius D. H., Lee M. E., Manco-Johnson M. L., Weingast G. R., Sedman A. B., Gabow P. A.** (1987)
Diagnosis of autosomal dominant polycystic kidney disease in utero and in the young infant. *J. Ultrasound Med.* 6, 249-255.
- Quinlan R. W., Cruz A. C., Huddleston J. F.** (1986)
Sonographic detection of fetal urinary tract anomalies. *Obstet. Gynecol.* 67, 558-565.

- Rempen A.** (1990)
Spontaneous regression of fetal megacystis in the 1st trimester.
Z. Geburtshilfe Perinatol. 194, 179-181.
- Rempen A., Feige A., Osterhage H. R., Fiedler K.** (1986)
Prenatal diagnosis and postnatal course in malformations of the kidneys and urinary tract.
Geburtshilfe Frauenheilkd. 46, 366-374.
- Reuss A., DenHollander J. C., Niermeijer M. F., Wladimiroff J. W., Van Diggelen O. P., Lindhout D., Los F. J.** (1989)
Prenatal diagnosis of cystic kidney disease with ventriculomegaly. A report of 6 cases in 2 related sibships.
Am. J. Med. Genet. 33, 385-389.
- Reuss A., Wladimiroff J. W., Scholtmeijer R. J., Stewart P. A., Sauer P. J. J., Niermeijer M. F.** (1988)
Prenatal evaluation and outcome of fetal obstructive uropathies.
Prenat. Diagn. 8, 93-102.
- Reuss A., Wladimiroff J. W., Stewart P. A., Niermeijer M. F.** (1990)
Prenatal diagnosis by ultrasound in pregnancies at risk for autosomal recessive polycystic kidney disease.
Ultrasound Med. Biol. 16, 355-359.
- Reznik V. M., Kaplan G. W., Murphy J. L., Packer M. G., Boychuck D., Griswold W. R., Leopold G. R., Mendoza S. A.** (1988)
Follow-up of infants with bilateral renal disease detected in utero. Growth and renal function.
Am. J. Dis. Child. 142, 453-456.
- Ring E., Petritsch P., Riccabona M., Zobel G., Vilits P.** (1990)
Management and outcome of prenatally recognized urinary tract malformations.
Wien. Klin. Wochenschr. 102, 463-466.
- Rizzo N., Gabrielli S., Pilu G., Perolo A., Cacciari A., Domini R., Bovicelli L.** (1987)
Prenatal diagnosis and obstetrical management of multicystic dysplastic kidney disease.
Prenat. Diagn. 7, 109-118.
- Romero R., Cullen M., Jeanty P., Grannum P., Reece E. A., Venus I., Hobbins J. C.** (1984)
The diagnosis of congenital renal anomalies with ultrasound. 2. Infantile polycystic kidney disease.
Am. J. Obstet. Gynecol. 150, 259-262.
- Rosendahl H.** (1990)
Ultrasound screening for fetal urinary tract malformations. A prospective study in general population.
Eur. J. Obstet. Gynecol. 36, 27-33.
- Scott J. E. S.** (1985)
Management of congenital posterior urethral valves.
Br. J. Urol. 57, 71-77.
- Scott J. E. S., Renwick M.** (1988)
Antenatal diagnosis of congenital abnormalities in the urinary tract. Result from the Northern region fetal abnormality survey.
Br. J. Urol. 62, 295-300.
- Seeds J. W., Mandell J.** (1986)
Congenital obstructive uropathies. Prenatal and postnatal treatment.
Urol. Clin. North Am. 13, 155-165.
- Selvaggi L., Loverro G., Pace G., Bettocchi C., Selvaggi F. P.** (1985)
The role of prenatal diagnosis in the perinatal management of urinary tract abnormalities.
J. Perinat. Med. 13, 79-85.
- Shalev J., Itzhak Y., Hertz M., Strauss S., Avigad I., Serr D. M.** (1983)
Antenatal ultrasound appearance of megacystis microcolon intestinal hypoperistalsis syndrome.
Isr. J. Med. Sci. 19, 76-78.
- Shenker L., Anderson C.** (1982)
Intrauterine diagnosis and management of fetal polycystic kidney disease.
Obstet. Gynecol. 59, 385-389.
- Shih W. J., Greenbaum L. D., Baro C.** (1982)
In utero sonogram in prune belly syndrome.
Urology 20, 102-105.
- Silver R. K., MacGregor S. N., Cook W. A., Sholl J. S.** (1990)
Fetal posterior urethral valve syndrome. A prospective application of antenatal prognostic criteria.
Obstet. Gynecol. 76, 951-955.
- Smedley M. G., Bailey R. R.** (1987)
Autosomal dominant polycystic kidney disease diagnosed in utero using ultrasonography.
N. Z. Med. J. 100, 606-606.
- Smith F. G., Robillard J. E.** (1989)
Pathophysiology of fetal renal disease.
Semin. Perinatol. 13, 305-319.
- Steele B. T., Demaria J., Toi A., Stafford A., Hunter D., Caco C.** (1987)
Neonatal outcome of fetuses with urinary tract abnormalities diagnosed by prenatal ultrasonography.
Can. Med. Assoc. J. 137, 117-120.
- Stiller R. J.** (1989)
Early ultrasonic appearance of fetal bladder outlet obstruction.
Am. J. Obstet. Gynecol. 160, 584-585.
- Sweeney I., Kang B. H., Lin P., Giovannello J.** (1981)
Posterior urethral obstruction caused by congenital posterior urethral valve.
N. Y. State J. Med. 81, 87-89.

- Thomas D. F. M., Gordon A. C.** (1989)
Management of prenatally diagnosed uropathies.
Arch. Dis. Child. 64, 58-63.
- Toma P., Lituanina M. A.** (1984)
Urinary tract malformations. Prenatal diagnosis and neonatal follow-up by monography.
Ann. Radiol. 27, 215-222.
- Turnock R. R., Shawis R.** (1984)
Management of fetal urinary tract anomalies detected by prenatal ultrasonography.
Arch. Dis. Child. 59, 962-965.
- Waldherr R., Zerres K., Gall A., Enders H.** (1989)
Polycystic kidney disease in the fetus.
Lancet 2, 274-275.
- Warshaw B. L., Hymes L. C., Trulock T. S., Woodard J. R.** (1985)
Prognostic features in infants with obstructive uropathy due to posterior urethral valves.
J. Urol. 133, 240-243.
- Wernecke K., Heckemann R., Bachmann H., Peters P. E.** (1985)
Sonography of infantile polycystic kidney disease.
Urol. Radiol. 7, 138-145.
- Willard D. A., Gabriele O. F.** (1986)
Megacystis-microcolon-intestinal hypoperistalsis syndrome in a male infant.
J. Clin. Ultrasound 14, 481-485.
- Woodard J. R.** (1990)
The impact of fetal diagnosis on the management of obstructive uropathy.
Postgrad. Med. 66, 37-43.
- Workman S. J., Kogan B. A.** (1990)
Fetal bladder histology in posterior urethral valves and the prune belly syndrome.
J. Urol. 144, 337-339.
- Young I. D., McKeever P. A., Brown L. A., Lang G. D.** (1989)
Prenatal diagnosis of the megacystis-microcolon-intestinal hypoperistalsis syndrome.
J. Med. Genet. 26, 403-406.
- Young L. W., Yunis E. J., Girdany B. R., Sieber W. K.** (1981)
Megacystis-microcolon-intestinal hypoperistalsis syndrome: Additional clinical, radiologic, surgical, and histopathologic aspects.
A. J. R. 137, 749-755.
- Zerres K., Hansmann M., Mallmann R., Gembruch U.** (1988)
Autosomal recessive polycystic kidney disease. Problems of prenatal diagnosis.
Prenat. Diagn. 8, 215-229.

Skeletal Dysplasias and Limb Defects

The limbs begin to appear towards the end of the fourth week as slight elevations of the ventrolateral body wall. The upper limb buds develop slightly before the lower limb buds. The tissues of the limb buds derive from two main sources: somatic mesoderm and ectoderm. Initially, the developing limbs are directed caudally; later, they project ventrally, and finally they rotate on their longitudinal axes. The upper and lower limbs rotate in opposite directions and to different degrees.

This Chapter deals with skeletal dysplasias and limb deficiencies which may be detected prenatally. This group of disorders (1) exhibits a wide range of severity; (2) the underlying biochemical defect is generally unknown; (3) the anatomical abnormalities can often be diagnosed on ultrasound. Minor limb defects are relatively common, but major limb malformations are generally rare. Abnormalities of the fingers and toes occur relatively often, but they can usually be corrected surgically. Although minor malformations are as a rule of no serious medical consequence, they may serve as indicators of more serious abnormalities; i.e., they may be part of a specific pattern of malformation syndrome. The main characteristics of some of the most important skeletal dysplasias and sequences associated with ossification disturbances are given in the Table.

Long bone biometry has been extensively used in predicting gestational age. Nomograms available for this purpose use the long bone as the independent variable and the esti-

mated fetal age as the dependent variable. For the proper use of these nomograms in pregnancies at high risk of skeletal dysplasias the clinician must know accurately the gestational age of the fetus. Our experience in the prenatal diagnosis of skeletal dysplasias indicates that affected fetuses show dramatic deviations from the 5th and 95th confidence limits. In skeletal dysplasias not only the length, but also the growth rates of the fetal bones are decreased. Therefore, growth rate may be a very sensitive parameter in the early detection of skeletal dysplasias.

The skull and most of the long bones are recognizable from the end of the first trimester, the metacarpals and metatarsals from the 16th week, and the phalanges from the 18th to 19th weeks. Any formation containing calcium (ossification centre) must reach 2 to 3 mm in diameter to become visible on ultrasound. Some of the carpal and tarsal bones remain cartilaginous throughout; the calcaneus and the talus ossify in the fifth and sixth months.

At the base of the cranium the sphenoid, the wing-like formation of the petrous portion of the temporal bone, the occipital bone and certain cranial fossae, and in the splanchnocranium the orbits, the root of the nose, the maxilla and the mandible are recognizable by weeks 16 to 18.

The scapula, clavicle, humerus, radius and ulna, as well as the femur, tibia and fibula, are easily identified. One should remember that the radius and ulna cross one another

when the hand is pronated. The femur is the bone that can be studied and measured with the greatest accuracy. The distal epiphysis of the femur, and the proximal epiphysis of the tibia can be clearly distinguished by the end of pregnancy. Their presence, irrespective of size, is an indication of fetal maturity. The ribs and the pelvis are useful points of orientation. The iliac, ischial and pubic ossification centres are identifiable by the third, fourth and sixth months, respectively.

Topographically the spine is very important. Fortunately, it can be seen in almost all positions of the fetus. In the longitudinal plane it is represented by three series of ossification centres (one anterior and two posterior). The posterior centres run nearly parallel; they are slightly divergent in the upper cervical and the lumbar regions, and converge in the sacral region. Being normally kyphotic, the spine cannot be demonstrated in its full length in a single longitudinal view; the position of the three ossification centres must be examined, in the transverse plane, segment by segment. (Appearance of the ischial ossification centres indicates that the lower end of the spine has been reached.)

If the fetal skeleton cannot be clearly visualized by ultrasound after 14-15 weeks of gestation as a result of under-ossification or the presence of extremely small ossified structures, the following diagnoses should be considered: osteogenesis imperfecta, hypophosphatasia, achondrogenesis and hypochondrogenesis.

Table

Skeletal dysplasias, limb anomalies and other ossification disturbances (*mode of inheritance in parentheses*)

Aarskog syndrome (faciodigitogenital syndrome) (hypertelorism, brachydactyly, cryptorchidism, shawl-like scrotum) (*XD*)

Achondrogenesis (neonatal lethal) (very short limbs, little or no ossification in lower spine and limbs) (*AR*)

Achondroplasia (short limbs, large head, deep nasal root, prominent forehead) (*AD*)

Amelia, hemimelia, hypomelia (usually sporadic, with low recurrence risk both to subsequent sibs and to offspring. Some cases will prove on closer examination to have resulted from amniotic bands (see ADAM complex))

Apert syndrome (acrocephalosyndactyly) (craniosynostosis, turri-cephaly, midface hypoplasia, cleft palate, syndactyly, wide distal phalanx of thumb and hallux) (*AD*)

Arachnodactyly (*AD*)

Arthrogryposis multiplex congenita (*AD, AR, XR*)

Brachydactyly (short fingers and toes) (*AD*)

Branchiootorenal (BOR) dysplasia (preauricular pits, deafness, renal dysplasia) (*AD*)

Campomelic dysplasia (neonatal lethal) (curved tibiae, hypoplastic scapula, flat face) (*AR*)

Camptodactyly (flexion contracture of one or more fingers or toes) (*AD, AR*)

Chondrodysplasia punctata (short humerus and femur, punctate calcification of epiphyses, coronal vertebral clefting) (*AR, AD, XD*)

Clubfoot (talipes) (*multifactorial determination, intrauterine mal-position*)

Cockayne syndrome (premature ageing with microcephaly, retinal degeneration, fine hair, and photosensitive atrophic skin) (*AR*)

Coffin-Lowry syndrome (short palpebral fissures, maxillary hypoplasia, flat nose, tapering fingers, severe mental retardation) (*XD*)

Cornelia de Lange syndrome [microbrachycephaly, synophrys (midline eyebrow fusion), thin upper lip, micromelia, severe growth and developmental retardation, often neonatal/infant death] (usually sporadic)

Diastrophic dysplasia (curved tubular bones, especially the first metacarpal, articular restriction, hypertrophic auricular cartilage) (*AR*)

Dubowitz syndrome (microcephaly, facial dysmorphism, lateral eyebrow deficiency, eczema, growth retardation) (*AR*)

Dysostosis craniofacialis (Crouzon disease) (shallow orbits, exophthalmos, craniosynostosis, maxillary hypoplasia) (*AD*)

Dysostosis mandibulofacialis (Collins-Franceschetti syndrome) (mandibular hypoplasia, downslanting palpebral fissures, lower eyelid defect, malformed external ear) (*AD, AR*)

Ectrodactyly (absent fingers, split hand) (*AD, AR*)

ECP syndrome (ectrodactyly, cleft palate) (*AD*)

EEC syndrome (ectrodactyly, ectodermal dysplasia, cleft lip/palate) (*AD*)

Ehlers-Danlos (ED) syndromes (hyperextensible joints, hyperelastic skin, abnormal scarring; premature delivery, following early spontaneous rupture of the membranes; in some ED syndromes spontaneous rupture of blood vessels, internal organs; eye abnormalities) (*AD, XR, AR*)

Ellis-van Creveld syndrome (chondroectodermal dysplasia) (chondrodysplasia, polydactyly, nail hypoplasia, hypodontia, atrial septal defect) (*AR*)

Goldenhar syndrome (facioauriculovertebral syndrome) (asymmetric/unilateral changes; maxillary and mandibular hypoplasia, small ears, preauricular skin tags and/or pits, vertebral hypoplasia or hemivertebrae) (*AR*)

Hallermann-Streiff syndrome (brachycephaly, microphthalmos, small nose, microstomia, hypotrichosis) (*AR*)

Holt-Oram syndrome (rounded narrow shoulders, radial ray defects—fingerlike or hypoplastic/absent thumb, abnormal carpus, and congenital heart defects—atrial/ventricular septal defect) (*AD*)

Ivemark syndrome (midline defects: asplenia, malposition of abdominal/thoracic organs, cardiovascular anomalies) (*AR*)

Jeune syndrome (asphyxiating thoracic dysplasia) (usually neonatal lethal) (very small chest, short limbs, hypoplastic hip, progressive renal disease in many surviving into childhood) (*AR*)

Kartagener syndrome (situs inversus, septal defect of the heart, recurrent sinusitis, bronchiectasis, disturbed movements of spermatozoa and cilia; affected men are sterile) (*AR*)

Langer-Giedion syndrome (multiple exostoses, flat nose, large ears, loose skin; chromosome locus 8q23) (*AD*)

Laurence-Moon-Biedl syndrome (mental retardation, retinal pigmentation, hypogenitalism, obesity, polydactyly) (*AR*)

Lowe syndrome (oculocerebrorenal syndrome) (cataract, mental retardation, renal tubular dysfunction with aminoaciduria) (*XR*)

Marfan syndrome (arachnodactyly, subluxation of the lens, aortic dilatation and aneurysm, increased stature, scoliosis) (*AD, AR*)

Meckel syndrome (occipital encephalocele, microcephaly, multicystic kidney dysplasia, polydactyly) (*AR*)

- Metatropic dysplasia (small chest, thoracic kyphoscoliosis) (*AR*, *AD*)
- Mohr syndrome (orofaciodigital syndrome II) (mild median cleft lip, cleft tongue, wide nasal bridge, deafness, partial duplication of the big toe) (*AR*)
- Multiple cartilaginous exostoses (*AD*)
- Osteogenesis imperfecta (fragile bones, otosclerosis, hyperextensibility, blue sclera) (*AD*, *AR*)
- Pfeiffer syndrome (acrocephalosyndactyly) (acrocephalic skull, prominent forehead, syndactyly of toes 2 and 3, large thumb, medially displaced big toe; intelligence is usually norm) (*AD*)
- Phocomelia (agenesis of proximal limb bones, seal-like limbs) (usually a constituent of multiple congenital anomalies; also occurs as an isolated defect, or resulting from teratogens, e.g., thalidomide)
- Pierre Robin sequence (Robin sequence) (mandibular hypoplasia, micrognathia, glossoptosis, palatoschisis) (?)
- Poland sequence (unilateral absence or hypoplasia of greater pectoral muscle or other shoulder-girdle muscles, ipsilateral syndactyly, and finger hypoplasia—the index finger being most severely affected and the thumb usually spared) (early damage to subclavian artery?) (sporadic)
- Polydactyly, postaxial (*AD*, *AR*)
- Polydactyly, preaxial (*AD*)
- Roberts syndrome [tetraphocomelia, severe midface defects (intermaxillary encephalocele, cleft lip/cleft palate)] (*AR*)
- Rubinstein-Taybi syndrome (broad thumbs and big toes, down-slanting palpebral fissures, epicanthus, hypoplastic maxilla, moderate to severe growth and developmental retardation) (usually sporadic; concordant in MZ twins)
- Russell-Silver syndrome (chondrodysplasia, skeletal asymmetry, bent fifth fingers, growth retardation with relatively large head and characteristic facies) (*AR*, *XR*)
- Saldino-Noonan syndrome (neonatal lethal) (chondrodysplasia, short ribs, polydactyly) (*AR*)
- Sirenomelia (associated with renal agenesis, oligohydramnios; predisposed to by maternal diabetes)
- Smith-Lemli-Opitz syndrome (turned-up nose, ptosis, syndactyly of toes 2 and 3, hypospadias, cryptorchidism, very severe growth and developmental retardation) (*AR*)
- Spondyloepiphyseal dysplasias (short trunk, delayed epiphyseal calcification, articular restriction, myopia; range from neonatal lethal to adult onset) (*AR*, *AD*, *XR*)
- Stickler syndrome (cleft lip and palate, flat face, myopia, deafness, hip dysplasia—very variable) (*AD*: some cases map to COL2AI locus on chromosome 12)
- Symphalangy (bony fusion at the interphalangeal joints) (*AD*)
- Syndactyly (fusion of the fingers or toes) (*AD*)
- Thanatophoric dysplasia (neonatal lethal) (short limbs, flat vertebrae, large head) (*AD*)
- VACTERL association (association of vertebral, anal, cardiac, tracheo-oesophageal, renal and limb malformations) (sporadic)
- Váradipapp syndrome (cleft lip/cleft palate, holoprosencephaly, arhinencephalia, mental retardation, polydactyly) (*AR*)
- Waardenburg syndrome (uni/bilateral severe nerve deafness, mild to gross telecanthus without hypertelorism, white forelock, heterochromia iridis) (*AD*)
- Wiedemann-Beckwith syndrome (exomphalos-macroglossia-gigantism = EMG syndrome (usually sporadic, with some *AD* families)
- Zellweger syndrome (cerebrohepatorenal syndrome) (macrogyria, polymicrogyria, hypotonia, prominent forehead, flat face, hepatosplenomegaly) (*AR*)

Figure 9-1. Achondrogenesis type II.



Figure 9-2. Achondrogenesis type II. Very poor ossification of limb bones; no ossification of sacral vertebrae or pubis or ischium; bony spurs on ilium; small rounded chest with short, broad, terminally-flared ribs.



Figure 9-3. Achondrogenesis type II. Poor ossification of limb bones and lower spine and pelvis; short stubby ribs; small iliac wings with bony spurs; short limb bones with flared, poorly-ossified metaphyses; prominent abdomen.

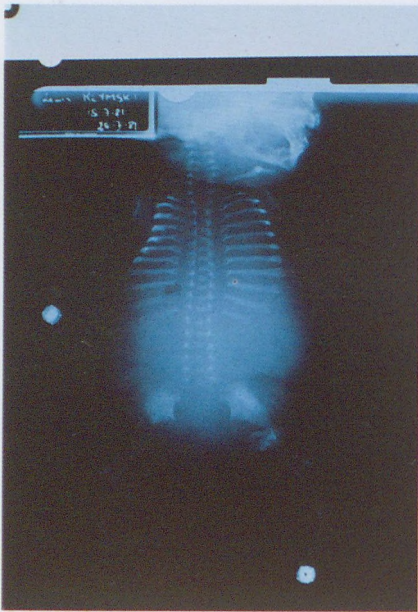


Figure 9-4. Achondroplasia, neonatal death. Moderately narrow chest; narrowed interpedicular space from L1 downwards; small square iliac wings with horizontal acetabular roof and medial beaking; moderate translucency at upper end of femur/metaphysis.



Figure 9-5. Achondroplasia, at 2 days. Lateral spine. Short lumbar pedicles; developing lumbar kyphus.



Figure 9-6. Achondroplasia, neonatal death. Narrow chest; small iliac wings with medial beaking to acetabulum; moderate shortening of proximal limb bones; slight flaring of metaphyses; increased translucency at upper end of femur.



Figure 9-7. Camptomelic dysplasia, neonatal lethal. Bell-shaped chest, small scapulae; marked bowing of slender femora and of shortened tibiae and fibulae; mild bowing of humerus and ulna (water-artefact on film!).



Figure 9-8. The extremely short and thickened tibia from a fetus with camptomelic dysplasia of autosomal recessive inheritance (36 gestational weeks).

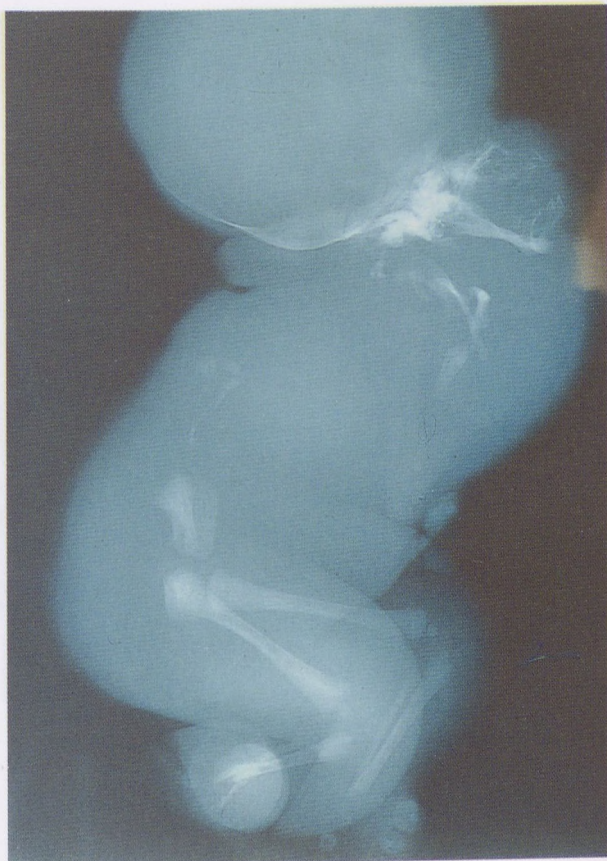


Figure 9-9. Parasitic twin, lateral X-ray: almost complete failure of vertebral, costal and cranial vault development, hypoplastic upper limbs.



Figure 9-10. Severely macerated 7 cm (CR) spontaneous abortus, with hydrops, prominent abdomen and short upper and lower extremities (short-limbed dwarfism?).

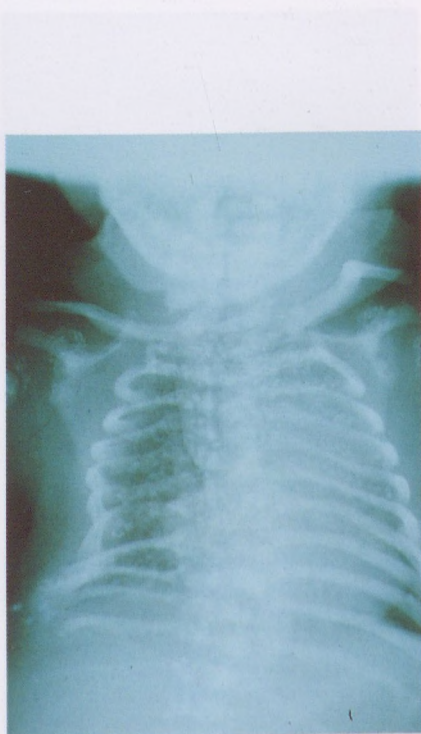


Figure 9-11. Chondrodysplasia punctata, X-linked dominant (?); female, death at 2 months. Chest: short ribs and asymmetric chest with snowstorm appearance (speckling of costal cartilages) and speckling of epiphyses on scapula, humerus and vertebral pedicles.



Figure 9-12. Chondrodysplasia punctata. Widespread epiphyseal speckling involving spine, ribs, pelvis and limbs. Moderate shortening of limb bones only. Asymmetric chest and scoliosis.



Figure 9-13. Diastrophic dysplasia. Moderate chest narrowing, with otherwise normal ribs; slight shortening of limb bones (femur); early scoliosis.



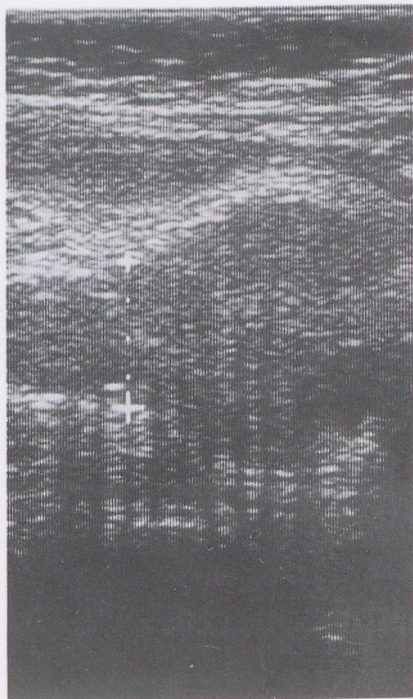
Figure 9-14. Diastrophic dysplasia. Age: 2 months. Flat upper face with mild proptosis, small nose and prominent ears; very low-set abnormal "hitch-hiker" thumbs; proximal limb shortening; narrow upper chest.



Figure 9-15. Diastrophic dysplasia. Ear: fleshy, swollen and dysplastic.

Figure 9-16. Diastrophic dysplasia. Age: 2 months. Legs: short femur, marked metatarsus varus, and tibial deviation of all toes. Note also the prominent abdomen and small chest, and abnormally placed thumb.





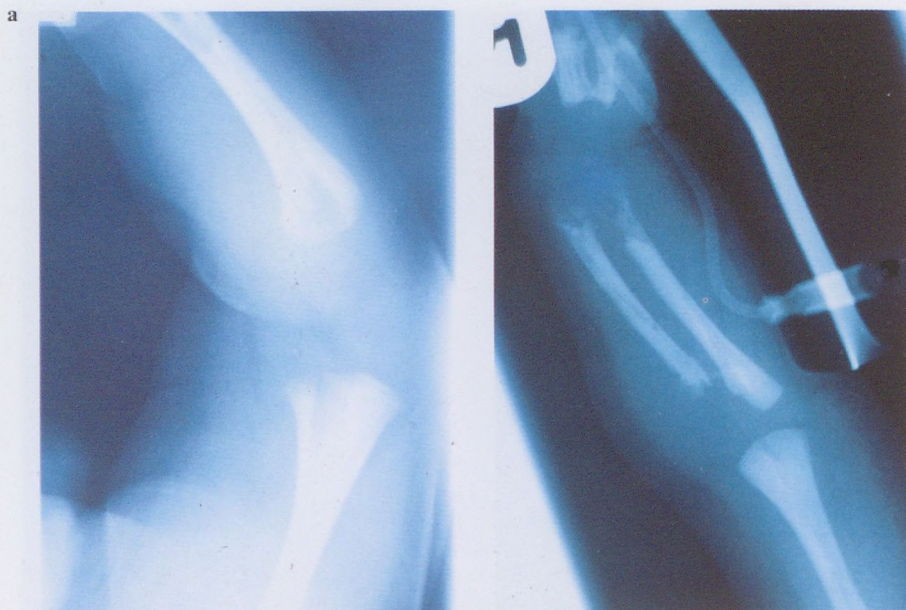
Figures 9-17 and 18. Jeune syndrome, asphyxiating thoracic dysplasia: upper chest extremely narrowed, and further compressed in the axillae (**Figure 17**); termination after prenatal ultrasound diagnosis characterized by a narrow thorax at 18 gestational weeks (**Figure 18**).



Figure 9-19. Asphyxiating thoracic dystrophy (Jeune). Bell-shaped chest with extreme shortening of upper and middle ribs; only slight shortening of long bones.



Figure 9-20. Asphyxiating thoracic dystrophy (Jeune). 17 weeks' pregnancy termination: postaxial polydactyly of left foot.



Figures 9-21a and b. Hypophosphatasia, severe neonatal lethal. Neonate, knee: V-shaped ossification defects in all metaphyses (a); forearm: moth-eaten appearance of metaphyses (ulna, radius), and V-shaped defect in humerus (b).



Figure 9-22. Severe rhizomelic form of chondrodysplasia punctata (autosomal recessive); neonatal lethal, female born to first-cousin parents. Speckled epiphyses, limbs and trunk; severe rhizomelic shortening; fifth rib removed for histology; small chest.

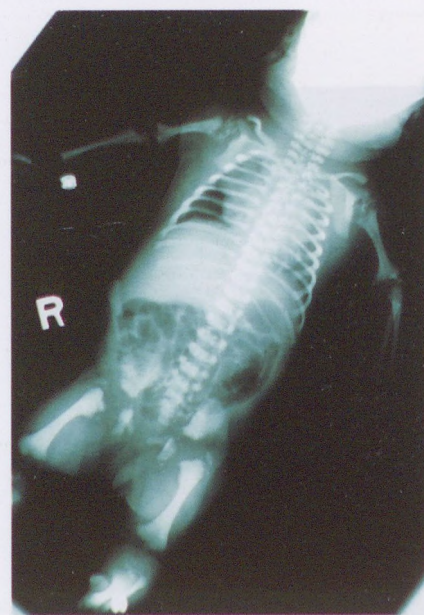


Figure 9-23. Severe rhizomelic form of chondrodysplasia punctata: sib of previous case. Speckling of all epiphyses, severe rhizomelic shortening, small chest.



Figure 9-24. Russell-Silver syndrome: newborn, 37 weeks' gestation, weight 1200 g, with relatively very large head.



Figure 9-25. Osteogenesis imperfecta, type IIa: broad shortened accordion-like femora, severe angulation of both tibiae, with multiple fractures.

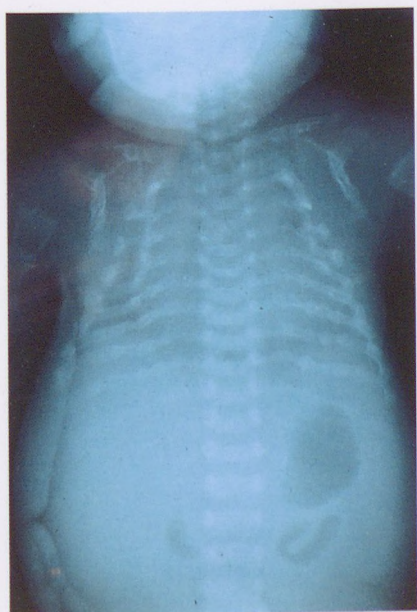


Figure 9-26. Osteogenesis imperfecta, type IIb: multiple rib fractures, narrowed upper thorax.



Figure 9-27. Osteogenesis imperfecta, type II. Multiple fractures in long bones, ribs and pelvis. The upper ribs are severely shortened, the chest bell-shaped. The proximal limb bones are long, slender and grossly deformed by fractures.

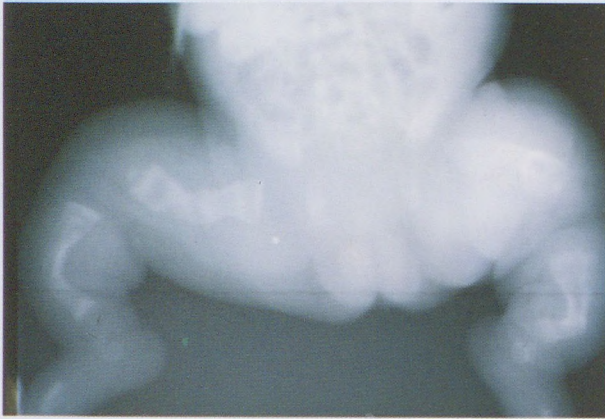


Figure 9-28. Osteogenesis imperfecta, type II. Bowing of femora and tibiae, with gross variation in bone density and multiple fractures. Moderately broad crumpled long bones.



Figure 9-29. Osteogenesis imperfecta, type II. Broad, short brick-like, crumpled femora.

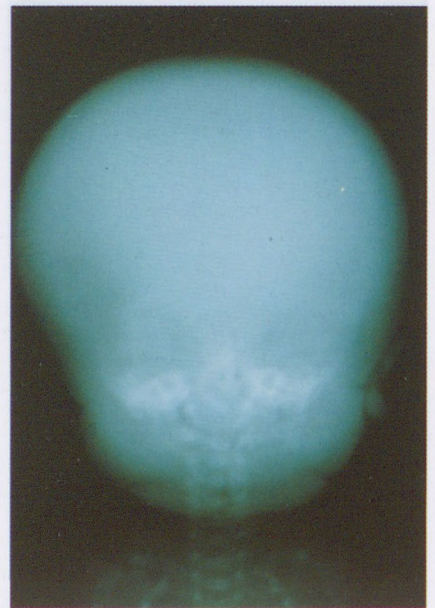


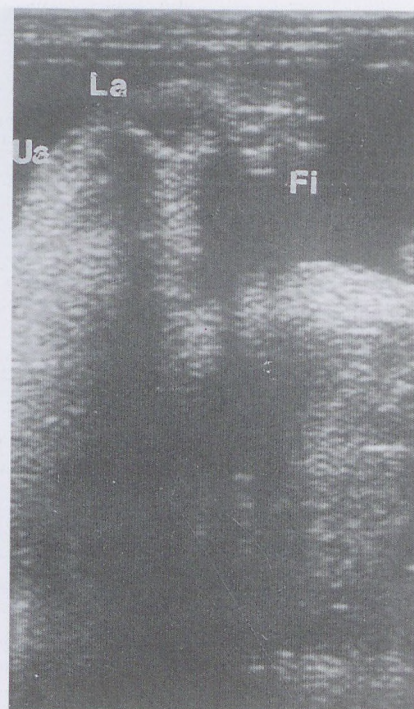
Figure 9-30. Osteogenesis imperfecta, type II. Skull: no ossification of cranial vault.



Figures 9-31a and b. Spondyloepiphyseal congenital dysplasia (late neonatal death associated with *Shigella* sepsis).



Figures 9-32a, b and c. Spondyloepiphyseal dysplasia: lateral whole body X-ray showing steep floor to anterior fossa, a defective ossification of the cervical vertebrae, pear-shaped vertebral bodies in the thoracolumbar spine (a); X-ray shows rhizomelic limb shortening, and failure of ossification of the pubic bones (b); prenatal ultrasound of shortened humerus at 24 gestational weeks (c).



Figures 9-33a and b. Thanatophoric dysplasia: short limbs, large head, neonatal lethal (a); ultrasound view of a limb: Ua = upper arm, La = lower arm and Fi = fingers (b).

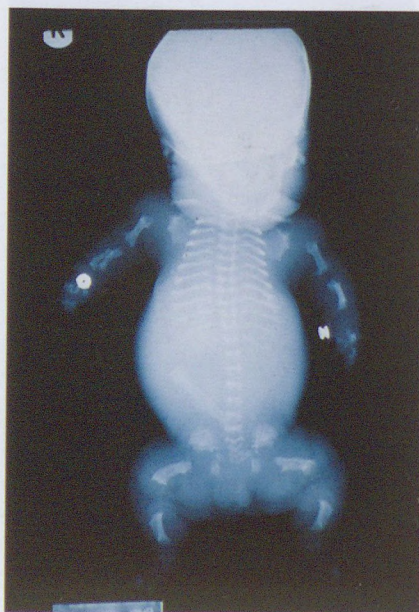


Figure 9-34a. Thanatophoric dysplasia. Large head, redundant skin at neck and in limbs; short ribs; marked platyspondylia; polygonal scapulae, small but relatively wide iliac wings; short curved femora with spiky metaphyseal projections.



Figure 9-34b. Thanatophoric dysplasia, died at 20 hours. Narrow chest and short ribs with flared costochondral junctions; extreme platyspondylia; short curved humerus, femur, tibia and fibula.



Figure 9-35. Longitudinal sections of a normal humerus (left) and the curved humerus of a fetus suffering from thanatophoric dysplasia (right).

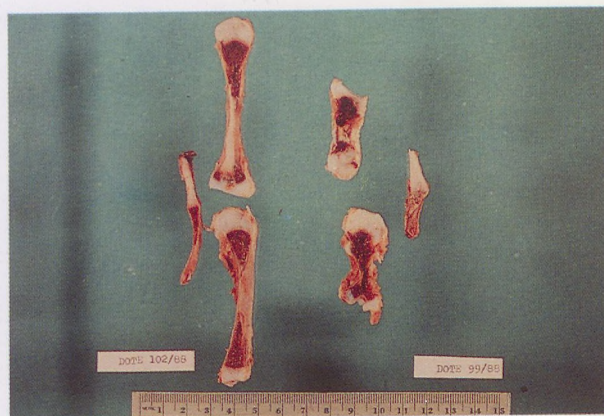


Figure 9-36. Rib and tibia from a normal fetus (left). The same, from a fetus with thanatophoric dysplasia (right), showing irregularities at the costochondral junction.

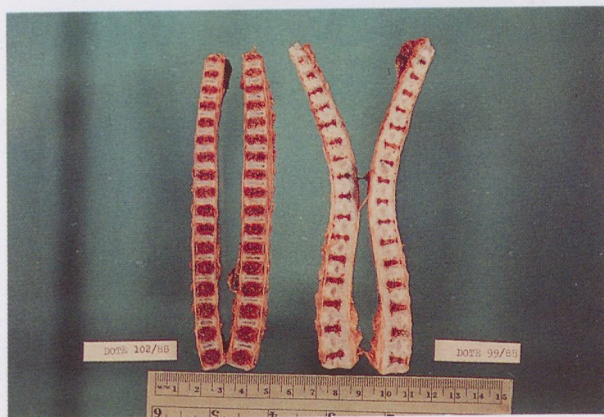


Figure 9-37. Coronal sections through vertebral column of a normal fetus (left) and of a fetus with thanatophoric dysplasia (right).



Figure 9-38. Macroscopic view of a plantar section of the fetal left leg showing amniotic band connecting to the deformed finger (17 gestational weeks).

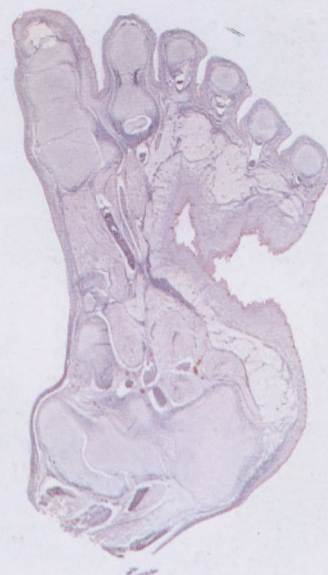


Figure 9-39. Plantar section of a mid-trimester fetal foot showing polydactyly.



Figure 9-40. Radial aplasia in a macerated stillborn: cause unknown.



Figure 9-41. Pfeiffer syndrome in mother and son: characteristic face, prominent forehead, large, medially deviated right thumb in parent, left thumb in child, other finger anomalies.

References

- Allanson J. E., Hall J. G. (1986)**
Obstetric and gynecologic problems in women with chondrodysplasias.
Obstet. Gynecol. 67, 74-78.
- Bendon R., Dignan P., Siddigi I. (1987)**
Prenatal diagnosis of arthrogryposis multiplex congenita.
J. Pediatr. 111, 942-947.
- Boos R., Schmidt W. (1986)**
Prenatal diagnosis of thanatophoric dwarfism with cloverleaf skull.
Z. Geburtshilfe Perinatol. 190, 225-228.
- Brons J. T. J., Van der Harten H. J., Wladimiroff J. W., Van Geijn H. P., Dijkstra P. F., Exalto N., Reuss A., Niermeijer M. F., Meijer C. J. L. M., Arts N. F. T. (1988)**
Prenatal ultrasonographic diagnosis of osteogenesis imperfecta.
Am. J. Obstet. Gynecol. 159, 175-180.
- Brons J. T. J., Van der Harten H. J. (1989)**
Skeletal dysplasias. Pre- and postnatal identification. An ultrasonographic, radiologic and pathologic study.
Vrije Universiteit Publication Amsterdam
- Brons J. T. J., Van der Harten H. J., Van Geijn H. P., Wladimiroff J. W., Reuss A., Stewart P., Meijer C. J. L. M., Arts N. F. T. (1989)**
Ratios between growth parameters for the prenatal ultrasonographic diagnosis of skeletal dysplasias.
Eur. J. Obstet. Gynecol. 34, 37-46.
- Cordone M., Lituania M., Zampatti C., Passamonti U., Magnano G. M., Toma P. (1989)**
In utero ultrasonographic features of campomelic dysplasia.
Prenat. Diagn. 9, 745-750.
- Csécsei K., Szeifert Gy., Nemes Z., Tóth Z., Vachter J., Papp Z. (1982)**
Pathomorphological findings of a prenatally diagnosed thanatophoric dwarf.
In: Papadatos C. J., Bartsocas C. S. (eds) *Skeletal Dysplasias*. Alan R. Liss, Inc., New York, pp. 505-518.
- Degani S., Shapiro I., Lewinsky R., Sharf M. (1990)**
Prenatal ultrasound diagnosis of isolated arthrogryposis of feet.
Acta Obstet. Gynecol. Scand. 68, 461-462.
- Delange M., Rouse G. A. (1990)**
Prenatal diagnosis of hypophosphatasia.
J. Ultrasound Med. 9, 115-117.
- Driscoll D. A. (1991)**
Fetal limbs. Normal and abnormal.
Semin. Roentgenol. 26, 12-20.
- Duff P., Harlass F. E., Milligan D. A. (1990)**
Prenatal diagnosis of chondrodysplasia punctata by sonography.
Obstet. Gynecol. 76, 497-500.
- Elejalde B. R., De Elejalde M. M., Pansch D. (1985)**
Prenatal diagnosis of Jeune-syndrome.
Am. J. Med. Genet. 21, 433-438.
- Elejalde B. R., Elejalde M. M. (1983)**
Prenatal diagnosis of perinatally lethal osteogenesis imperfecta.
Am. J. Med. Genet. 14, 353-359.
- Elejalde B. R., Elejalde M. M. (1985)**
Thanatophoric dysplasia: Fetal manifestations and prenatal diagnosis.
Am. J. Med. Genet. 22, 669-683.
- Escobar L. F., Bixler D., Weaver D. D., Padilla L. M., Golichow A. (1990)**
Bone dysplasias. The prenatal diagnostic challenge.
Am. J. Med. Genet. 36, 488-494.
- Filly R. A., Golbus M. S., Carey J. C., Hall J. G. (1981)**
Short-limbed dwarfism: Ultrasonographic diagnosis by mensuration of fetal femoral length.
Radiology 138, 653-656.
- Filly R. A., Golbus M. S. (1982)**
Ultrasonography of the normal and pathologic fetal skeleton.
Radiol. Clin. North Am. 20, 311-323.
- Gembruch U., Niesen M., Kehrberg H., Hansmann M. (1988)**
Diastrophic dysplasia. A specific prenatal diagnosis by ultrasound.
Prenat. Diagn. 8, 539-545.
- Glenn L. W., Teng S. S. K. (1985)**
In utero sonographic diagnosis of achondrogenesis.
J. Clin. Ultrasound 13, 195-198.
- Goldberg J. D., Chervenak F. A., Lipman R. A., Berkowitz R. L. (1986)**
Antenatal sonographic diagnosis of arthrogryposis multiplex congenita.
Prenat. Diagn. 6, 45-49.
- Graham D., Tracey J., Winn K., Corson V., Sanders R. C. (1983)**
Early 2nd trimester sonographic diagnosis of achondrogenesis.
J. Clin. Ultrasound 11, 336-338.
- Grange D. K., Lewis M. B., Marini J. C. (1990)**
Analysis of cultured chorionic villi in a case of osteogenesis imperfecta type-II. Implications for prenatal diagnosis.
Am. J. Med. Genet. 36, 258-264.
- Grannum P. A., Hobbins J. C. (1983)**
Prenatal diagnosis of fetal skeletal dysplasias.
Semin. Perinatol. 7, 125-137.

- Hegge F. N., Prescott G. H., Watson P. T.** (1986)
Utility of a screening examination of the fetal extremities during obstetrical sonography.
J. Ultrasound Med. 5, 639-645.
- Hobbins J. C., Bracken M. B., Mahoney M. J.** (1982)
Diagnosis of fetal skeletal dysplasias with ultrasound.
Am. J. Obstet. Gynecol. 142, 306-312.
- Hoefler S., Moser A. B., Watkins P. A., Chen W. W., Moser H. W.** (1988)
Prenatal diagnosis of rhizomelic chondrodysplasia punctata.
Prenat. Diagn. 8, 571-576.
- Issel E. P.** (1985)
Ultrasonic measurement of the growth of fetal limb bones in normal pregnancy.
J. Perinat. Med. 13, 305-313.
- Izquierdo L. A., Kushnir O., Aase J., Lantz P., Castellano T., Curet L. B.** (1990)
Antenatal ultrasonic diagnosis of dyssegmental dysplasia.
Prenat. Diagn. 10, 587-592.
- Jeanty P., Romero R., Dalton M., Venus I., Hobbins J. C.** (1985)
In utero sonographic detection of hand and foot deformities.
J. Ultrasound Med. 4, 595-601.
- Jones S. M., Robinson L. K., Sperazza R.** (1990)
Prenatal diagnosis of skeletal dysplasia identified postnatally as hypochondroplasia.
Am. J. Med. Genet. 36, 404-407.
- Kelly T. E., Hall J. G., Horton W., Scott C. I.** (1983)
Prenatal diagnosis of genetic osteochondrodysplasias.
Am. J. Med. Genet. 16, 285-287.
- Kim H. J., Costales F., Bouzouki M., Wallach R. C.** (1986)
Prenatal diagnosis of dyssegmental dwarfism.
Prenat. Diagn. 6, 143-150.
- Kirk J. S., Comstock C. H.** (1990)
Antenatal sonographic appearance of spondyloepiphyseal dysplasia congenita.
J. Ultrasound Med. 9, 173-175.
- Knisely A. S., Ambler M.** (1988)
Temporal-lobe abnormalities in thanatophoric dysplasia.
Pediatr. Neurosci. 14, 169-176.
- Kousseff B. G., Mulivor R. A.** (1981)
Prenatal diagnosis of hypophosphatasia.
Obstet. Gynecol. Suppl. 57, 9-12.
- Kurtz A. B., Filly R. A., Wapner R. J., Golbus M. S., Rifkin M. R., Callen P. W., Pasto M. E.** (1986)
In utero analysis of heterozygous achondroplasia variable time of onset as detected by femur length measurements.
J. Ultrasound Med. 5, 137-140.
- Kurtz A. B., Needleman L., Wapner R. J., Hilpert P., Kuhlman K., Burns P. N., Feld R. I., Mitchell D. G., Segal S., Blum L.** (1990)
Usefulness of a short femur in the in utero detection of skeletal dysplasias.
Radiology 177, 197-200.
- Loong E. P. L.** (1987)
The importance of early prenatal diagnosis of thanatophoric dysplasia with respect to obstetric management.
Eur. J. Obstet. Gynecol. 25, 145-152.
- Lynch J. R., Ogilvie D., Priestle L., Baigrie C., Smith R., Farndon P., Sykes B.** (1991)
Prenatal diagnosis of osteogenesis imperfecta by identification of the concordant collagen-1 allele.
J. Med. Genet. 28, 156-158.
- Mahoney M. J., Hobbins J. C.** (1977)
Prenatal diagnosis of chondroectodermal dysplasia (Ellis-van Creveld syndrome) with fetoscopy and ultrasound.
N. Engl. J. Med. 297, 258-260.
- Mantagos S., Weiss R. R., Mahoney M., Hobbins J. C.** (1981)
Prenatal diagnosis of diastrophic dwarfism.
Am. J. Obstet. Gynecol. 139, 111-113.
- Meinel K., Himmel D.** (1987)
The value of sonography and radiography in the detection of lethal osteochondrodysplasias.
Zentralbl. Gynäkol. 109, 1303-1313.
- Meizner I., Carmi R., Katz M.** (1991)
Prenatal ultrasonic diagnosis of mandibulofacial dysostosis (Treacher-Collins syndrome).
J. Clin. Ultrasound 19, 124-127.
- Menashe Y., Ben Baruch G., Rabinovitch O., Shalev Y., Katzenelson M. B. M., Shalev E.** (1989)
Exophthalmus prenatal ultrasonic features for diagnosis of Crouzon syndrome.
Prenat. Diagn. 9, 805-808.
- Merz E., Goldhofer W.** (1986)
Sonographic diagnosis of lethal osteogenesis imperfecta in the 2nd trimester. Case report and review.
J. Clin. Ultrasound 14, 380-383.
- Merz E., Kim-Kern M-S., Pehl S.** (1987)
Ultrasonic mensuration of fetal limb bones in the second and third trimesters.
J. Clin. Ultrasound 15, 175-183.
- Milsom I., Mattsson L. A., Dahlén-Nilsson I.** (1982)
Antenatal diagnosis of osteogenesis imperfecta by real time ultrasound: Two case reports.
Br. J. Radiol. 55, 310-312.
- Nyhan W. L., Sakati N. O. (eds)** (1976)
Genetic and Malformation Syndromes in Clinical Medicine.
Year Book Medical Publishers, Chicago
- O'Brien G. D., Rodeck C., Queenan J. T.** (1980)
Early prenatal diagnosis of diastrophic dwarfism by ultrasound.
Br. Med. J. 280, 1300-1300.
- Papadatos C. J., Bartsocas C. S. (ed)** (1982)
Skeletal Dysplasias.
Alan R. Liss, New York

- Patel Z. M., Shah H. L., Madon P. F., Ambani L. M.** (1983)
Prenatal diagnosis of lethal osteogenesis imperfecta (OI) by ultrasonography.
Prenat. Diagn. 3, 261-263.
- Pattarelli P., Pretorius D. H., Edwards D. K.** (1990)
Intrauterine growth retardation mimicking skeletal dysplasia on antenatal sonography.
J. Ultrasound Med. 9, 737-739.
- Pretorius D. H., Rumack C. M., Manco-Johnson M. L., Manchester D., Meier P., Bramble J., Clewell W.** (1986)
Specific skeletal dysplasias in utero. Sonographic diagnosis.
Radiology 159, 237-242.
- Robinson L. P., Worthen N. J., Lachman R. S., Adomian G. E., Rimoin D. L.** (1987)
Prenatal diagnosis of osteogenesis imperfecta type-III.
Prenat. Diagn. 7, 7-15.
- Romero R., Athanassiadis A. P., Jeanty P.** (1990)
Fetal skeletal anomalies.
Radiol. Clin. North Am. 28, 75-99.
- Shaff M. I., Fleischer A. C., Battino R., Herbert C., Boehm F. H.** (1980)
Antenatal sonographic diagnosis of thanatophoric dysplasia.
J. Clin. Ultrasound 8, 363-365.
- Shapiro J. E., Phillips J. A., Byers P. H., Sanders R., Holbrook K. A., Levin L. S., Dorst J., Barsh G. S., Peterson K. E., Goldstein P.** (1982)
Prenatal diagnosis of lethal perinatal osteogenesis imperfecta (OI type II).
J. Pediatr. 100, 127-133.
- Shechter S. A., Sherer D. M., Geilfuss C. J., Metlay L. A., Woods J. R.** (1990)
Prenatal sonographic appearance and subsequent management of a fetus with oromandibular limb hypogenesis syndrome associated with pulmonary hypoplasia.
J. Clin. Ultrasound 18, 661-665.
- Skiptunas S. M., Weiner S.** (1987)
Early prenatal diagnosis of asphyxiating thoracic dysplasia (Jeune's syndrome). Value of fetal thoracic measurement.
J. Ultrasound Med. 6, 41-43.
- Smith W. L., Breitweiser T. D., Dinno N.** (1981)
In utero diagnosis of achondrogenesis, type I.
Clin. Genet. 19, 51-54.
- Spirit B. A., Oliphant M., Gottlieb R. H., Gordon L. P.** (1990)
Prenatal sonographic evaluation of short-limbed dwarfism. An algorithmic approach.
Radiograph. 10, 217-236.
- Spranger J. W., Opitz J. M., Bidder U.** (1971)
Heterogeneity of chondrodysplasia punctata.
Hum. Genet. 11, 190-212.
- Stephens T. D., Shepard T. H.** (1983)
A review of limb defects in a large fetus collection.
Am. J. Hum. Genet. 35, 508-519.
- Stoll C., Manini P., Bloch J., Roth M. P.** (1985)
Prenatal diagnosis of hypochondroplasia.
Prenat. Diagn. 5, 423-426.
- Taybi H.** (1975)
Radiology of Syndromes and Metabolic Disorders.
Year Book Medical Publishers, Chicago-London
- Tóth Z., Vachter J., Szeifert Gy., Nemes Z., Csécséi K., Török O., Harsányi Á., Papp Z.** (1982)
Antenatally diagnosed thanatophoric dysplasia.
Acta Paediatr. Hung. 23, 441-448.
- Török O., Tóth Z., Szeifert G. T., Papp Z.** (1989)
Prenatal diagnosis and management of chondrodysplasias.
Acta Chir. Hung. 30, 281-289.
- Van Dongen P. W., Hamel B. C. J., Nijhuis J. G., De Boer C. N.** (1990)
Prenatal follow-up of hypophosphatasia by ultrasound.
Eur. J. Obstet. Gynecol. 34, 283-288.
- Von Recher K. N.** (1985)
Early diagnosis of osteogenesis imperfecta by ultrasound.
Z. Geburtshilfe Perinatol. 189, 268-270.
- Weiner C. P., Williamson R. A., Bonsib S. M.** (1986)
Sonographic diagnosis of cloverleaf skull and thanatophoric dysplasia in the second trimester.
J. Clin. Ultrasound 14, 463-465.
- Weldner B. M., Persson P. H., Ivarsson S. A.** (1985)
Prenatal diagnosis of dwarfism by ultrasound screening.
Arch. Dis. Child. 60, 1070-1072.
- Whitley C. B., Langer L. O., Ophoven J., Gilbert E. F., Gonzales C. H., Mammel M., Coleman M., Rosenberg S., Rodrigues C. J., Sibley R., Horton W. A., Opitz J. M.** (1984)
Fibrochondrogenesis: Lethal autosomal recessive chondrodysplasia with distinctive histopathology.
Am. J. Med. Genet. 19, 265-275.
- Wilkenjen C.** (1990)
Decreased maternal serum alpha-fetoprotein associated with arthrogryposis multiplex congenita.
Eur. J. Obstet. Gynecol. 37, 261-263.
- Wladimiroff J. W., Niermeijer M. F., Laar J., Jahoda M., Stewart P. A.** (1984)
Prenatal diagnosis of skeletal dysplasia by real-time ultrasound.
Obstet. Gynecol. 63, 363-364.
- Yang S. S., Kitchen E., Gilbert E. F., Rimoin D. L.** (1986)
Histopathologic examination in osteochondrodysplasia.
Arch. Pathol. Lab. Med. 110, 10-12.
- Zimmer E. Z., Weinraub Z., Rajman A., Pery M., Peretz B. A.** (1984)
Antenatal diagnosis of a fetus with an extremely narrow thorax and short limb dwarfism.
J. Clin. Ultrasound 12, 112-114.

Hydropic Anomalies

Unlike "immune hydrops", resulting from fetomaternal blood-group incompatibility, "non-immune hydrops" develops in the absence of blood group incompatibility and without erythroblastosis. Non-immune hydrops has assumed growing importance in prenatal diagnosis and management as Rh-haemolytic disease is better controlled and prevented.

Non-immune hydrops is characterized by a generalized oedema (anasarca, oedematous placenta, polyhydramnios, etc.) and accumulation of fluid in serous-lined cavities (ascites, hydrothorax, chylothorax, etc.). Isolated ascites or isolated hydrothorax may be the first sign. Hepatomegaly is rarely present.

The earlier designation "idiopathic" non-immune hydrops suggested a process without a known cause. Today the causes of non-immune hydrops can often be revealed by appropriate investigations.

The most frequently occurring causes are the following.

1. Infection (toxoplasmosis, CMV infection, syphilis, leptospirosis, hepatitis, etc.).

2. Severe anaemia and/or hypoproteinaemia of mother and/or fetus.

3. Untreated maternal diabetes mellitus.

4. α -thalassaemia.

5. Cardiac abnormalities (malformations, teratoma, rhabdomyoma, arrhythmia, etc.).

6. Pulmonary malformations (congenital cystic adenomatous malformation, diaphragmatic hernia, intrathoracic teratoma, etc.).

7. Gastrointestinal abnormalities (meconium peritonitis, atresia, volvulus, etc.).

8. Hydrops of hepatic origin (calcification, fibrosis, polycystic liver disease, etc.).

9. Urethral obstruction, persistent cloaca, prune-belly syndrome, etc.).

10. Abnormalities of the lymphatic system (congenital lymphoedema, chylothorax, etc.).

11. Cystic hygroma complicating Ullrich-Turner's syndrome or autosomal (21, 18, and 13) trisomies, sometimes isolated but often with generalized oedema.

12. Feto-fetal transfusion syndrome in twin pregnancy.

The initial diagnosis of hydrops is likely to be made by ultrasound; this diagnosis can be established at a routine examination, or following referral, with a suspicion of hydrops, on the basis of clinical polyhydramnios or diminished fetal movements. The localization and extent of the hydrops can be seen on ultrasound—signs include polyhydramnios and ascites (loops of intestine float freely when there is more than 100 ml of fluid in the abdominal cavity, and there is a clear space between the liver and the diaphragm); hydrothorax, generalized oedema and a thickened enlarged placenta, and the oedematous fetus makes little or no movement. Localized fetal malformations can be seen on ultrasound: they may be directly responsible for the hydrops, e.g., cardiac tumours, or suggest the presence of a trisomy or a Ullrich-Turner's fetus.

Maternal-fetal blood group incompatibility should be excluded, likewise diabetes mellitus, anaemia or hypoproteinaemia, maternal infection as well as the possibility of a fetal haemoglobinopathy.

It may be helpful to examine amniotic fluid or fetal blood for grouping, chromosome analysis, bacteriological and virological tests, etc.

Once non-immune hydrops has been diagnosed, all reasonable steps must be taken to determine its cause. When maternal disease is responsible, it should receive specific treatment. Hydrops of undetermined cause remains a problem, requires intensive prenatal investigation, and may be best managed by empiric treatments such as thoracocentesis, digoxin, albumin and blood transfusions. If hydrops is diagnosed before the 20th week, pregnancy termination should be offered (especially if there is coexisting fetal malformation). When hydrops is first diagnosed after 20 weeks attempts should be made to save the fetus, though the chances of success are poor.

Fetal thoracocentesis or abdominal paracentesis may be performed via the maternal abdominal wall, and can result in a transient remission; hydrops soon returns. Fetal abdomino-amniotic shunts usually fail. The prognosis for non-immune hydrops is poor; at least 50% of fetuses die in utero.

The recurrence risk depends on the primary cause of the hydrops. Further pregnancies may be undertaken, but prenatal diagnosis is usually advisable.

Unlike "immune hydrops," resulting from intrauterine blood-group incompatibility, "non-immune hydrops" develops in the absence of blood-group incompatibility and without erythroblastosis fetalis. Immune hydrops has numerous etiologies, but the most important is congenital hemolytic disease, and management is Rh-incompatibility. It is better controlled and prevented.

Non-immune hydrops is characterized by a generalized edema (anasarca, edematous placenta, polyhydramnios, etc.) and accumulation of fluid in extra-thoracic cavities (ascites, hydrothorax, hydropericardium, etc.). Isolated ascites or isolated hydrothorax may be the first sign. Lymphoedema is rarely present. The earlier designation "hydrops fetalis" was immune hydrops suggested a process without a known cause. Today the cause of non-immune hydrops can often be revealed by appropriate investigation. The most frequently occurring causes are the following:

1. Infection (toxoplasmosis, CMV infection, syphilis, leptospirosis, hepatitis, etc.)
2. Severe anemia and/or hypoproteinemia of another pathologic cause
3. Unilateral maternal diabetes mellitus
4. Atherosclerosis
5. Cardiac abnormalities (congenital, valvular, obstructive, etc.)
6. Pulmonary malformation (congenital cystic adenomatoid malformation, diaphragmatic hernia, neurogenic tumors, etc.)

7. Gastrointestinal abnormalities (meconium peritonitis, atresia, volvulus, etc.)
8. Hydrops of hepatic origin (congenital, chronic, postnatal liver disease, etc.)
9. Urinary obstruction, persistent cloaca, prune-belly syndrome, etc.
10. Abnormalities of the lymphatic system (congenital lymphoedema, chylothorax, etc.)
11. Cystic hygroma complicating Ullrich-Turner's syndrome or other anomalies isolated but often with generalized edema
12. Fetal malformation syndrome in two pregnancy

The initial diagnosis of hydrops is likely to be made by ultrasound. The diagnosis can be established if a routine examination or following referral with a suspicion of hydrops on the basis of clinical polyhydramnios or oligohydramnios is accompanied by the localization and extent of the hydrops can be seen on ultrasound—eg, ascites, hydrothorax, and pericardial effusion (polyhydramnios and ascites (foetus of maternal death) when there is a more than 100 ml of fluid in the abdominal cavity, and there is a clear space between the liver and the diaphragm; hydrothorax, eg, no fluid between the lungs and the chest; polyhydramnios and oligohydramnios, eg, no amniotic fluid and no fetal movement. Localized fluid malformations can be seen on ultrasound. They may be directly responsible for the hydrops, eg, an atresia, or suggest the presence of a urinary or a lymphatic abnormality.

Maternal fetal blood group incompatibility should be excluded. Ultrasound, obstetric, neonatal, and pathological examinations, maternal infection as well as the possibility of a fetal haemorrhage. It may be useful to examine amniotic fluid or fetal blood for grouping, cross-reacting analysis, haematological and virological tests, etc. Once non-immune hydrops has been diagnosed, all obstetric steps must be taken to deliver as early as possible. When maternal disease is responsible, it should receive specific treatment. Hydrops of another origin causes maternal problems, eg, polyhydramnios, pre-eclampsia, etc., and may be best managed by cesarean section with or without amniotic drainage, followed by a routine neonatal examination. If hydrops is diagnosed before the 30th week, pregnancy termination should be refused, especially if there is ascending fetal malformation. When hydrops is first diagnosed after 30 weeks, amniotic drainage should be made to ease the fetus, though the chance of success is poor. Fetal thoracostomy or drainage and paracentesis may be performed in the maternal abdominal wall, and can result in a transient relief. After drainage, amniotic fluid usually returns to normal. The prognosis for improvement is good, at least 50% of fetuses die in utero. The outcome also depends on the primary cause of the hydrops. Further prognosis may be particularly poor, but prenatal diagnosis is not always available.

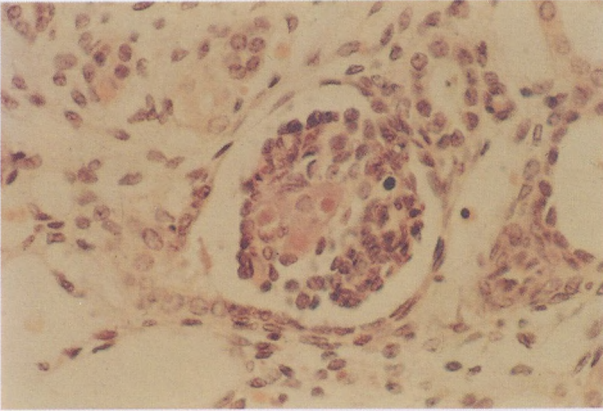


Figure 10-1. Intrauterine cytomegalovirus infection: viral inclusion bodies in glomerular mesangium (HE, x400).

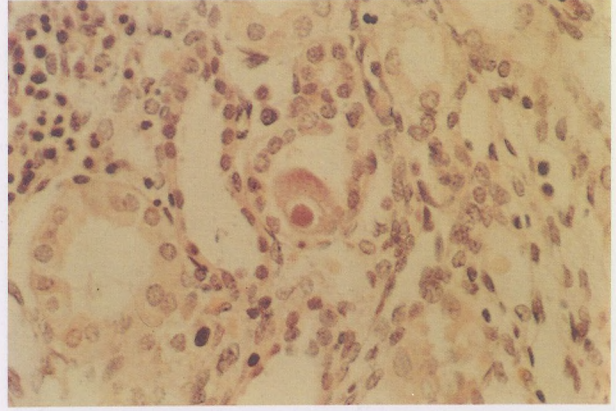


Figure 10-2. Intrauterine cytomegalovirus infection, renal tubules: CMV inclusion body in a tubular epithelial cell (HE, x400).

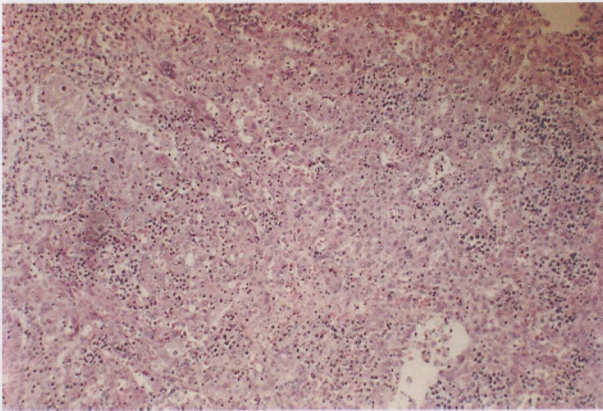


Figure 10-3. Cytomegalovirus infection with hepatitis: irregular pattern of hepatocytes and sinusoids (HE, x100).



Figure 10-4. Intrauterine cytomegalovirus infection: prominent abdomen, with ascites.

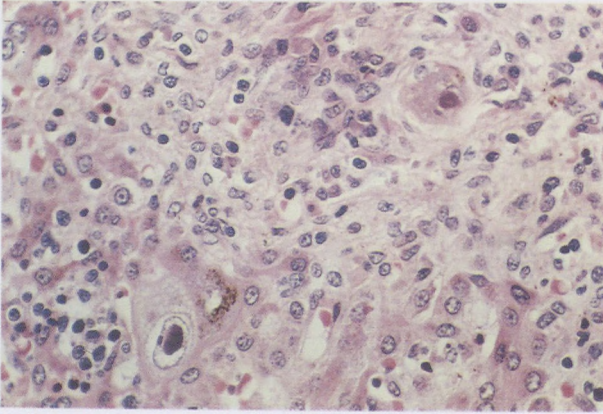


Figure 10-5. Cytomegalovirus infection with hepatitis, characteristic inclusion bodies within hepatocytes (HE, x400).

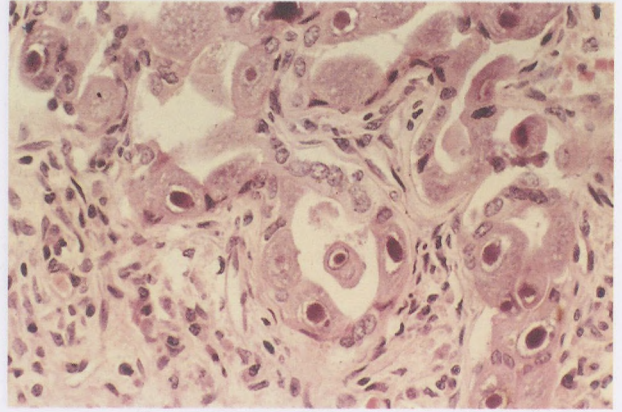


Figure 10-6. Cytomegalovirus hepatitis, bile ducts: typical inclusion bodies within epithelial cells (HE, x400).

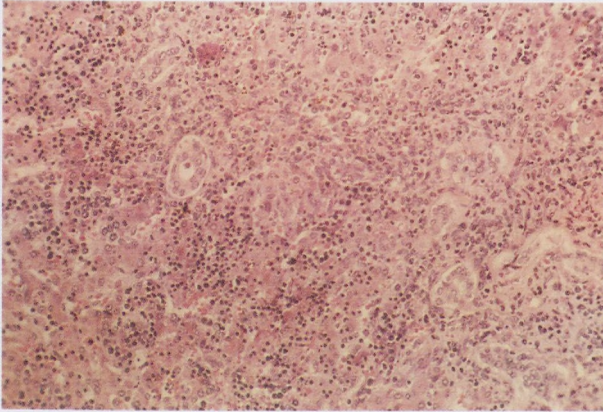


Figure 10-7. Cytomegalovirus hepatitis: disorganized hepatocytes and proliferation of the pseudobile ducts (HE, x160).

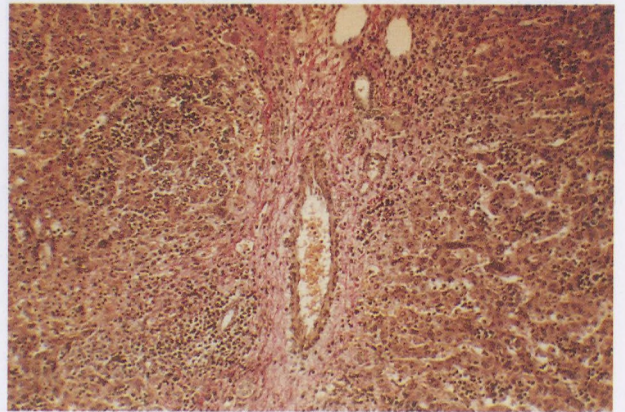


Figure 10-8. Cytomegalovirus hepatitis: increased connective tissue about the sinusoids and in the periportal space (Van Gieson, x100).

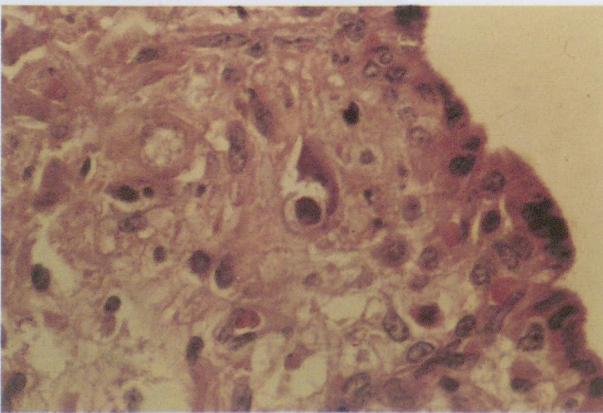


Figure 10-9. Intrauterine cytomegalovirus infection, placenta: CMV inclusion body in stromal cells suggest transplacental spread (HE, x400).

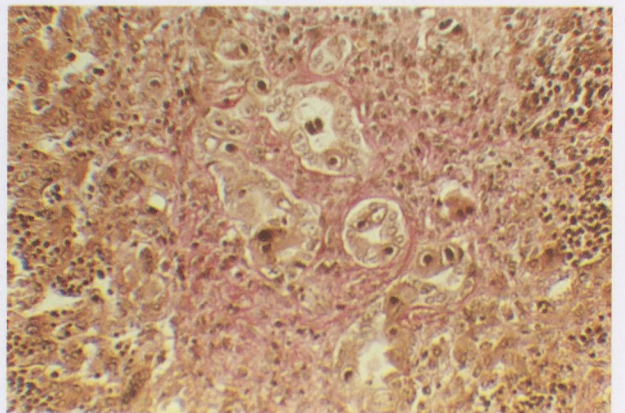
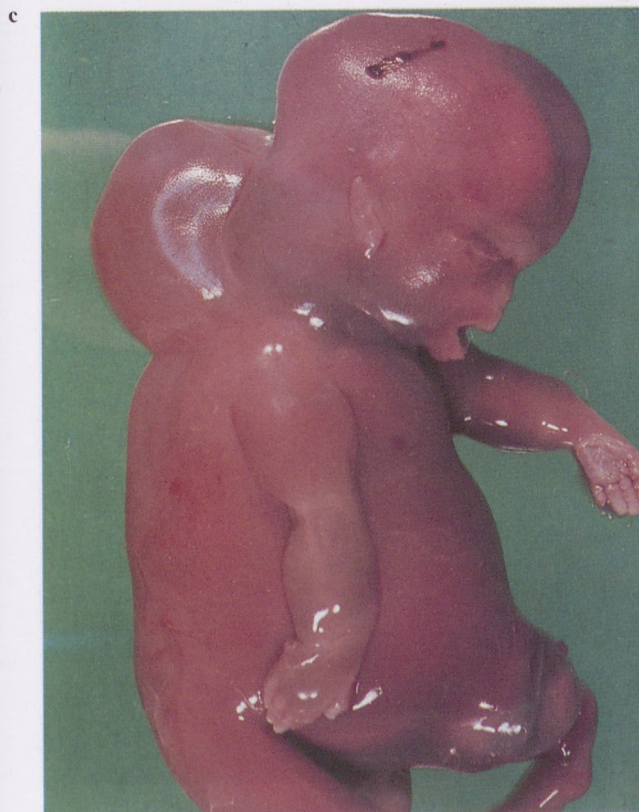
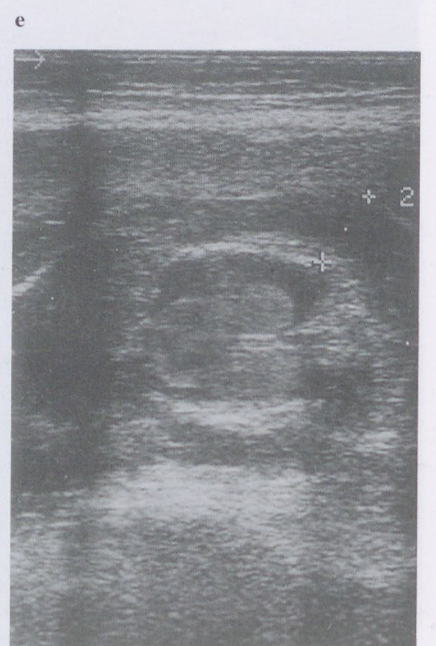
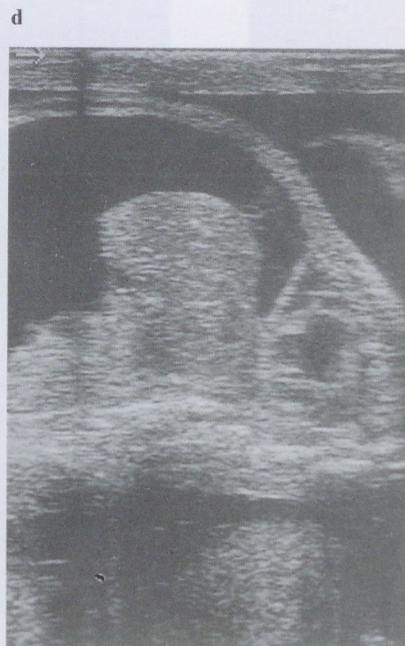
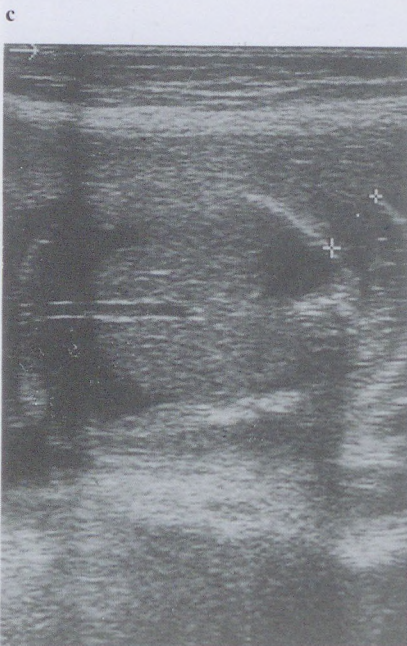
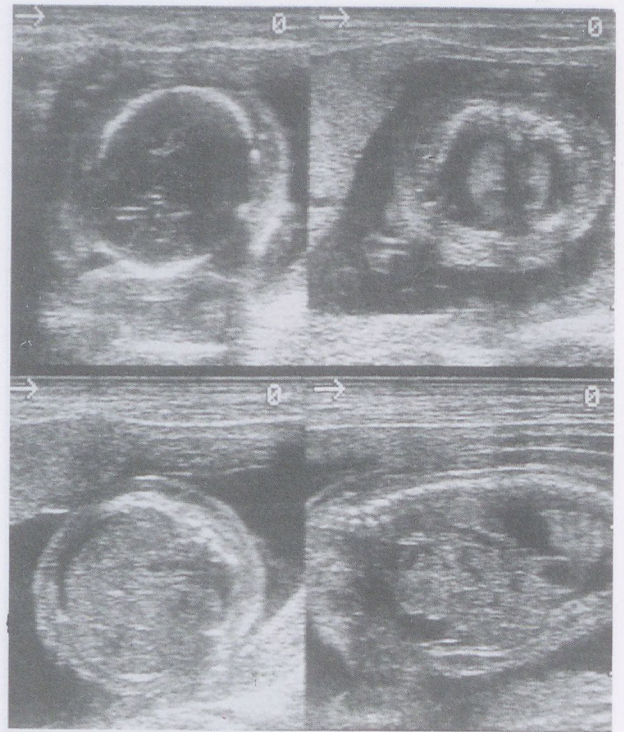
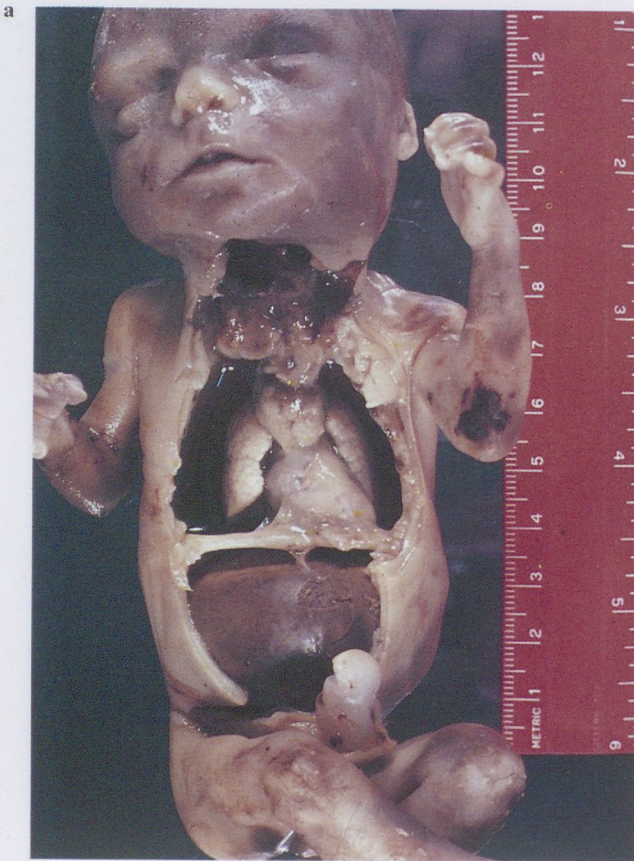


Figure 10-10. Pseudobile duct proliferation in the liver from a case of CMV infection (Van Gieson, x400).



Figures 10-11a, b, c and d. Different forms of severe cystic hygroma in mid-trimester fetuses diagnosed prenatally.



Figures 10-12a, b, c, d and e. Prenatally diagnosed non-immune hydrops (anasarca, hydrothorax with lung hypoplasia, and ascites) can be seen on the ultrasound views.



Figure 10-13. Nodular surface of the liver in congenital cirrhosis.



Figure 10-14. The inferior surface of the liver in congenital nodular cirrhosis.

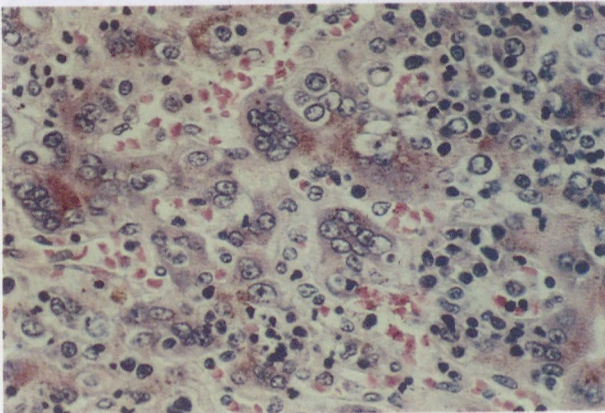


Figure 10-15. Giant-cell hepatitis: multinucleate hepatocytes with bile pigment stasis (their cytoplasm packed with bile pigment) (HE, x400).

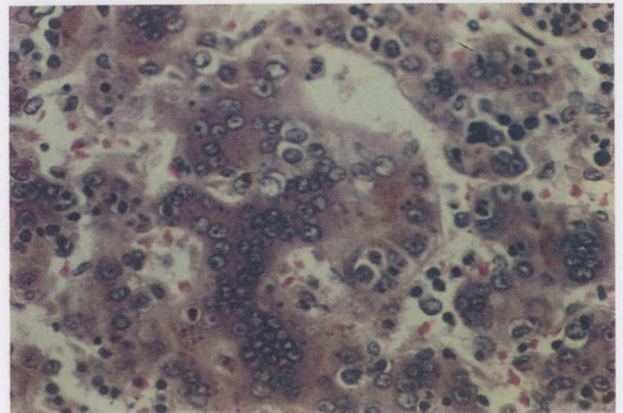


Figure 10-16. Giant-cell hepatitis: hepatocytes transformed into giant multinucleate syncytial cells (HE, x400).

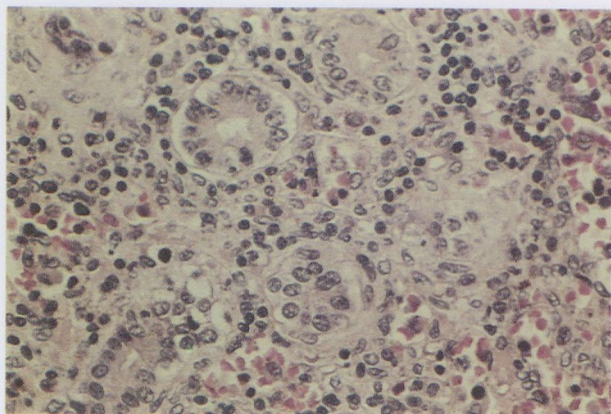


Figure 10-17. Bile duct proliferation in giant-cell hepatitis (HE, x400).

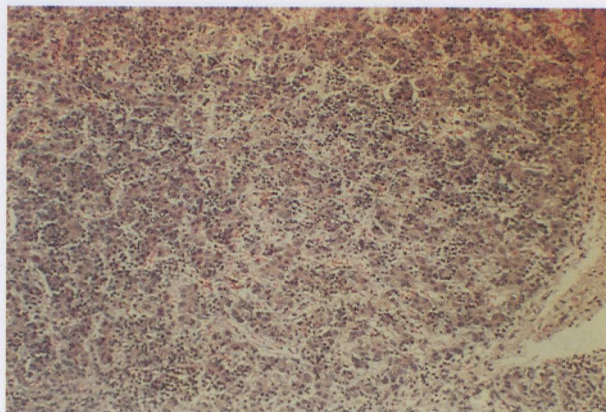


Figure 10-18. Giant-cell hepatitis: nodular liver structure with irregularly arranged hepatocytes (HE, x100).

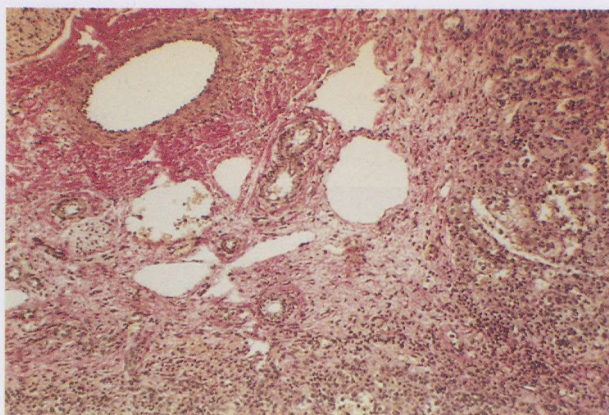


Figure 10-19. Giant-cell hepatitis: concentric bands of proliferating peripartal connective tissue (Van Gieson, x400).

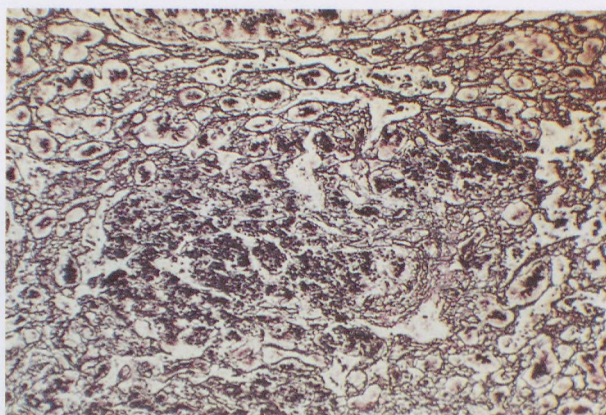
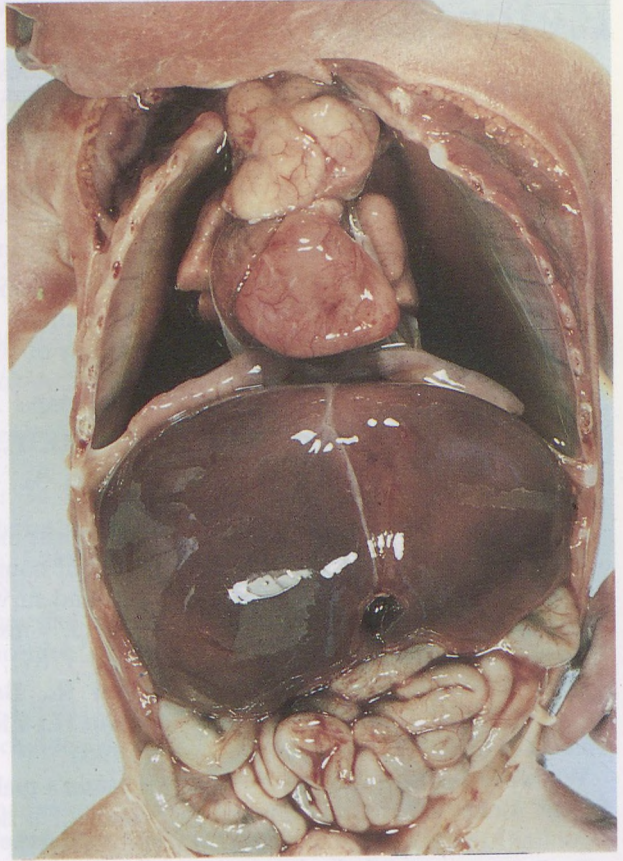


Figure 10-20. Giant-cell hepatitis: reticulin fibres at the periphery of a liver nodule (Gömöri's silver, x100).

a



b



Figures 10-21a and b. Severe non-immune hydropic fetus with cheilognathopalatoschisis diagnosed prenatally. The mother has hare lip.



Figure 10-22. Severely macerated hydropic fetus (non-immune hydrops).

References

- Abramowitz J. S., Warsof S. L., Coyle D. L., Smith D., Levy D. L. (1989)**
Congenital cystic hygroma of the neck diagnosed prenatally. Outcome with normal and abnormal karyotype.
Prenat. Diagn. 9, 321-327.
- Achiron R., Zakut H. (1986)**
Hydrops fetalis: Diagnostic work-up and antenatal sonography for better clinical management.
J. Foetal Med. 6, 47-52.
- Allan L., Little D., Campbell S., Whitehead M. I. (1981)**
Fetal ascites associated with congenital heart disease.
Br. J. Obstet. Gynaecol. 88, 453-456.
- Benacerraf B. B., Frigoletto F. D., Wilson M. (1986)**
Successful midtrimester thoracentesis with analysis of the lymphocyte population in the pleural effusion.
Am. J. Obstet. Gynecol. 155, 398-399.
- Binder N. D., Buckmast J. W., Benda G. I. (1988)**
Outcome for fetus with ascites and cytomegalovirus infection.
Pediatrics 82, 100-103.
- Blaakaer J. (1986)**
Ultrasonic diagnosis of fetal ascites and toxoplasmosis.
Acta Obstet. Gynecol. Scand. 65, 653-654.
- Boulley A. M., Vial M., Bessis R., Imbert M. C. (1984)**
Antenatal diagnosis of cytomegalovirus infection in 2 cases.
Arch. Fr. Pediatr. 41, 123-125.
- Bronshstein M., Blumenfeld Z. (1990)**
Spontaneous resolution of a nuchal fetal cystic hygroma diagnosed early in the 2nd trimester of pregnancy.
Am. J. Obstet. Gynecol. 163, 267-269.
- Brown B. S. J. (1986)**
The ultrasonographic features of nonimmune hydrops fetalis. A study of 30 successive patients.
J. Can. Assoc. Radiol. 37, 164-168.
- Carlson D. E., Platt L. D., Me-dearis A. L., Horenstein J. (1990)**
Prognostic indicators of the resolution of nonimmune hydrops fetalis and survival of the fetus.
Am. J. Obstet. Gynecol. 163, 1785-1787.
- Chaoui R., Bollmann R., Hoffmann H., Zienert A., Bartho S. (1990)**
Ebstein's malformation as a rare cause of a nonimmune hydrops fetalis (NIHF). Prenatal diagnosis using Doppler echocardiography.
Klin. Pädiatr. 202, 173-175.
- Chaoui R., Hoffmann H., Bollmann R., Wauer R. (1989)**
Prenatal diagnosis of a premature closure of the ductus arteriosus with subsequent development of a nonimmune hydrops fetalis (NIHF).
Geburtshilfe Frauenheilkd. 49, 1096-1098.
- Clark S. L., Vitale D. J., Minton S. D., Stoddard R. A., Sabey P. L. (1987)**
Successful fetal therapy for cystic adenomatoid malformation associated with 2nd-trimester hydrops.
Am. J. Obstet. Gynecol. 157, 294-295.
- Cyr D. R., Guntheroth W. G., Nyberg D. A., Smith J. R., Nudelman S. R., Ek M. (1988)**
Prenatal diagnosis of an intrapericardial teratoma. A cause for non-immune hydrops.
J. Ultrasound Med. 7, 87-90.
- Distell B. M., Hetzberg B. S., Bowie J. D. (1990)**
Spontaneous resolution of a nuchal fetal cystic hygroma diagnosed early in the 2nd trimester of pregnancy.
A. J. R. 154, 903-903.
- Downing G. J., Kilbride H. W., Yeast J. D. (1990)**
Non-immune hydrops fetalis caused by a massive fetomaternal hemorrhage associated with elevated maternal serum alpha fetoprotein levels. A case report.
J. Reprod. Med. 35, 444-446.
- Edwards M. J., Graham J. M. (1990)**
Posterior nuchal cystic hygroma.
Clin. Perinatol. 17, 611-640.
- Eliezer S., Ester F., Ehud W., Henryk Z. (1984)**
Fetal splenomegaly: Ultrasound diagnosis of cytomegalo-virus infection.
J. Clin. Ultrasound 12, 520-521.
- Eliezer S., Ester F., Ehud W., Henryk Z. (1984)**
Fetal splenomegaly, ultrasound diagnosis of cytomegalovirus infection: A case report.
J. Clin. Ultrasound 12, 520-521.
- Fadel H. E., Ruedrich D. A. (1988)**
Intrauterine resolution of nonimmune hydrops associated with cytomegalovirus infection.
Obstet. Gynecol. 71, 1003-1005.
- Fleischer A. C., Killam A. P., Boehm F. H., Hutchinson A. A., Jones T. B., Shaff M. I., Barrett J. M., Lindsey A. M., James A. E. (1981)**
Hydrops fetalis: Sonographic evaluation and clinical implications.
Radiology 141, 163-168.
- Gembruch U., Niesen M., Hansmann M., Knopfle G. (1987)**
Listeriosis. A cause of non-immune hydrops fetalis.
Prenat. Diagn. 7, 277-282.

- Gonen R., Fong K., Chiasson D. A.** (1989)
Prenatal sonographic diagnosis of hepatic hemangioendothelioma with secondary nonimmune hydrops fetalis.
Obstet. Gynecol. 73, 485-487.
- Gough J. D., Keeling J. W., Castle B., Iliff P. J.** (1986)
The obstetric management of non-immunological hydrops.
Br. J. Obstet. Gynecol. 93, 226-234.
- Graves G. R., Baskett T. F.** (1984)
Nonimmune hydrops fetalis: Antenatal diagnosis and management.
Am. J. Obstet. Gynecol. 148, 563-565.
- Gudmundsson S., Wood D. C., Tulzer G., Cohen A. W., Weiner S.** (1991)
Venous Doppler ultrasonography in the fetus with nonimmune hydrops.
Am. J. Obstet. Gynecol. 164, 33-37.
- Holzgreve W., Holzgreve B., Curry C. J. R.** (1985)
Nonimmune hydrops fetalis. Diagnosis and management.
Semin. Perinatol. 9, 52-67.
- Hsieh F. J., Chang F. M., Ko T. M., Chen H. Y.** (1987)
Percutaneous ultrasound-guided fetal blood sampling in the management of nonimmune hydrops fetalis.
Am. J. Obstet. Gynecol. 157, 44-49.
- Imua S. S., Rizos N., Joutsu P., Shime J., Benzie R. J.** (1984)
Nonimmunologic hydrops fetalis.
Am. J. Obstet. Gynecol. 148, 566-569.
- Kirkinen P., Jouppila P., Leisti J.** (1987)
Transient fetal ascites and hydrops with a favorable outcome. A report of 2 cases.
J. Reprod. Med. 32, 379-382.
- Lenke R. R., Cyr D. R., Mack L. A., Norwood T. H.** (1986)
Fetal hydrops secondary to a paratracheal hemangiomatous malformation.
J. Ultrasound Med. 5, 223-225.
- Levy I., Shohat M., Levy Y., Alpert G., Nitzan M.** (1989)
Recurrent ascites in an infant with perinatally acquired cytomegalovirus infection.
Eur. J. Pediatr. 148, 531-532.
- Machin G. A.** (1989)
Hydrops revisited. Literature review of 1,414 cases published in the 1980s.
Am. J. Med. Genet. 34, 366-390.
- Maconoch I. K., Chong S. K. F., Mieli-Vergani G., Lake B. D., Mowat A. P.** (1989)
Fetal ascites. An unusual presentation of Niemann-Pick disease type-C.
Arch. Dis. Child. 64, 1391-1393.
- McGahan J. P., Scheider J. M.** (1986)
Fetal neck hemangioendothelioma with secondary hydrops fetalis. Sonographic diagnosis.
J. Clin. Ultrasound 14, 384-388.
- Meizner I., Carmi R., Katz M., Inslar V.** (1989)
Prenatal ultrasonic diagnosis of cystic hygroma associated with fetal hydrops.
Isr. J. Med. Sci. 25, 51-53.
- Meizner I., Levy A., Cohen J.** (1990)
Spontaneous resolution of a nuchal fetal cystic hygroma diagnosed early in the 2nd trimester of pregnancy.
A. J. R. 154, 903-903.
- Meizner I., Levy A., Cohen J.** (1990)
Spontaneous resolution of a nuchal fetal cystic hygroma diagnosed early in the 2nd trimester of pregnancy.
Am. J. Obstet. Gynecol. 163, 267-268.
- Murayama K., Jimbo T., Matsu-moto Y., Mitsuishi G., Nishida N.** (1987)
Fetal pulmonary hypoplasia with hydrothorax.
Am. J. Obstet. Gynecol. 157, 119-120.
- Naides S. J., Weiner C. P.** (1989)
Antenatal diagnosis and palliative treatment of non-immune hydrops fetalis secondary to fetal parvovirus-B19 infection.
Prenat. Diagn. 9, 105-114.
- Phillips H. E., McGahan J. P.** (1981)
Intrauterine fetal cystic hygromas: Sonographic detection.
A. J. R. 136, 799-802.
- Robertson L., Ott A., Mack L., Brown Z. A.** (1985)
Sonographically documented disappearance of nonimmune hydrops fetalis associated with maternal hypertension.
West. J. Med. 143, 382-383.
- Samuels P., Ludmir J.** (1990)
Nonimmune hydrops fetalis. A heterogeneous disorder and therapeutic challenge.
Semin. Roentgenol. 25, 353-360.
- Sarno A. P., Bruner J. P., Southgate W. M.** (1990)
Congenital chyloperitoneum as a cause of isolated fetal ascites.
Obstet. Gynecol. 76, 955-957.
- Schmid G., Fahrenstoch H., Redel D. A., Gembruch U., Niesen M., Kowalewski S.** (1988)
Nonimmunologic hydrops fetalis. A survey of 31 cases.
Klin. Pädiatr. 200, 287-293.
- Shah Y. P., Hadlock F. P.** (1990)
Hydrops and ascites.
In: *Diagnostic ultrasound of fetal anomalies*. Ed. Nyberg, D. A., Mahony, B. S., Proterius, D. H., Year Book Medical Publishers, Inc., Chicago, pp. 563-591.
- Stagno S., Pass R. F., Dworsky M. E., Alford C. A.** (1983)
Congenital and perinatal cytomegalovirus infections.
Semin. Perinatol. 7, 31-42.

- Szeifert G. T., Csécssei K., Tóth Z., Papp Z. (1985)**
Prenatal diagnosis of ascites caused by cytomegalovirus hepatitis.
Acta Paediatr. Hung. 26, 311-316.
- Toma P., Magnano G. M., Mezzano P., Lazzini F., Bonacci W., Serra G. (1989)**
Cerebral ultrasound images in prenatal cytomegalovirus infection.
Neuroradiology 31, 278-279.
- Villaespesa A. R., Mier M. P. S., Ferrer P. L., Baleriola I. A., Gonzalez J. I. (1990)**
Nonimmunologic hydrops fetalis. An etiopathogenetic approach through the postmortem study of 59 patients.
Am. J. Med. Genet. 35, 274-279.
- Warsof S. L., Nicolaides K. H., Roddeck C. (1986)**
Immune and non-immune hydrops.
Clin. Obstet. Gynecol. 29, 533-542.
- Watson J., Campbell S. (1986)**
Antenatal evaluation and management in nonimmune hydrops fetalis.
Obstet. Gynecol. 67, 589-593.
- Weiner C., Varner M., Pringle K., Hein H., Williamson R., Smith W. L. (1986)**
Antenatal diagnosis and palliative treatment of non-immune hydrops fetalis secondary to pulmonary extralobar sequestration.
Obstet. Gynecol. 68, 275-279.
- Weinraub Z., Gembruch U., Fodisch H. J., Hansmann M. (1989)**
Intrauterine mediastinal teratoma associated with non-immune hydrops fetalis.
Prenat. Diagn. 9, 369-372.
- Zarabi M., Mieczkowski G. C., Mazer J. (1983)**
Cystic hygroma associated with Noonan's syndrome.
J. Clin. Ultrasound 11, 398-400.

Chromosome Aberrations

Human cells normally carry 46 chromosomes. The systematically arranged chromosome set characteristic of a given individual is the *karyotype*. The photographed chromosomes, cut out from a specific metaphase, are displayed in order of size.

The human chromosomes are conventionally examined in lymphocyte cultures prepared from peripheral blood, but they can be examined in any dividing human cell (e.g., bone marrow, endometrium or chorionic villi) or in cultured cells (e.g., amniotic fluid cells, skin fibroblasts).

Chromosome aberrations are mutations of the inheritance material, involving duplication/trisomy, deletion/monosomy or rearrangements of the chromosomes large enough to be observed with the light-microscope. Available methods allow recognition of an excess or deficiency down to about 0.2% of the genome, i.e., about 6 million base pairs; a little more resolution, to 2-3 megabases, may sometimes be attained with high-resolution techniques.

Individuals with a chromosome duplication or deletion are "chromosomally unbalanced", while those having a complete chromosome set but in a rearranged form are "chromosomally balanced". Most balanced rearrangements and a few unbalanced aberrations are without serious clinical consequences; pregnancies with chromosomally balanced fetuses are usually left to go to term. However, an unbalanced chromosome constitution is usually

associated with mental retardation and more or less severe multiple physical defects; there is a case for prenatal screening and discussion of pregnancy termination. Duplication/trisomy involving more than 1-2% of the genome, or deletion/monosomy involving more than 0.5-1%, is usually not compatible with survival to live birth.

Chromosome aberrations can be divided into numerical or structural, and into those involving autosomes and those involving the sex chromosomes.

Chromosome aberrations are present, at conception, in nearly 10% of zygotes. Chromosomally abnormal zygotes are of reduced viability, and most of the affected embryos die, aborting spontaneously. Only 0.6% of live-born infants are affected. Chromosome aberrations are present in 60% of early abortions, in 6% of mid-trimester abortions and in 4-5% of stillborn fetuses.

Although there are exceptions, in general additional chromosomal material is more compatible with life than a deficiency. In abortion material we find mainly trisomies and triploidy. The monosomic zygotes die and are eliminated without any clinical sign of abortion; among the monosomic zygotes only those with X monosomy are viable. (Nevertheless, only 2% of these survive the intrauterine period; these are born with Ullrich-Turner syndrome.) In samples from spontaneous abortions trisomy for any of the chromosomes, except chromosome 1 and 5, may be found; trisomy 16 occurs

most frequently. Trisomy 16 leads to abortion in every case, but a small number of some of the other trisomies escape intrauterine selection and may be born alive (1-2% of trisomy 13, 5-10% of trisomy 18 and 15-25% of trisomy 21).

Live-born children can be classified into three groups, depending on whether they are phenotypically affected, and if so, how severely. It is a general rule that autosomal aberrations produce more severe problems than aberrations and reduplications of the sex chromosomes.

Balanced chromosome rearrangements (these occur the most frequently) cause no clinical symptoms, and virtually all are compatible with a healthy life (the risk is to the children!).

On the other hand, autosomal trisomies and unbalanced rearrangements may lead to severe multiple malformation syndromes and severe mental retardation. Life expectancy is reduced; there is even a high mortality in the neonatal period.

Mortality for sex chromosome aneuploidies is not high. There may be problems with sexual differentiation. Other aspects of physical and mental development are scarcely affected, if at all. However, some prenatally diagnosed sex chromosome aneuploidies may sometimes be terminated, at the request of the couple concerned.

Among the chromosome disorders, trisomies of chromosomes 21, 18 and 13, duplication-deletion syndromes and the sex chromosome disorders, are clinically the most important.

Trisomy 21

The abnormality characteristic of Down syndrome, is of outstanding importance, being the commonest of all the chromosome disorders resulting in mental retardation (it accounts for 25-30% of the severely subnormal population surviving beyond the age of 5 years), and because its birth prevalence, 1/700 at present, can be reduced by intervention. The frequency of trisomy 21 is much higher at conception, but some 85% of affected embryos/fetuses die *in utero*, as spontaneous abortions or late fetal losses (stillbirths).

Characteristics include brachycephaly, a flat profile, upward-slanting (mongoloid) palpebral fissures, Brushfield spots (in the iris), epicanthus, small nose, apparently low-set small ears and large tongue. There are excess skin folds, especially at the nape of the neck. The hands are small but broad; there is usually a complete transverse palmar crease (uni- or bilateral), and abnormal flexion creases on the bent little fingers (*clinodactyly*). The finger dermal ridges, on hands and feet, also show characteristic deviations from normal. About 40% have congenital heart defects (ASD, VSD), and duodenal atresia, Hirschsprung disease, hypothyroidism, and congenital leukaemia are each present in 1% or more of newborn infants. Many signs of Down syndrome can be seen in affected fetuses terminated in mid-trimester.

Growth retardation is characteristic of Down syndrome. The average weight of the newborn infant and placenta is less than that of normal infants (weight is 0.5 kg less), and height does not reach 150 cm in many adults.

Life expectancy depends on the associated problems (cardiac and duodenal defects, and bone marrow disease). Some decades ago, 50% of affected children died before their first birthday; now, due to improving social conditions and better

medical care, more reach adulthood (about 50% of all live-born survive into the third decade of life).

Prenatal diagnosis. Despite the most devoted parental or institutional care, children with Down syndrome impose a considerable emotional, practical and financial burden on their families and on the community/social services and public health. For a number of reasons couples are unwilling or unhappy to bear children with Down syndrome, and request pregnancy diagnosis and termination.

Prenatal diagnosis involves chromosome analysis of fetal cells from amniotic fluid or chorionic villus samples. Amniocentesis/CVS may be offered to all mothers whose age-specific risk exceeds a pre-set level: this will be determined by the local availability of obstetric and cytogenetic services and also by public awareness and demand.

Recently, a number of studies have shown the maternal serum AFP (MSAFP) to be reduced in Down syndrome pregnancies (means of 0.7-0.8 MoM). The individual pregnancy risk for Down syndrome can be calculated from maternal age and MSAFP. Prospective studies suggest this is an effective way of screening for Down syndrome (and for trisomy 18 also). Fewer amniocenteses need be done in older mothers (those with MSAFP of 1.0-2.0 MoM will be at lower risk for Down syndrome); amniocentesis can be offered to some younger mothers, particularly in age groups 28-34 years (those with low MSAFP). With much more selective amniocentesis a greater proportion of prenatal chromosome analyses will yield an abnormality (combining AFP and maternal age screening). Use of two or three maternal serum tests (AFP, oestriol, gonadotropin) gives an even higher detection rate (relatively more trisomic pregnancies for fewer amniocenteses).

The ultrasound method (measuring the thickness of skin at the back

of the neck) offers possibilities, but further data are needed before such screening should be adopted.

One should remember that risks for all the common autosomal trisomies are maternal age-related, and they too will be detected in Down syndrome screening programmes. It is not yet clear whether the introduction of chorionic villus sampling (CVS) has made it easier to undertake large-scale screening programmes, although, for the mother herself, it has obvious advantages.

Trisomy 18

Ninety-five per cent of trisomy 18 embryos will die *in utero*, mostly in the first trimester; the remainder will be born alive, with a characteristic multiple malformation syndrome (Edwards syndrome). Most of the live-born infants are female. Prevalence at birth: 1/3000.

Severe growth retardation is characteristic; birth weight seldom exceeds 2000 g at term. Many infants are delivered prematurely, by caesarean section, on account of growth retardation and poor indexes of fetal wellbeing and placental function. About 10-15% have omphalocele and/or neural tube defects, and may be picked up on fetal malformation screening. Most others could be identified by screening for aneuploidies (they are often born to older mothers, and there is low MSAFP).

Other malformations frequently include congenital heart and renal defects; the characteristic profile, crossed fingers and abnormal hallux can be seen on mid-trimester ultrasound. The occiput is prominent, the forehead rounded, the nose small, the chin receding, and ears low-set. Dermatoglyphic analysis shows most fingers and toes to carry a simple arch pattern. At least 30%, probably more, die within a month of birth; only 1-2% survive to the first birthday (these are virtually all female); developmental retardation is extreme.

The trisomy almost always arises *de novo*, presumably following a meiotic error in a parent (parents have normal chromosomes). Very rarely the trisomy derives from a parental translocation (3:1 segregation). Although a few children with long survival have been shown to be mosaics (with a normal cell-line also), mosaicism for trisomy 18 usually produces a different clinical picture, with a variable degree of growth and mental retardation and with a very asymmetric pattern of malformations.

Trisomy 13

Ninety-nine per cent of embryos with trisomy 13 will die *in utero*; 1% are born alive, with characteristic multiple malformation syndrome (Patau syndrome). Prevalence at birth: 1/5000.

Most characteristic is the holoprosencephaly sequence (hypotelorism, micro/anophthalmos, severe clefts of lip and palate—bilateral more often than midline, with ultrasound evidence of a malformed forebrain): the holoprosencephaly can be detected on mid-trimester ultrasound. Other striking and commonly-found abnormalities include a scalp defect (usually over the vertex, and sometimes very large, exposing the brain), and postaxial polydactyly of hands or feet. Facial characteristics include a large straight nose with a hooked tip, apparently low-set ears, and the cranium is high and rounded. Long

narrow finger-nails and abnormal dermatoglyphics are present, together with heart and kidney defects. A Meckel diverticulum and uterus bicornis are common.

The disease is very severe; 50% of live-born infants die within a week, and virtually all within six months.

In 75% of cases the extra chromosome 13 results from a parental meiotic error: the parents have normal chromosomes and there is a low risk of recurrence.

In 20% of cases a parent is a balanced 13/14 translocation carrier; in such cases the recurrence risk for trisomy 13 may not be very great, but prenatal chromosome analysis in subsequent pregnancies is probably advisable. Five per cent of cases are mosaic, with a low risk of recurrence (< 1%); mosaics may survive longer.

Trisomy 13 pregnancy in primiparous women may be associated with severe pre-eclampsia.

Duplication and Deficiency (Deletion) Syndromes

Partial trisomies (duplications) and partial monosomies (deficiencies, deletions) are associated with structural changes of the chromosomes. They usually result in multiple congenital anomaly syndromes with mental retardation. Some are much more severe than others: many result in death *in utero* or in the newborn period, but a few are compatible with life and even normal schooling and employment. Birth prevalence is about 1/2000.

Partial monosomies and trisomies may arise as new (chromosomal) mutations, or may derive, by unbalanced segregation, or recombination, from a balanced rearrangement in a parent. Parental chromosomes must always be checked carefully before advising on recurrence risk and management of further pregnancies.

When parents are chromosomally normal, risks of recurrence are low, although one cannot exclude the possibility of germ-line mosaicism with a clone of abnormal cells in a parental gonad.

Should a parent carry a chromosome rearrangement (translocation, inversion, insertion, etc.), the risk of a further chromosomally unbalanced child is usually appreciable; prenatal chromosome analysis can be done in subsequent pregnancies.

Once a rearrangement has been found in a parent, close relatives should be examined, as they also may be carriers.

A number of unusual syndromes, usually of sporadic occurrence, have been recognized recently as associated with very small interstitial deletions, just at the limit of resolution using the light microscope (2000-5000 kb). There is a spectrum of deletions ranging from the microscopically visible to those detectable only by DNA technology. Deletions involving more than 30,000 kb are likely to be lethal *in utero*, but deletions involving only part of a single gene, which may be as small as only few kb, can be almost as damaging.

a



b



a



b



Figures 11-1a and b. Trisomy 21: nuchal oedema, abnormal ear, characteristic facial profile – flattening of the upper face.

Figures 11-2a and b. Down's syndrome: termination at 20 weeks, mother a known carrier of a Robertsonian 14q21q translocation.



Figure 11-3. Trisomy 21, induced abortion at 20 weeks; previous trisomy.



Figures 11-4a and b. Termination of pregnancy followed finding of *de novo* balanced reciprocal translocation with breakpoints at 1p22 and 5q35. (Amniocentesis had been done for raised maternal serum AFP.) There were no striking internal or external anatomical defects.



Figures 11-5a and b. Cystic hygroma, lateral (a) and frontal (b) view: this fetus had a *de novo* chromosome deletion - del(7)(p13p15) - found at amniocentesis for maternal age.



Figures 11-6a and b. "Cri-du-chat" found at amniocentesis for high serum alfafetoprotein: *de novo* rearrangement of chromosomes 5 and 22.



Figure 11-7. X-monosomy with typical cystic hygroma (nuchal bleb).



Figure 11-8. Trisomy 18, liveborn, face. High rounded forehead, small nose, small mouth, micrognathia. Low frontal and temporal hairline.



Figure 11-9. Trisomy 18, liveborn, profile. Prominent occiput, micrognathia, ear low-set and dysplastic, with preauricular skin tag.



Figure 11-10. Trisomy 18, liveborn, hand. Long fingers, thumb and index flexed across middle finger; small deep-set nails on index, middle and little fingers. Ulnar deviation at wrist.



Figure 11-11. Trisomy 18, liveborn, foot. Short stubby hallux in hammer-toe position.



Figure 11-12. Trisomy 18, phenotype of the infant: low-set ear, cleft lip and palate, shortened right arm and fingers are also present.



Figure 11-13. Trisomy 18, median cleft lip and palate, broad nasal tip, malformed ears and high rounded forehead.



Figure 11-14. Trisomy 18, lateral view: characteristic facial profile and prominent occiput, left wrist deformity and prominent heels.



Figure 11-15. Trisomy 18, postaxial polydactyly (postminimi, no bony tissue).



Figure 11-16. Trisomy 18, X-ray, chest. Thirteen ribs; ribs very slender.

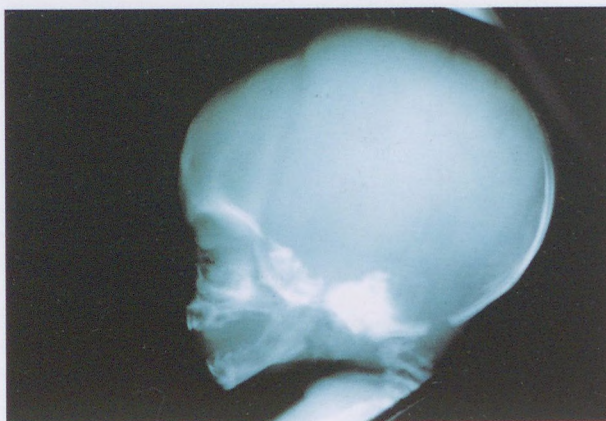


Figure 11-17. Trisomy 18, X-ray, lateral skull. Long AP diameter with prominent occiput and relatively small face. Very marked hypodontia.



Figure 11-18. Trisomy 18, X-ray, hand. Extremely short first metacarpal; short middle phalanx in little finger.



Figure 11-19. Trisomy 18: characteristic position of wrist and fingers.

Figure 11-20. Trisomy 18: lateral view of a fetus.



Figure 11-21. Trisomy 18 (microcephaly with distal limb defects): termination at the 18th gestational week.



Figure 11-22. Trisomy 9: high rounded cranial vault, severe micrognathia and deformed ear.



Figure 11-23. Trisomy 13: pregnancy terminated at 22 weeks. Bilateral cleft lip and palate.



Figure 11-24. Trisomy 13: profile showing short, thick neck, high cranial vault, deep-set eyes, cleft lip (and palate) with prominent premaxilla, moderate micrognathia.



Figure 11-25. Trisomy 13, neonate: microphthalmia and characteristic large nose, holoprosencephaly and death at one week.

References

- Achiron R., Zaidel L., Zakut H.** (1986)
Antenatal diagnosis of duodenal atresia associated with nonimmunologic hydrops fetalis in a 21 trisomy fetus.
J. Foetal Med. 6, 74-76.
- Basaran S., Miny P., Pawlowitzki I. H., Horst J., Holzgreve W.** (1988)
Rapid karyotyping for prenatal diagnosis in the second and third trimesters of pregnancy.
Prenat. Diagn. 8, 315-320.
- Bell J., Hilden J., Bowling F., Pearn J., Brownlee A., Martin N.** (1986)
The impact of prenatal diagnosis on the occurrence of chromosome abnormalities.
Prenat. Diagn. 6, 1-11.
- Benacerraf B. B., Barss V. A., Laboda L. A.** (1985)
A sonographic sign for the detection in the second trimester of the fetus with Down's syndrome.
Am. J. Obstet. Gynecol. 151, 1078-1079.
- Benacerraf B. B., Cnann A., Gelman R., Laboda L. A., Frigoletto F. D.** (1989)
Can sonographers reliably identify anatomic features associated with Down syndrome in fetuses?
Radiology 173, 377-380.
- Benacerraf B. B., Frigoletto F. D., Laboda L. A.** (1985)
Sonographic diagnosis of Down syndrome in the second trimester.
Am. J. Obstet. Gynecol. 153, 49-52.
- Benacerraf B. B., Frigoletto F. D., Greene M. F.** (1986)
Abnormal facial features and extremities in human trisomy syndromes. Prenatal ultrasonographic appearance.
Radiology 159, 243-246.
- Benacerraf B. B., Frigoletto F. D.** (1990)
The current role of sonography in the detection of Down syndrome.
Obstet. Gynecol. 75, 472-472.
- Benacerraf B. B., Gelman R., Frigoletto F. D.** (1988)
Sonographic identification of Dows's syndrome.
N. Engl. J. Med. 318, 1399-1399.
- Benacerraf B. B., Harlow B., Frigoletto F. D.** (1990)
Are choroid plexus cysts an indication for 2nd trimester amniocentesis?
Am. J. Obstet. Gynecol. 162, 1001-1006.
- Benacerraf B. B., Mandell J., Estroff J. A., Harlow B. L., Frigoletto F. D.** (1990)
Fetal pyelectasis. A possible association with Down syndrome.
Obstet. Gynecol. 76, 58-60.
- Benacerraf B. B., Miller W. A., Frigoletto F. D.** (1988)
Sonographic detection of fetuses with trisomy 13 and trisomy 18. Accuracy and limitations.
Am. J. Obstet. Gynecol. 158, 404-409.
- Benacerraf B. B., Neuberger Donna, Frigoletto F. D.** (1991)
Humeral shortening in second-trimester fetuses with Down syndrome.
Obstet. Gynecol. 77, 223-227.
- Benacerraf B. B., Saltzman D. H., Estroff J. A., Frigoletto F. D.** (1990)
Abnormal karyotype of fetuses with omphalocele. Prediction based on omphalocele contents.
Obstet. Gynecol. 75, 317-319.
- Brumfield C. G., Hauth J. C., Cloud G. A., Davis R. O., Henson B. V., Cosper P.** (1989)
Sonographic measurements and ratios in fetuses with Down syndrome.
Obstet. Gynecol. 73, 644-646.
- Bundy A. L., Saltzman D. H., Poher B., Fine C., Emerson D., Doubilet P. M.** (1986)
Antenatal sonographic findings in trisomy-18.
J. Ultrasound Med. 5, 316-364.
- Canki N., Warburton D., Byrne J.** (1988)
Morphological characteristics of monosomy-X in spontaneous abortions.
Ann. Genet. 31, 4-13.
- Carr R. F., Ochs R. H., Ritter D. A., Kenny J. D., Frider J. L., Ming P. L.** (1986)
Fetal cystic hygroma and Turner's syndrome.
Am. J. Dis. Child. 140, 580-583.
- Cheung S. W., Kolacki P. L., Watson M. S., Crane J. P.** (1988)
Prenatal diagnosis, fetal pathology, and cytogenetic analysis of mosaic trisomy-14.
Prenat. Diagn. 8, 677-682.
- Chodirker B. N., Harman C. R., Greenberg C. R.** (1988)
Spontaneous resolution of a cystic hygroma in a fetus with Turner syndrome.
Prenat. Diagn. 8, 291-296.
- Chodirker B. N., Harman C. R., Greenberg C. R.** (1990)
Survival of fetuses with abnormal karyotypes and cystic hygromas detected prenatally.
Prenat. Diagn. 10, 136-136.
- Cuckle H. S., Wald N. J., Quinn J., Royston P., Butler L.** (1989)
Ultrasound fetal femur length measurement in the screening for Down's syndrome.
Br. J. Obstet. Gynaecol. 96, 1369-1378.
- DeGrouchy J., Turleau C.** (1984)
Clinical Atlas of Human Chromosomes.
John Wiley and Sons, New York

- Dicke J. M., Gray D. L., Songster G. S., Crane J. P. (1989)**
Fetal biometry as a screening tool for the detection of chromosomally abnormal pregnancies.
Obstet. Gynecol. 74, 726-729.
- Droste S., Fitzsimmons J., Pascoe-Mason J., Shepard T. H. (1990)**
Growth of linear parameters in trisomy 18 fetuses.
Am. J. Obstet. Gynecol. 163, 158-161.
- Eydoux P., Choiset A., Lepporrie N., Thepot F., Scpirota S., Alliei J., Ramond S., Viel J. F., Gautier E., Morichon N. (1989)**
Chromosomal prenatal diagnosis. Study of 936 cases of intrauterine abnormalities after ultrasound assessment.
Prenat. Diagn. 9, 255-268.
- Fitzsimmons J., Droste S., Shepard T. H., Pascoe-Mason J., Chinn A., Mack L. A. (1989)**
Long-bone growth in fetuses with Down syndrome.
Am. J. Obstet. Gynecol. 161, 1174-1177.
- Fitzsimmons J., Wilson D., Pascoe-Mason J., Shaw C. M., Cyr D. R., Mack L. A. (1989)**
Choroid plexus cysts in fetuses with trisomy 18.
Obstet. Gynecol. 73, 257-260.
- Fryns J. P., Kleczkowska A., Moerman F., Van der Berghe K., Van der Berghe H. (1986)**
The fetal phenotype in 2p trisomy.
Ann. Genet. 29, 269-271.
- Fujimoto A., Broom D. L., Shinno N. W., Wilson M. G. (1983)**
Nonimmune fetal hydrops and Down syndrome.
Am. J. Med. Genet. 14, 533-537.
- Ginsberg N., Cadkin A., Pergament E., Verlinsky Y. (1990)**
Ultrasonographic detection of the 2nd trimester fetus with trisomy 18 and trisomy 21.
Am. J. Obstet. Gynecol. 163, 1186-1190.
- Gocke H., Muradow I., Stein W. (1988)**
The fetal phenotype of the 18p-syndrome. Report of a male fetus at 21 weeks.
Ann. Genet. 31, 60-64.
- Heller R. H., Adams J. E., Hirschfeld R. L., Tapper A. J. (1981)**
Ultrasonic detection of an abnormal mass in a fetus later shown to have trisomy 18.
Prenat. Diagn. 1, 223-226.
- Hentemann M., Rauskolb R., Ulbrich R., Bartels I. (1989)**
Abnormal pregnancy sonogram and chromosomal anomalies. Four years experience with rapid karyotyping.
Prenat. Diagn. 9, 605-612.
- Hill L. M., Guzick D., Belfar H. L., Hixson J., Rivello D., Rusnak J. (1989)**
The current role of sonography in the detection of Down syndrome.
Obstet. Gynecol. 74, 620-623.
- Hill L. M., Guzick D. S. (1990)**
The current role of sonography in the detection of Down syndrome.
Obstet. Gynecol. 75, 472-472.
- Hoagland M. H., Frank K. A., Hutchins G. M. (1988)**
Prune-belly syndrome with prostatic hypoplasia, bladder wall rupture, and massive ascites in a fetus with trisomy-18.
Arch. Pathol. Lab. Med. 112, 1126-1128.
- Holzgreve W., Golabi M., Bradley J. (1986)**
Multiple congenital anomalies in a child born after prenatal diagnosis of trisomy-20 mosaicism.
Clin. Genet. 29, 342-344.
- Hook E. B., Cross P. K., Schreinemachers D. M. (1983)**
Chromosomal abnormality rates at amniocentesis and in live-born infants.
J. Am. Med. Assoc. 249, 2034-2038.
- Hsieh F. J., Hsu C. H., Ko T. M., Chang F. M., Chen H. Y., Jean H. H., Chuang S. M. (1988)**
Rapid karyotyping in fetuses with abnormal sonogram.
Acta Obstet. Gynecol. Scand. Suppl. 67, 621-625.
- Hunter A. G. W., DesLauriers G. E., Gillieson M. S., Muggah H. F. (1982)**
Prenatal diagnosis of Turner's syndrome by ultrasonography.
Can. Med. Assoc. J. 127, 401-401.
- Jacobs P. A., Nassold T. J., Henry A., Pettay D., Takaesu N. (1987)**
Trisomy-13 ascertained in a survey of spontaneous abortions.
J. Med. Genet. 24, 721-724.
- Kuhlmann R. S., Werner A. L., Abramowicz J., Warsof S. L., Arrington J., Levy D. L. (1990)**
Placental histology in fetuses between 18 and 23 weeks gestation with abnormal karyotype.
Am. J. Obstet. Gynecol. 163, 1264-1270.
- Kurjak A., Kirkinen P. (1982)**
Ultrasonic growth pattern of fetuses with chromosomal aberrations.
Acta Obstet. Gynecol. Scand. 61, 223-225.
- Lazjuk G., Zolotukhina T. V., Kirillova I., Lurie I., Novikova I., Abasheva G. (1987)**
Prenatal morphology of partial monosomy 18q.
Zentralbl. Gynäkol. 109, 126-129.
- Méhes K. (1973)**
Clinically recognisable autosomal anomalies in neonates.
Lancet 1, 1262-1263.
- Méhes K. (1988)**
Informative Morphogenetic Variants in the Newborn Infant.
Akadémiai Kiadó, Budapest
- Moerman P. H., Fryns J. P., Goddeeris P., Lauweryns J. M. (1982)**
Spectrum of clinical and autopsy findings in trisomy 18 syndrome.
J. Genet. Hum. 30, 17-38.

- Nyberg D. A., Fitzsimmons J., Mack L. A., Hughes M., Pretorius D. H., Hickok D., Shepard T. H.** (1989)
Chromosomal abnormalities in fetuses with omphalocele. Significance of omphalocele contents. *J. Ultrasound Med.* 8, 299-308.
- Nyberg D. A., Resta R. G., Hickok D. E., Hollenbach K. A., Luthy D. A., Mahony B. S.** (1990)
Femur length shortening in the detection of Down syndrome. Is prenatal screening feasible? *Am. J. Obstet. Gynecol.* 162, 1247-1252.
- Nyberg D. A., Resta R. G., Luthy D. A., Hickok D. E., Mahony B. S., Hirsch J. H.** (1990)
Prenatal sonographic findings of Down syndrome. Review of 94 cases. *Obstet. Gynecol.* 76, 370-377.
- Perrella R., Duerinckx A. J., Grant E. D., Tessler F., Tabsh K., Crandall B. F.** (1988)
Sonographic identification of Down's syndrome. *N. Engl. J. Med.* 318, 1399-1399.
- Peters M. T., Lockwood C. J., Miller W. A.** (1989)
The efficacy of fetal sonographic biometry in Down syndrome screening. *Am. J. Obstet. Gynecol.* 161, 297-300.
- Rezai K., Holzgreve W., Schloo R., Tercanli S., Horst J., Miny P.** (1991)
Prenatal chromosome findings after sonographic diagnosis of fetal abnormalities. *Geburtshilfe Frauenheilkd.* 51, 211-216.
- Rizzo N., Pittalis M. C., Pilu G., Orsini L. F., Perolo A., Bovicelli L.** (1990)
Prenatal karyotyping in malformed fetuses. *Prenat. Diagn.* 10, 17-23.
- Rochelson B. L., Kaplan C., Guzman E., Arato M., Hansen K., Trunca C.** (1990)
A quantitative analysis of placental vasculature in the third-trimester fetus with autosomal trisomy. *Obstet. Gynecol.* 75, 59-63.
- Rodis J. F., Vintzileos A. M., Campbell W. A., Nochimson D. J.** (1988)
Spontaneous resolution of fetal cystic hygroma in Down syndrome. *Obstet. Gynecol.* 71, 976-977.
- Schwanitz G., Zerres K., Gembruch U., Bald R., Hansmann M.** (1989)
Rate of chromosomal aberrations in prenatally detected hydrops fetalis and hygroma colli. *Hum. Genet.* 84, 81-82.
- Sperber G. H., Honore L. H., Machin G. A.** (1989)
Microscopic study of holoprosencephalic facial anomalies in trisomy-13 fetuses. *Am. J. Med. Genet.* 32, 443-451.
- Stevens M. J., Dumon J., Jacquemyn Y., Vanroy B., Delbeke L., Gerris J., Buytaert P.** (1987)
Antenatal ultrasonographic diagnosis of trisomy-18 (Edwards syndrome). *Eur. J. Obstet. Gynecol. Reprod. Biol.* 26, 353-358.
- Thorpe-Beeston J. G., Gosden C. M., Nicolaidis K. H.** (1990)
Choroid plexus cysts and chromosomal defects. *Br. J. Radiol.* 63, 783-786.
- Toftager K., Benzie R. J., Doran T. A., Miskin M., Allen L. C., Becker L.** (1983)
Alpha-fetoprotein and ultrasound scanning in the prenatal diagnosis of Turner's syndrome. *Prenat. Diagn.* 3, 35-40.
- Toi A., Simpson G. F., Filly R. A.** (1987)
Ultrasonically evident fetal nuchal skin thickening: Is it specific for Down syndrome? *Am. J. Obstet. Gynecol.* 156, 150-153.
- Tonge M., Rodeck C.** (1989)
Is ultrasound of any value in screening for Down's syndrome? *Br. J. Obstet. Gynaecol.* 96, 1369-1371.
- Voigt H. J., Claussen U., Ulmer R.** (1986)
Fetal nuchal edema. An early sonographic sign of a chromosome anomaly. *Geburtshilfe Frauenheilkd.* 46, 879-882.
- Walker S., Howard P. J.** (1986)
Cytogenetic prenatal diagnosis and its relative effectiveness in the Mersey region and North Wales. *Prenat. Diagn.* 6, 13-23.
- Weingast G. R., Hopper K. D., Gottesfeld S. A., Manco-Johnson M. L.** (1988)
Congenital lymphangiectasia with cystic hygroma: Report of two cases with coexistent Down's syndrome. *J. Clin. Ultrasound* 16, 663-668.
- Williamson R. A., Weiner C. P., Patil S., Benda J., Varner M. W., Abu-Yousef M. M.** (1987)
Abnormal pregnancy sonogram: Selective indication for fetal karyotype. *Obstet. Gynecol.* 69, 15-20.
- Wladimiroff J. W., Stewart P. A., Reuss A., Sachs E. S.** (1989)
Cardiac and extracardiac anomalies as indicators for trisomy 13 and trisomy 18. A prenatal ultrasound study. *Prenat. Diagn.* 9, 515-520.

1. J. H. D. ...
2. J. H. D. ...
3. J. H. D. ...
4. J. H. D. ...
5. J. H. D. ...
6. J. H. D. ...
7. J. H. D. ...
8. J. H. D. ...
9. J. H. D. ...
10. J. H. D. ...
11. J. H. D. ...
12. J. H. D. ...
13. J. H. D. ...
14. J. H. D. ...
15. J. H. D. ...
16. J. H. D. ...
17. J. H. D. ...
18. J. H. D. ...
19. J. H. D. ...
20. J. H. D. ...
21. J. H. D. ...
22. J. H. D. ...
23. J. H. D. ...
24. J. H. D. ...
25. J. H. D. ...
26. J. H. D. ...
27. J. H. D. ...
28. J. H. D. ...
29. J. H. D. ...
30. J. H. D. ...
31. J. H. D. ...
32. J. H. D. ...
33. J. H. D. ...
34. J. H. D. ...
35. J. H. D. ...
36. J. H. D. ...
37. J. H. D. ...
38. J. H. D. ...
39. J. H. D. ...
40. J. H. D. ...
41. J. H. D. ...
42. J. H. D. ...
43. J. H. D. ...
44. J. H. D. ...
45. J. H. D. ...
46. J. H. D. ...
47. J. H. D. ...
48. J. H. D. ...
49. J. H. D. ...
50. J. H. D. ...
51. J. H. D. ...
52. J. H. D. ...
53. J. H. D. ...
54. J. H. D. ...
55. J. H. D. ...
56. J. H. D. ...
57. J. H. D. ...
58. J. H. D. ...
59. J. H. D. ...
60. J. H. D. ...
61. J. H. D. ...
62. J. H. D. ...
63. J. H. D. ...
64. J. H. D. ...
65. J. H. D. ...
66. J. H. D. ...
67. J. H. D. ...
68. J. H. D. ...
69. J. H. D. ...
70. J. H. D. ...
71. J. H. D. ...
72. J. H. D. ...
73. J. H. D. ...
74. J. H. D. ...
75. J. H. D. ...
76. J. H. D. ...
77. J. H. D. ...
78. J. H. D. ...
79. J. H. D. ...
80. J. H. D. ...
81. J. H. D. ...
82. J. H. D. ...
83. J. H. D. ...
84. J. H. D. ...
85. J. H. D. ...
86. J. H. D. ...
87. J. H. D. ...
88. J. H. D. ...
89. J. H. D. ...
90. J. H. D. ...
91. J. H. D. ...
92. J. H. D. ...
93. J. H. D. ...
94. J. H. D. ...
95. J. H. D. ...
96. J. H. D. ...
97. J. H. D. ...
98. J. H. D. ...
99. J. H. D. ...
100. J. H. D. ...

Perinatal Brain Damage

Perinatal injury may result from obstetric complications about the time of birth, or from difficulties or inadequacies of neonatal care. It remains a cause of long-term neurological damage and mental retardation. Perinatal mortality is accepted as a critical index of the quality of work within an obstetric department. Current interests and methods of assessment ignore much perinatal morbidity; damage/injury at delivery and in the newborn period may not always manifest as a serious problem till years later, when there may be irreversible mental and neurological damage. Serious mechanical injury at birth (e.g., tear of the tentorium cerebelli), rarely occurs nowadays. Most damage derives from fetal hypoxia. Animal experiments have shown that the degree of hypoxia necessary to provoke prolonged neurological damage is slightly less than that sufficient to cause death. A newborn infant that has survived a hypoxic episode may prove later to be neurologically damaged.

Hypoxia accounts for 4-5 neonatal deaths per 1000 live births as well as 3-4 cases of severe mental handicap and 1-2 cases of severe neurological damage. About 6% of cerebral palsy cases can be attributed to neonatal or birth asphyxia. The most important causes of fetal hypoxia are discussed below. [One should note that it is not always easy to distinguish extrinsic causes of perinatal damage from intrinsic ones. A baby with a chromosome disorder may be difficult to resuscitate at birth, and prone to hypoxia; such babies often grow slowly *in utero*,

and aneuploidy may predispose to maternal hypertension (toxaemia), but not all such "damaged babies" will be immediately recognizable as chromosomally abnormal!]

Perinatal Cerebral Haemorrhage

Intracranial haemorrhage is a complication of traumatic delivery or premature birth. With few exceptions it occurs in the first 24 h following delivery. It is a major cause of death of premature infants, and an important factor in the pathogenesis of central nervous system damage. Fifty years ago, half of all intracranial bleedings were subdural and a fifth were intraventricular. With improving obstetric care subdural bleedings are now rare and most haemorrhages are intraventricular. The different types of haemorrhage can be distinguished on ultrasound or computed tomography (CT).

Cephalhaematoma. Cephalhaematoma, or subperiosteal haemorrhage of the cranial bones, involves the outer surface of the calvaria, and is not an intracranial haemorrhage. It may follow a difficult delivery, and is easy to recognize. It respects the sutures and does not extend across the border between bones. Occasionally it is confused with encephalocoele. It heals spontaneously, and late neurological complications are unusual.

Subdural haematoma. This very rare type of haemorrhage develops after birth trauma or as a complication of a haemorrhagic diathesis

(haemophilia). The dura, the tentorium and/or the falx may be ruptured and the superficial bridging veins injured. It is difficult to diagnose by ultrasound. Neonatal subdural haematoma may be fatal.

Subarachnoid haemorrhage. The haemorrhage derives from small vessels of the subarachnoid space or, secondarily, from the ventricular system. In primary cases, lumbar puncture yields bloody cerebrospinal fluid. Disregarding those rare haemorrhages that cause cerebral compression, subarachnoid haemorrhage is generally asymptomatic.

Parenchymal haemorrhages. Most of these are extensions of periventricular haemorrhage. In situ intraparenchymatous haemorrhage is rare: it may be caused by haemorrhagic diathesis, angioma, trauma or infection.

Haemorrhage of the choroid plexus. This can be diagnosed with ultrasound: the plexus looks large and asymmetric, and the ipsilateral occipital horn is dilated.

Periventricular haemorrhage. This is now the most common form of cerebral haemorrhage. The subependymal type originates in the capillary-rich germinal matrix and localizes to the head of the caudate nucleus. Since the subependymal layer is the most developed between 24 and 34 weeks gestation, most such haemorrhages occur in that period. After 34 weeks the germinal matrix involutes, and has practically disappeared in the term infant who rarely suffers this type of haemorrhage. Bleeding may extend into the cavities of the lateral ventricles (intraventricular haemorrhage), and in

20% of cases it extends into the cerebral parenchyma (parenchymal haemorrhage). Haemorrhages are recognized during the first postnatal week, and regress by two to three weeks. The extent of bleeding can be monitored by sonography.

The course and prognosis cannot be predicted. The ultrasound changes may completely regress, or sequelae, ventricular dilatation or porencephaly, persist. Posthaemorrhagic ventricular dilatation is usually asymmetric. It may be transient, persistent or progressive. Progressive dilatation leads to hydrocephalus. Permanent cystic change in the paraventricular tissues is termed porencephaly.

Ischaemic cerebral changes. The outcome of hypoxic (ischaemic) damage relates to the degree of pre-

maturity and the nature of the insult. Beyond 32-34 weeks gestation, the pattern of cerebral blood supply alters. The germinal matrix regresses and cortex and white matter predominate. Cerebral damage in premature infants develops in the periventricular tissues at the boundary of the areas supplied with blood by the central (centrifugal) and cortical (centripetal) vessels (periventricular leukomalacia). In mature neonates the damage develops between areas supplied by the large arteries and those supplied by vessels in the depths of the sulci (subcortical leukomalacia). In survivors, hypoxic encephalomalacia leads to cystic degeneration, atrophy or calcification.

Cerebral haemorrhage and leukomalacia is usually fatal for the

newborn. The survivors develop severe neurological problems, the distressing signs of Little disease.

It should be noted that cerebral haemorrhage may also occur *in utero*, resulting from rupture of a congenital aneurysm, arteriovenous malformation, isoimmune thrombocytopenia, or germinal matrix haemorrhage penetrating a ventricle.

Meningoencephalitis and ventriculitis. The diverse inflammatory lesions can be demonstrated successfully by ultrasound as abnormal parenchymal echogenicity, consistent with calcific deposits, cystic development of the brain and as changes in ventricular size, ventricular wall regularity and echogenicity of cerebrospinal fluid, and ventricular septation.

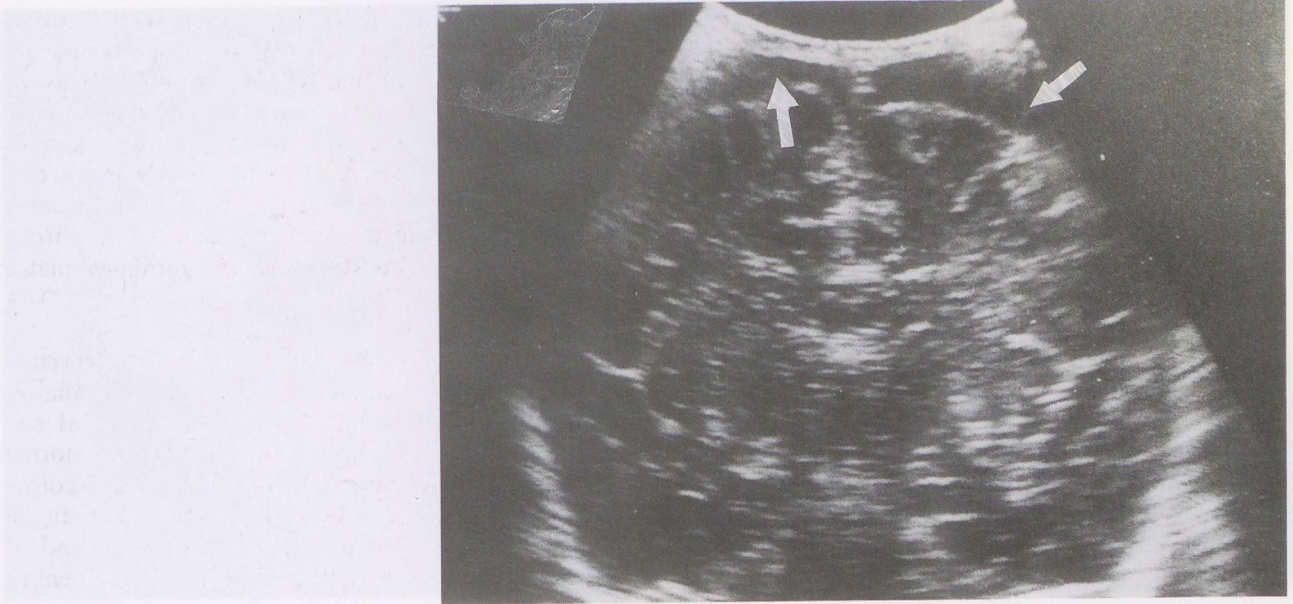


Figure 12-1. Subdural haemorrhage. Coronal scan in a mature newborn infant. An echo-free band lies in the frontal region between the flattened gyrus and the bone (arrowed).



Figure 12-2. Cerebral oedema with subarachnoid haemorrhage (arrow) after severe hypoxic-ischaemic insult in a term infant.

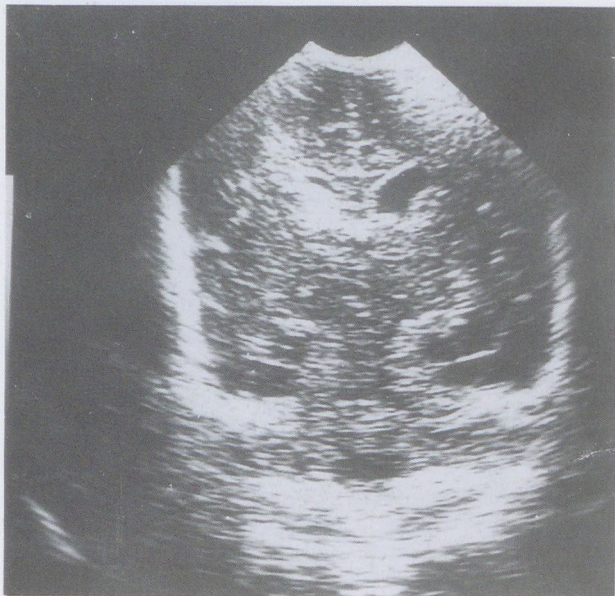


Figure 12-3. Subependymal haemorrhage below the frontal horn (left side).

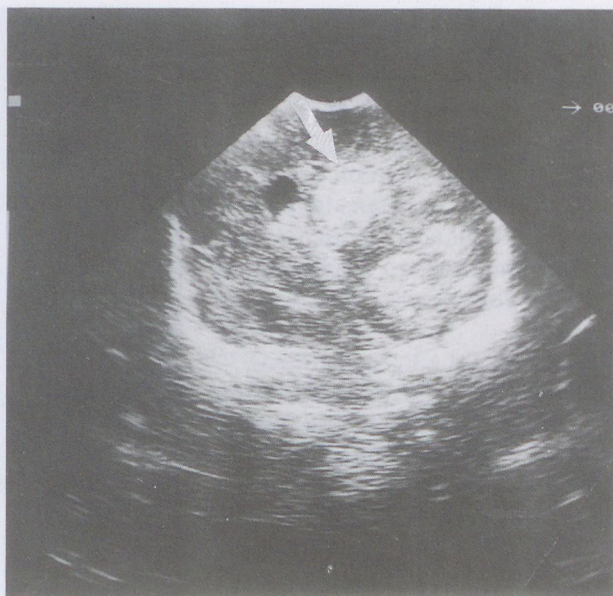


Figure 12-4. Massive intraventricular haemorrhage. Dense echoes are seen in the right frontal and temporal horns on the coronal view (arrows).

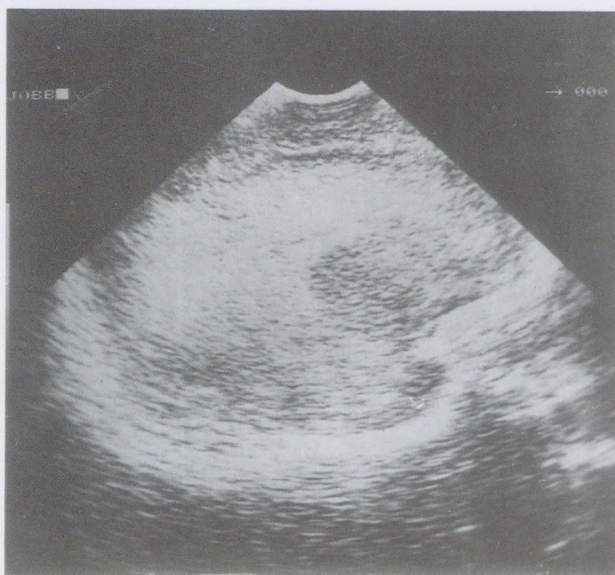


Figure 12-5. Intraventricular haemorrhage extending into the parenchyma on the parasagittal section.

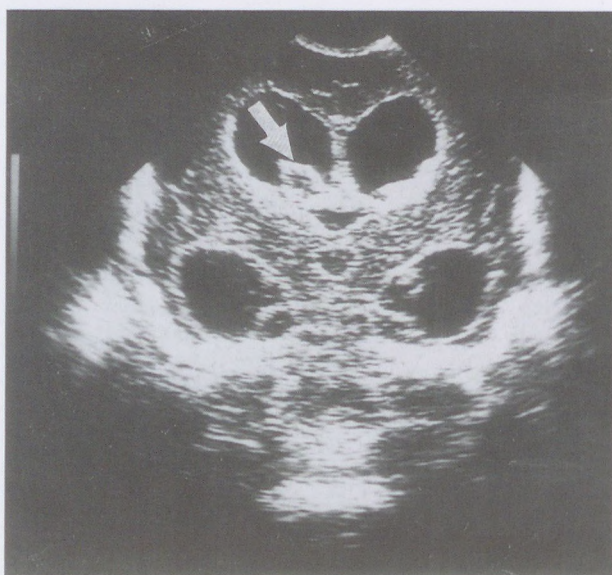


Figure 12-6. Hydrocephalus following intraventricular haemorrhage. Thrombus (arrow) lying within the frontal horn of the left lateral ventricle.

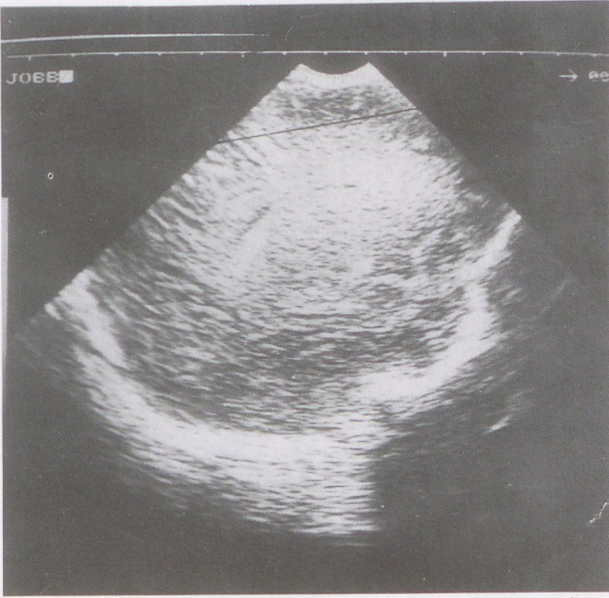


Figure 12-7. Periventricular leukomalacia two days after hypoxic-ischaemic insult in a premature newborn infant; parasagittal scan showing distinct periventricular echoes around the frontal pole of the lateral ventricle.

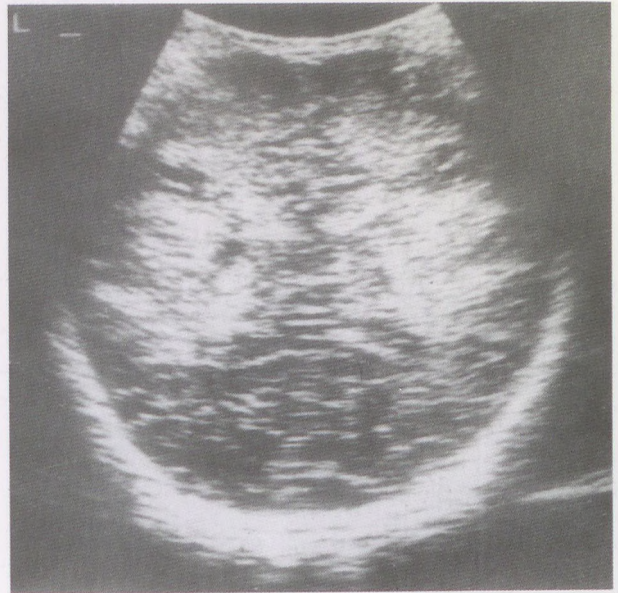


Figure 12-8. Symmetric increased echogenicity in the periventricular region without any evidence of haemorrhage on the posterior coronal view.

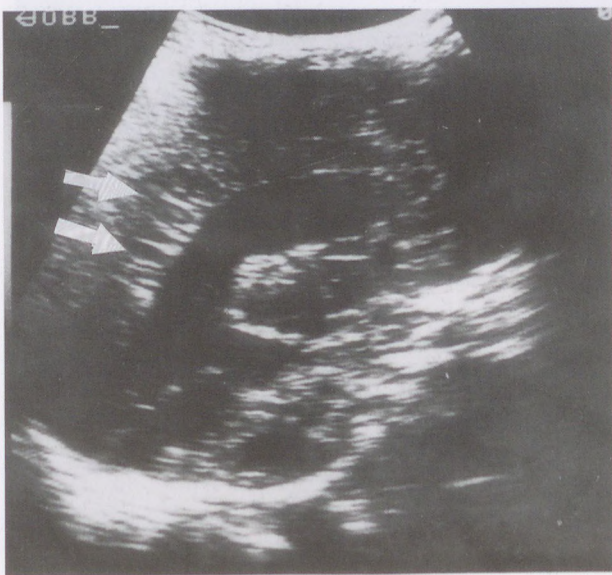


Figure 12-9. Periventricular cystic leukomalacia four weeks after hypoxic-ischaemic insult: echo-free areas (arrows) along the body of the lateral ventricle (parasagittal view).



Figure 12-10. Extended periventricular cysts developed along the entire contour of the lateral ventricle in parasagittal section (periventricular cystic leukomalacia).

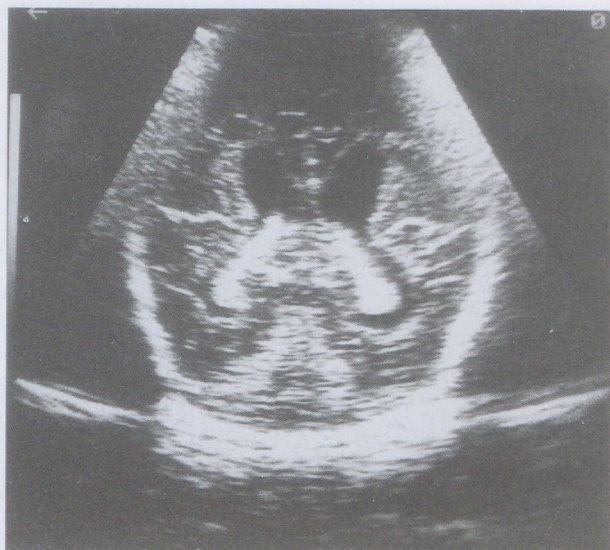


Figure 12-11. Periventricular cystic leukomalacia in the posterior coronal view. (The symmetric echogenic structures in the ventricles represent the choroid plexus.)

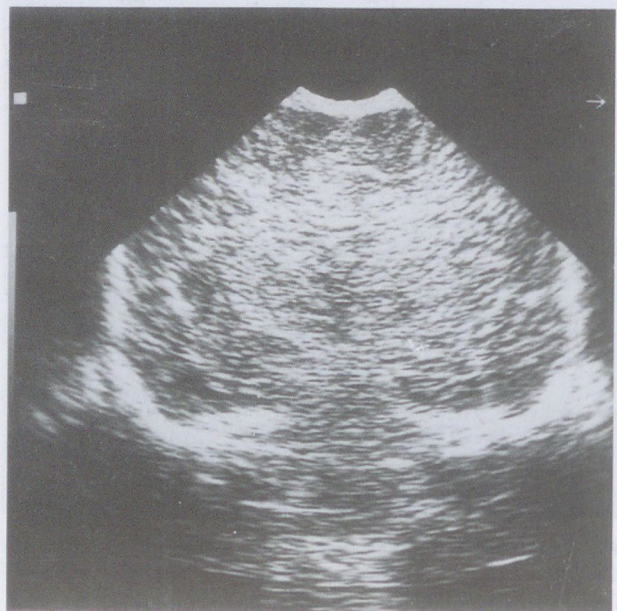
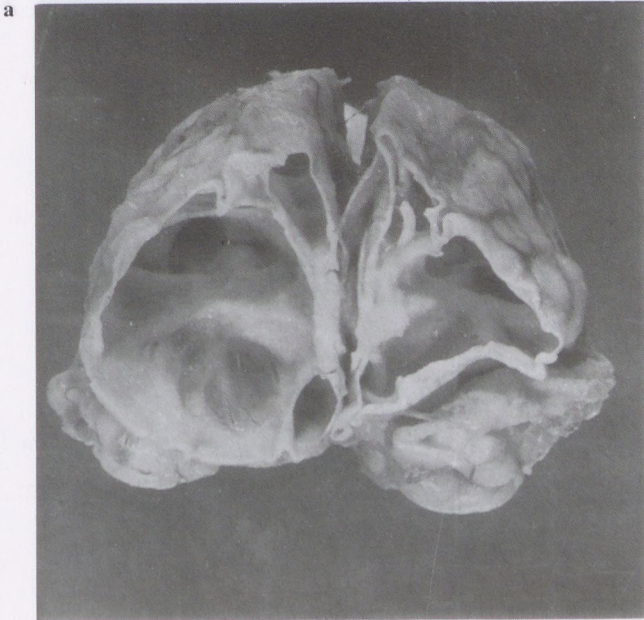
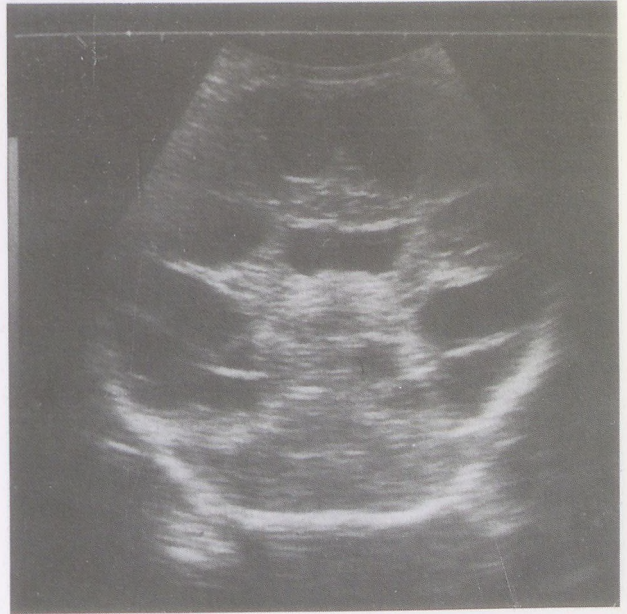


Figure 12-12. Diffuse increased echodensities obscuring normal cerebral structures. (Cerebral oedema after hypoxic-ischaemic insult in a term newborn infant.)

Figure 12-13. Coronal ultrasound scan from a term newborn infant showing marked subcortical cystic cavities (subcortical leukomalacia).



Figures 12-14a and b. Postmortem specimen showing extensive subcortical cysts.

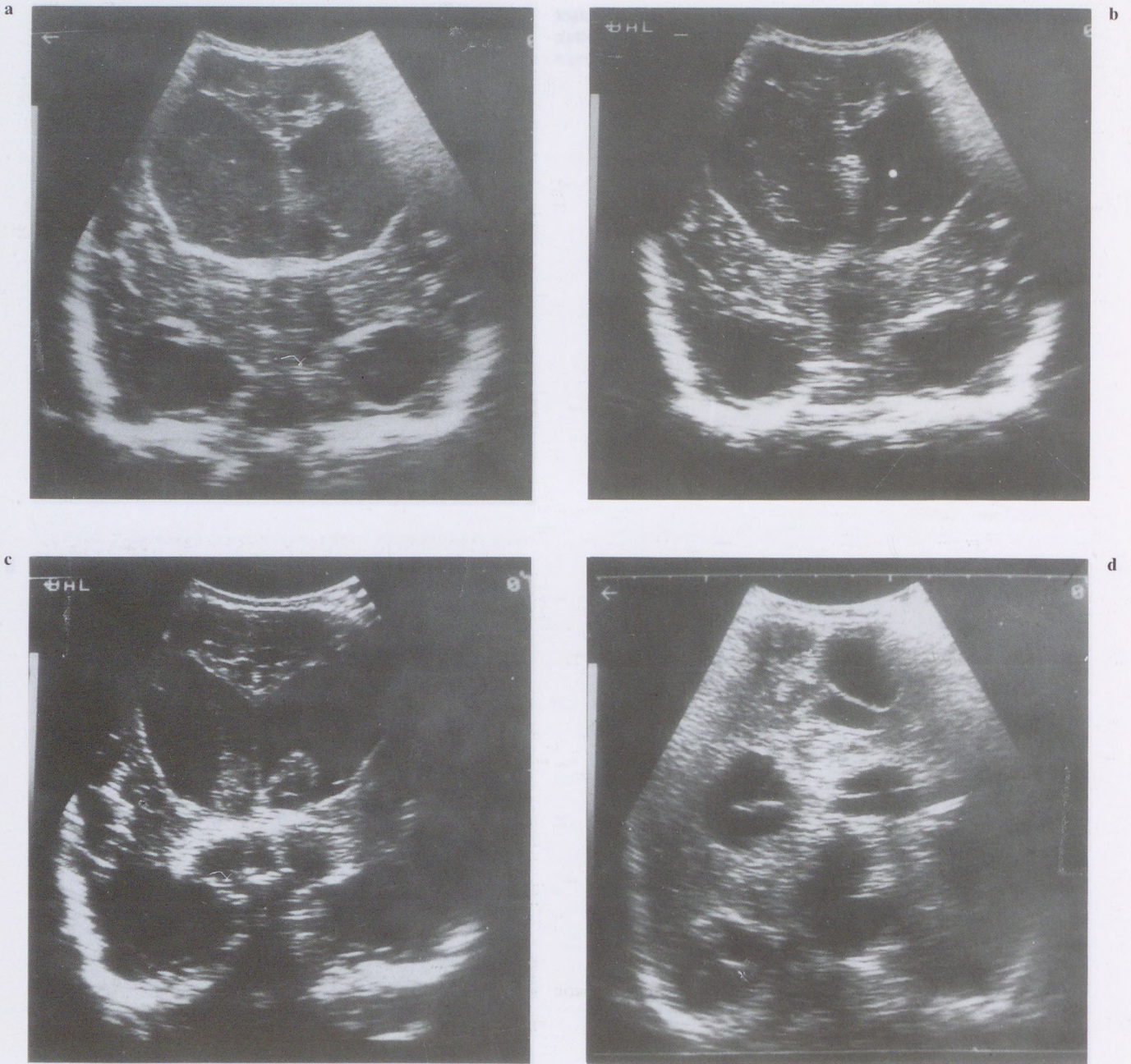


Figure 12-15. Stages of ventriculitis in a term newborn infant: echogenic ependyma and cerebrospinal fluid space (a); cerebrospinal fluid echogenicity decreased, debris within the ventricles (b); echo-free lateral ventricles with narrow stands between the opposite walls (c); multicystic brain (d).

Figure 12-16. Meningoencephalitis due to bacterial infection in a term newborn infant: echogenic ependyma lining the lateral ventricles; the normally echo-free cerebral spinal fluid is now moderately echogenic; increased echogenicity in the parenchyma around the ventricles (coronal section).

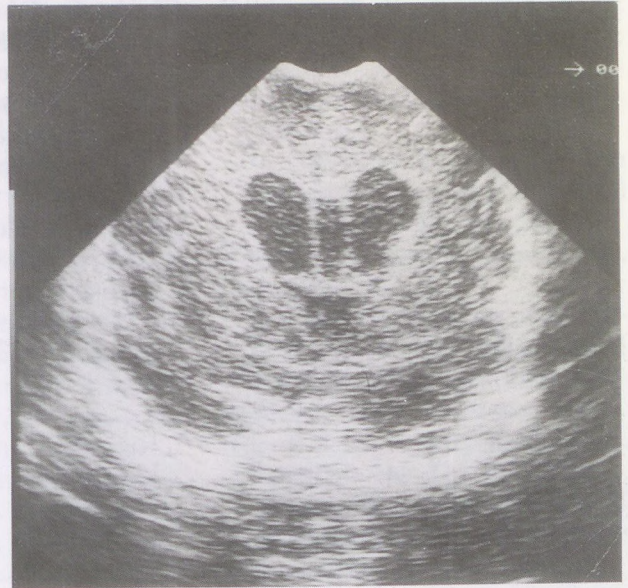


Figure 12-17. Widened subarachnoid space and interhemispheric fissure due to cerebral loss after herpes meningoencephalitis (atrophia cerebri).



References

- Babcock D. S.** (1984)
The normal, absent, and abnormal corpus callosum: Sonographic findings.
Radiology 151, 449-453.
- Babcock D. S., Ball W.** (1983)
Postasphyxial encephalopathy in full term infants: Ultrasound diagnosis.
Radiology 148, 417-423.
- Bann A. W.** (1986)
Hypoxic-ischaemic encephalopathy (asphyxia).
Pediatr. Clin. North Am. 33, 451-464.
- Beverley D. W., Chance G. W., Coates C. F.** (1984)
Intraventricular haemorrhage: Timing of occurrence and relationship to perinatal events.
Br. J. Obstet. Gynaecol. 9, 1007-1013.
- Bondurant S., Boehm F. H., Fleischer A. C., Machin J. E.** (1984)
Antepartum diagnosis of fetal intracranial hemorrhage by ultrasound.
Obstet. Gynecol. 63, 25-27.
- Bowerman R. A., Donn S. M., DiPietro M. A., D'Amato C. J., Hicks S. P.** (1984)
Periventricular leukomalacia in the preterm newborn infant: Sonographic and clinical features.
Radiology 151, 383-388.
- Bozynski M. E., DiPietro M. A., Meisels S. J., Plunkett J. W., Burpee B., Claflin C. J.** (1990)
Cranial sonography and neurological examination of extremely preterm infants.
Dev. Med. 32, 575-581.
- Carson S. C., Hertzberg B. S., Bowie J. D., Burger P. C.** (1990)
Value of sonography in the diagnosis of Intracranial hemorrhage and periventricular leukomalacia. A postmortem study of 35 cases.
A. J. R. 155, 595-601.
- Chow P. P., Horgan J. G., Taylor K. J. W.** (1985)
Neonatal periventricular leukomalacia. Real-time sonographic diagnosis with CT correlation.
A. J. R. 145, 155-160.
- Dewbury K. C., Bates R. I.** (1983)
Neonatal intracranial hemorrhage. The cause of ultrasound appearances.
Br. J. Radiol. 56, 783-789.
- Dubowitz L. M. S., Bydder G. M., Mushin J.** (1985)
Developmental sequence of periventricular leukomalacia.
Arch. Dis. Child. 60, 349-355.
- Ennis M. G., Kaude J. V., Williams J. L.** (1985)
Sonographic diagnosis of subarachnoid hemorrhage in premature newborn infants. A retrospective study with histopathologic and CT correlation.
J. Ultrasound Med. 4, 183-187.
- Fischer A. Q., Aziz E.** (1986)
Diagnosis of cerebral atrophy in infants by near-field cranial sonography.
Am. J. Dis. Child. 140, 774-777.
- Fogarty K., Cohen H. L., Haller J. O.** (1989)
Sonography of fetal intracranial hemorrhage. Unusual causes and a review of the literature.
J. Clin. Ultrasound 17, 366-370.
- Grant E. G. (ed.)** (1986)
Neurosonography of the Preterm Neonate.
Springer Verlag, New York
- Grant E. G.** (1986)
Sonography of the premature brain: Intracranial hemorrhage and periventricular leukomalacia.
Neuroradiology 28, 476-490.
- Grant E. G., Schellinger D., Smith Y., Uscinski R. H.** (1986)
Periventricular leukomalacia in combination with intraventricular hemorrhage: Sonographic features and sequelae.
A. J. N. R. 7, 443-447.
- Graziani L. J., Pasto M., Stanley C., Pidcock F., Desai H., Desai S., Branca P., Goldberg B.** (1986)
Neonatal neurosonographic correlates of cerebral palsy in preterm infants.
Pediatrics 78, 88-95.
- Han B. K., Babcock D. S., McAdams L.** (1985)
Bacterial meningitis in infants: Sonographic findings.
Radiology 154, 645-650.
- Hill A. E., Morgan M. E. I.** (1985)
Posthemorrhagic hydrocephalus in newborn term infants.
Arch. Dis. Child. 60, 706-709.
- Landman J., Weitz R., Dulitzki F., Shuper A., Sirota L., Aloni D., Barziv J., Gadoth N.** (1989)
Radiological colpocephaly. A congenital malformation or result of intrauterine and perinatal brain damage.
Brain Develop. 11, 313-316.
- Levene M. I., Williams J. L., Fawer C. L.** (1985)
Ultrasound of the Infant Brain.
Blackwell Scient. Publ. Ltd., Oxford
- Mahony B. S., Nyberg D. A., Hirsch J. H., Petty C. N., Hendricks S. K., Mack L. A.** (1988)
Mild idiopathic lateral cerebral ventricular dilatation in utero. Sonographic evaluation.
Radiology 169, 715-721.
- Naidich T. P., Quencer R. M. (eds.)** (1987)
Clinical Neurosonography. Ultrasound of the Central Nervous System.
Springer Verlag, New York

- Noorbehesht B., Enzmann D. R., Sullender W., Bradley J. S., Arvin A. M. (1987)**
Neonatal herpes simplex encephalitis. Correlation of clinical and CT findings.
Radiology 162, 813-819.
- Perlman J. M. (1989)**
Systemic abnormalities in term infants following perinatal asphyxia. Relevance to long-term neurologic outcome.
Clin. Perinatol. 16, 475-484.
- Reeder J. D., Sanders R. C. (1983)**
Ventriculitis in the neonate. Recognition by sonography.
A. J. N. R. 4, 37-41.
- Rorke L. B. (1982)**
Pathology of Perinatal Brain Injury.
Raven Press, New York
- Saliba E., Bertrand P., Gold F., Vaillant M. C., Laugier J. (1990)**
Area of lateral ventricles measured on cranial ultrasonography in preterm infants. Reference range.
Arch. Dis. Child. 65, 1029-1032.
- Saliba E., Bertrand P., Gold F., Marchand S., Laugier J. (1990)**
Area of lateral ventricles measured on cranial ultrasonography in preterm infants. Association with outcome.
Arch. Dis. Child. 65, 1033-1037.
- Saliba E., Pottier J. M., Chergui A., Bloc D., Gold F., Laugier J. (1985)**
Ultrasonographic supervision of post-hemorrhagic ventricular dilatations in premature neonates. Interest of the determination of a ventricular index.
Arch. Fr. Pediatr. 42, 281-284.
- Schellinger D., Grant E. G., Richardson J. D. (1984)**
Cystic periventricular leukomalacia: Sonographic and CT findings.
A. J. N. R. 5, 439-445.
- Trounce J. Q., Fagan D., Levene M. I. (1986)**
Intraventricular haemorrhage and periventricular leukomalacia: Ultrasound and autopsy correlation.
Arch. Dis. Child. 61, 1203-1207.
- Vannucci R. C., Voorhies T. M. (1984)**
Perinatal cerebral hypoxia-ischaemia: Pathogenesis and neuropathology.
In: Sarnat H. B. (ed.) *Topics in Neonatal Neurology*. Grune and Stratton, Orlando, pp. 27-59.
- Váradi V., György I., Karmazsin L. (1988)**
Sonographic diagnosis of subcortical cystic leukomalacia.
Zentralbl. Gynäkol. 110, 461-464.
- Váradi V., György I., Karmazsin L. (1990)**
Neonatal periventricular leukomalacia: Diagnosis and monitoring by real-time ultrasound.
Acta Paediatr. Hung. 30, 43-51.
- Váradi V., György I., Karmazsin L. (1990)**
Sonography of meningoencephalitis and ventriculitis in infancy.
Acta Paediatr. Hung. 30, 53-62.
- Volpe J. J. (1987)**
Neurology of the Newborn.
W. B. Saunders, Philadelphia

Subject index

Aarskog syndrome 196
 acardia 69, 71
 achondrogenesis 196, 199
 achondroplasia 196, 200
 ADAM complex 38, 55, 58, 64, 139, 196
 alopecia 82
 amniocentesis 15
 amnion 13, 21, 32, 34, 38, 39
 amniotic bands 55, 57, 58, 61, 63, 65
 amniotic fluid 14, 45
 ANAE staining 40
 anencephaly 40, 41, 71, 117, 119, 120, 121, 126
 Apert syndrome 94, 196
 arachnodactyly 196
 arhinencephalia 88
 Arnold-Chiari malformation 89, 94, 117
 arthrogryposis multiplex congenita 196
 biparietal diameter 12
 blighted ova 29
 brachydactyly 196
 branchiogenic cyst 147
 branchiootorenal dysplasia 196
 campomelic dysplasia 196, 200
 camptodactyly 196
 cardiac tumours 139
 caudal regression syndrome 51
 cebocephaly 88, 100
 cephalhaematoma 243
 cerebral haemorrhage 243
 chorioamniotic adhesions 57, 59
 chondrodysplasia punctata 196, 201, 204
 chorion 13, 14, 32, 39, 63
 chorionic villi 12, 17, 33
 chorionic villus sampling 15
 choroid plexus cyst 88, 105
 choroid plexus papilloma 107
 chromosome aberrations 227
 cleft lip et palate 88, 100, 119

clubfoot 196
 Cockayne syndrome 196
 Coffin-Lowry syndrome 196
 colour Doppler ultrasound 19, 21, 23, 25
 congenital cystic adenomatoid malformation 140, 145, 146, 147
 congenital heart defects 139
 congenital skin defect 82
 conjoined twins 69, 76, 77, 78
 Cornelia de Lange syndrome 196
 corpus callosum, agenesis 95, 96, 97
 "cri-du-chat" syndrome 233
 cyclopia 88, 98, 99
 cyclotia 88
 cystic fibrosis 141
 cystic hygroma 215, 219, 232, 233
 cytomegalovirus infection 215, 217, 218, 221, 222
 Dandy-Walker sequence 88, 105
 decidua 13, 14, 33
 deletion syndromes 229
 diaphragmatic hernia 140, 151
 diastrophic dysplasia 196, 202
 disruption sequence 61, 63
 Dubowitz syndrome 196
 duodenal atresia 141, 151
 dysostosis craniofacialis 196
 dysostosis mandibulofacialis 196
 Ebstein anomaly 139
 ECP syndrome 196
 ectopia cordis 139, 148
 ectopic pregnancy 23, 25
 ectrodactyly 196
 EEC syndrome 196
 Ehlers-Danlos syndrome 196
 Ellis-van Creveld syndrome 196
 embryopathies 12
 encephalocele 118, 123, 124, 125, 126, 127, 181
 Endes trichrome staining 34
 ethmocephaly 88
 exencephaly 98, 117, 122, 124
 exomphalos 30
 exstrophy of the bladder 170
 extraembryonic coeloma 21, 31
 fertilization 11
 fetus 13, 31
 fetus papyraceus 65, 70, 79, 80, 81
 gastroschisis 140, 154
 gestational sac 12, 17, 19, 21, 23, 25, 27, 28, 29, 30

Goldenhar syndrome 196
 growth retardation 14, 28, 30
 Hallermann-Streiff syndrome 196
 holoprosencephaly 87, 91, 98, 100, 101, 102, 103
 Holt-Oram syndrome 196
 hydatidiform mole 41
 hydranencephaly 87, 104
 hydrocephalus 87, 91, 92, 93, 94, 100, 109, 246
 hydronephrotic kidney 169, 184, 185
 hypodipic anomalies 215, 220, 223
 hygroma colli 143, 144
 hypophosphatasia 204
 hypoplastic left heart 139
 iniencephaly 118, 133, 134
 innocent amniotic bands 55, 64, 65
 implantation 11
 ischaemic cerebral changes 244, 245
 Ivemark syndrome 196
 Jeune syndrome 196, 203
 Kartagener syndrome 196
 Klippel-Trenaunay-Weber syndrome 110
 Langer-Giedion syndrome 196
 Laurence-Moon-Biedl syndrome 196
 limb defects 195
 Lowe syndrome 196
 Marfan syndrome 196
 Mayer-Rokitansky-Küster-Hauser syndrome 24
 Meckel syndrome 87, 181, 196
 meconium ileus 141, 155
 megacystis-microcolon-hypoperistalsis syndrome 170, 184, 189
 meningoencephalitis 244, 251
 metatropic dysplasia 197
 microcephaly 87, 125, 181
 missed abortion 25, 28, 29, 36
 Mohr syndrome 197
 multicystic kidney dysplasia 169, 176, 177, 178, 179, 180, 181
 multiple cartilaginous exostoses (AD) 197
 neural tube defect 28, 71, 117

- oesophageal atresia 141, 151, 158
oligohydramnios sequence 45, 47, 49, 50, 60, 178
omphalocele 59, 60, 140, 150, 152, 153
osteogenesis imperfecta 196, 205, 206
- PAS staining 39, 157
periventricular cystic leukomalacia 247, 248
periventricular haemorrhage 243
Pfeiffer syndrome 197, 210
phocomelia 58, 197
Pierre Robin sequence 197
placenta 13, 32, 64
placentation 69
Poland sequence 197
polycystic kidney, adult type 169, 182, 183
polycystic kidney, infantile type 169, 173, 174, 175
polydactyly 103, 181, 197
polymerase chain reaction 15
Potter syndrome 45, 47, 48, 49, 51, 52, 149
prune-belly syndrome 188
Prussian blue staining 39
pulmonary agenesis 140
pulmonary hypoplasia 48, 178
pulmonary stenosis 139
- radial aplasia 210
renal agenesis 47, 49, 50
- Roberts syndrome 197
Rubinstein-Taybi syndrome 197
Russell-Silver syndrome 197, 205
- sacroccygeal teratoma 72, 73, 74, 75
Saldino-Noonan syndrome 197
scalp defect 82
scoliosis 60, 201
single umbilical artery 15, 38, 64, 71
sirenomelia sequence 51, 52, 197
skeletal dysplasias 195
skin 32, 82
Smith-Lemli-Opitz syndrome 197
spina bifida 28, 71, 117, 122, 123, 127, 128, 129, 131, 132
spontaneous abortion 28, 30
spondyloepiphyseal dysplasias 197, 207
Stickler syndrome 197
subcortical leukomalacia 249
subdural haematoma 243, 245
Sudan-red staining 39
syncytiotrophoblast 33
- tetralogy of Fallot 139
thanatophoric dysplasia 197, 208, 209
toxoplasmosis 88, 108, 109, 215
transposition of the great vessels 139
transvaginal ultrasound 19, 21, 23, 25, 26, 27
trisomy-9 237
trisomy-13 229, 238
- trisomy-18 228, 234, 235, 236, 237
trisomy-21 149, 151, 215, 228, 231, 232
tuberous sclerosis 93
twins 69
- Ullrich-Turner syndrome 215
umbilical cord 14, 23, 34, 35, 36, 38, 47, 60, 62, 64, 71, 150
urinary tract malformation, obstructive 186, 187, 188, 215
- VACTERL association 197
vanishing twins 69
Váradí-Papp syndrome 107, 197
velamentous insertion 34
ventricular septal defect 139, 149
ventriculitis 244
ventriculomegaly 71, 87, 92, 110
- Waardenburg syndrome 197
Wiedemann-Beckwith syndrome 140, 158, 197
- yolk sac 12, 13, 19, 21, 25, 31
yolk stalk 12
- Zellweger syndrome 197

687378

UNIVERSITY OF CHICAGO