Advances in Clinical Obstetrics and Gynecology

Volume 1

Edited by

Howard J. Osofsky, M.D., Ph.D.

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Howard J. Osofsky, M.D., Ph.D.
Clinical Professor of Obstetrics and Gynecology,
University of Kansas Medical Center;
Adjunct Professor of Obstetrics and Gynecology,
Temple University Health Sciences Center;
Staff Psychiatrist,
Menninger Foundation

Series Editor
Howard J. Osofsky, M.D., Ph.D.

Editorial Consultant
Raja W. Abdul-Karim, M.D.
Professor of Obstetrics and Gynecology,
Upstate Medical Center,
Syracuse, New York

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Preface

Obstetrics and Gynecology has changed profoundly as a discipline during recent years. It is a markedly different specialty from what it was only a decade ago. We have all been affected to a major extent by the genuine increases in knowledge and the alterations in practice that improved technology has made possible—and at times mandated. We have also been affected by numerous other issues—shifts in patients being served, alterations in their expectations of themselves and of the health care system, changes in the role of the government, increases in malpractice litigation, and questions about the role of the discipline, to name but a few. As we move forward in the 1980's we have a new set of challenges and tastes.

When the publisher and a number of colleagues asked me to undertake and edit this new series, I gave considerable thought to the request and reflected on the needs which we all have at this time. As a result, I decided to have this series focus on what is in essence the new basics—our foundations, the current state of knowledge, and the directions that seem likely in the coming years.

In this and subsequent issues we will attempt to focus on key issues of importance in clinical Obstetrics and Gynecology. We have given the contributors the task and challenge of pulling together in an important area material that is thorough, clinically relevant, and forward-looking. We will appreciate both our readers' suggestions about topics that should be included in the series and evaluations of how well the chapters are meeting the stated goals of the series. They will be helpful in making the series a meaningful one for all of us.

Contributors

Raja W. Abdul-Karim, M.D.
Professor, Department of Obstetrics and Gynecology, Upstate Medical Center, Syracuse, New York

Sidney F. Bottoms, M.D.
Assistant Professor, Department of Obstetrics and Gynecology, and the Perinatal Clinical Research Center, Cleveland Metropolitan General Hospital/Case Western Reserve University, Cleveland, Ohio

William E. Brenner, M.D.
Associate Professor, Department of Obstetrics and Gynecology, University of Nevada, Reno, Nevada

William J. Cameron, M.D., F.A.C.O.G.
Professor, Department of Obstetrics and Gynecology, University of Kansas Medical Center, College of Health Sciences and Hospital, Kansas City, Kansas

Willard Cates, Jr., M.D.
Chief, Abortion Surveillance Branch, Family Planning Evaluation Division, Center for Health Promotion and Education, Department of Health and Human Services, Public Health Service, Center for Disease Control, Atlanta, Georgia

David A. Clark, M.D.
Assistant Professor, Department of Pediatrics, Upstate Medical Center, Syracuse, New York

Maurice L. Druzin, M.D.
Assistant Professor, Department of Obstetrics and Gynecology, Cornell University Medical College, New York, New York

Gere S. diZerega, M.D.
Assistant Professor, Department of Obstetrics and Gynecology, Women's Hospital, Los Angeles County, University of Southern California Medical Center, Los Angeles, California

Fritz Fuchs, M.D.
Professor, Department of Obstetrics and Gynecology, Cornell University Medical College, New York, New York

Celso-Ramon Garcia, M.D.
The William Shippen, Jr. Professor of Human Reproduction, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Daniel R. Hill
American College of Obstetricians and Gynecologists, Chicago, Illinois

Gary D. Holtz, M.D.
Assistant Professor, Department of Obstetrics and Gynecology, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma

Raphael Jewelewicz, M.D.
Associate Professor, Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, New York

Kermit E. Krantz, M.D.
Professor and Chairman, Department of Obstetrics and Gynecology, Professor of Anatomy, Associate to the Executive Vice-Chancellor for Facilities Development, University of Kansas Medical Center, College of Health Sciences and Hospital, Kansas City, Kansas

Jack Lippes, M.D.
Chairman, Department of Obstetrics and Gynecology, Deaconess Hospital, Buffalo, New York

James A. Low, M.D.
Professor and Chairman, Department of Obstetrics and Gynecology, Queen's University at Kingston, Kingston, Ontario, Canada

Andrew Loucopoulos, M.D.
Assistant Clinical Professor, Department

of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, New York

Luigi Mastroianni, Jr., M.D.
Professor and Chairman, Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, Pennsylvania

Paul G. McDonough, M.D.
Professor, Department of Obstetrics and Gynecology, Chief, Reproductive Endocrine Division, Medical College of Georgia, Augusta, Georgia

Daniel R. Mishell, Jr., M.D.
Professor and Chairman, Department of Obstetrics and Gynecology, University of Southern California School of Medicine, LAC/USC Medical Center, Women's Hospital, Los Angeles, California

Kenneth R. Niswander, M.D.
Professor and Chairman, Department of Obstetrics and Gynecology, University of California at Davis, Davis, California

W. N. Piercy, M.D.
Assistant Professor, Department of Obstetrics and Gynecology, Queen's University at Kingston, Kingston, Ontario, Canada

Richard H. Reindollar, M.D.
Instructor, Department of Obstetrics and Gynecology, Research Fellow, Reproductive Endocrine Division, Medical College of Georgia, Augusta, Georgia

Ralph M. Richart, M.D.
Professor of Pathology, Columbia University College of Physicians and Surgeons; Director, Division of Obstetrical and Gynecological Pathology, The Sloane Hospital for Women, New York, New York

Peter T. Rogge, M.D.
Associate Professor, Department of Obstetrics and Gynecology, University of California, Davis, Medical Center, Sacramento, California

Mortimer G. Rosen, M.D.
Head, Department of Obstetrics and Gynecology and the Perinatal Clinical Research Center, Cleveland Metropolitan General Hospital/Professor of Obstetrics and Gynecology, Case Western University, Cleveland, Ohio

Rudy E. Sabbagha, M.D.
Associate Professor of Obstetrics and Gynecology, Director, Diagnostic Ultrasound Center, Northwestern University Medical School, Prentice Women's Hospital and Maternity Center, Chicago, Illinois

Robert J. Sokol, M.D.
Professor, Department of Obstetrics and Gynecology and the Perinatal Clinical Research Center, Cleveland Metropolitan General Hospital/Case Western Reserve University, Cleveland, Ohio

Ralph K. Tamura, M.D.
Assistant Professor of Obstetrics and Gynecology, Associate Director, Diagnostic Ultrasound Center, Northwestern University Medical School, Prentice Women's Hospital and Maternity Center, Chicago, Illinois

Duane E. Townsend, M.D.
Clinical Professor of Obstetrics and Gynecology, Cedar Sinai Medical Center, Los Angeles, California

Carl W. Tyler, Jr., M.D.
Assistant Director for Science, Center for Health Promotion and Education, Department of Health and Human Services, Public Health Service, Center for Disease Control, Atlanta, Georgia

Robert C. Wallach, M.D.
Director, Department of Obstetrics and Gynecology, Beth Israel Medical Center, New York, New York

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Contents

CHAPTER 1

Diagnostic Uses of Amniocentesis

MAURICE L. DRUZIN, M.D.
FRITZ FUCHS, M.D., DR.MED.

During the last two decades, outer space has been explored to an extent previously only imagined by authors of science fiction. During the same period of time, an "inner space" has been explored, and the findings have had considerable impact on human life and offer great promises for the future. Previously a *terra incognita*, the womb of the pregnant woman has been made accessible, permitting exploration and in some cases even treatment of the unborn. Like some of the other new diagnostic tools, amniocentesis has had great impact on the modern practice of obstetrics.

Amniocentesis (from Greek *amnion* = fetal membrane, and *kentesis* = pricking or puncture) was originally used for removal of excess fluid in polyhydramnios. Prenatal diagnosis of fetal disorders on the basis of examination of samples of amniotic fluid was first done about 30 years ago when Bevis[1] (1952) in England examined the content of bile pigment in cases of erythroblastosis fetalis due to Rh isoimmunization of the mother. Some years later, it was demonstrated by Fuchs and Riis[2] (1956) and immediately confirmed by others that examination of the cells in the amniotic fluid could reveal the fetal sex and also the fetal ABO blood group,[3] features which could both be used as genetic markers. This led to the prediction, as early as 1956,[4] that other genetic markers could be identified by examination of the amniotic fluid, making it possible to diagnose hereditary disorders before birth.

The year 1956 was a memorable year in human genetics in more than one respect. In that year, it was discovered that the human chromosome complement was 46 and not 48 as previously believed.[5] This discovery was the result of improved techniques for visualization of chromosomes, and it did not take long before the thought of antenatal study of fetal chromosomes came up. The determination of fetal sex and blood groups was of limited value, although antenatal sex determination did become the basis for the first selective interruptions of pregnancy, namely in carriers of sex-linked diseases, as reported by Riis and Fuchs in 1960.[6] For the study of fetal chromosomes it was necessary to be able to grow amniotic fluid cells in tissue culture. Although many of the cells in the fluid looked viable under the microscope, there was no assurance that they would multiply in tissue culture. But they did, and in the mid 1960s it was shown by several groups in the United States that antenatal chromosome analysis was indeed possible.[7,8] The prospects were exciting both to geneticists and to clinicians interested in inherited disorders, such as obstetricians and pediatricians.

By coincidence, 1956 was also the year of the discovery by Bergstrand and Czar[9] in Sweden of a specific protein in the human

fetal blood called α-fetoprotein (AFP). In the early 1970s it was found that a group of fetal malformations, the so-called *neural tube defects*, were associated with elevated levels of this protein both in amniotic fluid and in maternal plasma. The development of sensitive assays for AFP, which can measure the levels in the maternal blood, has permitted the screening of large groups of pregnant women for these malformations.

The scientific approach to clinical medicine has led to the elucidation of the biochemical defect of a number of genetic disorders collectively known as "inborn errors of metabolism." Most of these disorders, which are associated with severe, debilitating diseases, are currently incurable, but when diagnosis in pregnancies of individuals at risk is made in the first half of pregnancy by examination of the amniotic fluid, selective abortion becomes an important alternative.

Following the work of Bevis, amniocentesis in the third trimester has become an indispensible diagnostic tool in the management of pregnancies complicated by Rh isoimmunization. But a quantitatively more important use of amniocentesis in the third trimester is for the determination of fetal lung maturity.[10, 11] One of the most dreaded complications of preterm birth is the idiopathic respiratory distress syndrome (RDS) which is due to lack of surfactant in the immature lung. We shall discuss the diagnostic methods that permit an evaluation of the degree of maturity of the fetal lungs.

A relatively recent indication for third trimester amniocentesis is in threatened premature birth to diagnose amniotic infection, another threat to an infant born before term.

While therapeutic amniocentesis in polyhydramnios and intrauterine transfusion will only be touched upon, we shall conclude this chapter with a look at the future use of amniocentesis.

TECHNIQUES

Sampling of amniotic fluid for the diagnosis of genetic disorders of the fetus is usually done at 16 or 17 weeks of gestation. This time has been found optimal because the volume of amniotic fluid at this stage is 175–225 ml,[12] thus permitting the removal of 20–25 ml without substantial reduction of the fluid space. It usually takes 2–3 weeks for a culture of amniotic fluid cells to yield enough cells for cytogenetic examination or enzyme activity studies; if an abnormality is found, the gestation can be interrupted well before fetal viability. Earlier sampling is technically more difficult and requires the removal of a larger fraction of the amniotic fluid, thus increasing the risks to the fetus. Amniocentesis for the monitoring of Rh isoimmunization or fetal lung maturity is not done until well into the second half of pregnancy when the amniotic fluid volume is much greater than at 16–17 weeks and more easily accessible.

The first amniocenteses for genetic diagnosis were done transvaginally, with insertion of a needle from the anterior fornix, but the incidence of miscarriage was high, and the transabdominal approach soon proved to be superior. Until the development of ultrasonography, early amniocentesis had to be done blindly without knowledge of fetal position or the location of the placenta. With the use of ultrasonography, the procedure has become much easier and much safer.

In addition to helping in the selection of the site for insertion of the needle, ultrasound is valuable for (1) establishment of fetal age by measurement of the biparietal diameter of the head, (2) detection of multiple gestation, (3) localization of the placental insertion, (4) exclusion of fetal demise, (5) identification of uterine anomalies, such as malformations or fibroids, and (6) identification of gross fetal malformations.

Special transducers have been constructed which permit continuous imaging during the actual puncture. For routine amniocentesis such a transducer is rarely necessary, but for intrauterine transfusions it can be very helpful.

One of the problems that may be encountered is the "dry tap" in which no fluid is obtained. This is more likely to happen when the puncture site is in the fundus or close to the lateral margins of the uterus because tangential insertion of the needle often results in a contraction. Another problem is the bloody tap, most often due to puncture of the placenta. At 16–18 weeks the placenta covers a large proportion of the inside of the uterine

wall, and it is not always possible to avoid going through the placenta. Ultrasonography has greatly reduced the incidence of dry and bloody taps. Furthermore, it permits a check of the fetal heart after the procedure. It also facilitates double taps in twin gestations. In some instances, scanning can show the location of the membranous septum separating the two sacs, and if fluid is then withdrawn from points well away from the septum, one can be reasonably sure that both sacs have been tapped. If the septum cannot be visualized, one can ascertain that both sacs are reached by injecting a dye in the first sac. A recent suggestion has been to substitute the dye with a glucose solution and use a paper strip indicator to differentiate between the amniotic fluid containing the high concentration of glucose and the fluid from the uninjected sac.

Amniocentesis should always be carried out with sterile precautions; not only is it necessary to avoid intrauterine infection, it is also essential to keep the samples of fluid sterile, lest the culture be contaminated and thereby rendered useless. It is preferable to aspirate two samples of about 10 ml with plastic syringes. The samples are transported to the laboratory in the capped syringes. Small aliquots are then taken for chemical assays while the remaining fluid is transferred to tissue culture flasks and incubated with suitable culture media. The routine procedure is to examine the fetal chromosomes, but when one or another inborn error of metabolism has to be ruled out, other procedures may be required.

Amniocentesis in the second half of gestation can be done without the aid of ultrasonography, if necessary, provided the fetal position can be easily palpated. Behind the fetal neck there is usually an accessible pool of fluid. In modern practice, however, use of ultrasonographic guidance is mandatory, with rare exceptions. Even for late amniocentesis, the 2-syringe technique is preferable. If something happens to the sample during transport or in the laboratory, the second sample comes in handy.

When amniocentesis is performed in women who are Rh-negative with no evidence of isoimmunization, it is recommended to give the patient an intramuscular injection of Rh immunoglobulin following the procedure, to prevent isoimmunization from fetal cells which may have entered the maternal circulation as a result of the procedure.

Amniocentesis for genetic diagnosis should always be preceded by genetic counseling of the patient and, whenever possible, of her husband, to explain the purpose of the procedure and the risks associated with it and to obtain informed consent. If the tests show an abnormality or the results are ambiguous, repeat counseling becomes mandatory to clarify the options. The advice given in such cases should be documented in writing.

RISKS

Carried out by experienced physicians, with proper aseptic precautions, and with the aid of ultrasonography, midtrimester amniocentesis carries a very small risk. In the United States collaborative study[13] of 1,040 amniocentesis cases and 992 control pregnancies, the total fetal loss was 3.5% versus 3.2%; the difference was not statistically different. The accuracy was 99.4%. A Canadian study of 1,233 amniocenteses[14] without matched controls showed 3.4% fetal losses and 0.7% neonatal deaths; these percentages were not different from background Canadian data, nor from the United States study. Our own figures indicate that the risk of fetal loss is $<1\%$.[15]

The fetal risks include (1) rupture of the membranes, leading to miscarriage, (2) fetal exsanguination due to laceration of a major fetal vessel, (3) infection of the amniotic cavity with septic abortion, and (4) puncture lesions of the fetus, usually not lethal or of any major consequence. In addition, it is conceivable that the puncture site in the membranes can cause premature rupture of the membranes. We have observed a case in which rupture of the membranes occurred in association with a "bumpy" landing of a commercial aircraft at 29 weeks in a woman who underwent genetic amniocentesis at 17 weeks.

The risk of miscarriage is greater in twin gestations, considerably more than twice the risk in singleton pregnancies. We lost 2 of our first 8 twin pregnancies, and others seem

to have had the same experience, although we have not come across any statistics. A recent paper described the diagnosis of adrenocortical hyperplasia in twins of a mother whose first child suffered from the same disease. She did not want an abortion even if the syndrome was diagnosed in the twins, but she did miscarry spontaneously at 25 weeks and a causal relationship of the amniocentesis cannot be excluded.[16]

The maternal risks are quite small; they include puncture of the bladder, intestines, or a major uterine or parietal vessel. Secondary risks are those associated with miscarriages, particularly septic abortion. Mention must also be made of the fact that a finding of a severe genetic disease can cause severe depression and marital disruption, particularly when it affects a first child.

A frequent question from parents at risk is whether amniocentesis can cause any lesions or malformations of the fetus, or any complications at delivery. These questions were answered by a recent follow-up study of 2,000 pregnancies in which midtrimester amniocentesis had been performed.[17] One control group (group 1) consisted of women who were screened with AFP assays on maternal blood and had normal levels. As there were too few women over 35 years available for controls, women 28 years and older were included. Apart from this age bias, the women tended to be from the same socioeconomic background. A second control group (group 2), analyzed retrospectively, was composed of women 28 years and older who delivered at UCLA during the same period. Patients with high-risk pregnancies were excluded. Many of these patients came from lower socioeconomic groups than the amniocentesis groups. Group 2 had less complete data on pregnancy but more complete data on delivery and on the newborn than group 1 and was more similar to the study group.

It is evident from the results (Table 1.1) that amniocentesis did not increase the risk of spontaneous abortion, preterm birth, perinatal death, or congenital malformations. It should be noted that the study group only included 23 women with elevated serum AFP. An earlier collective study from the United Kingdom[18] had a higher rate of fetal loss in the amniocentesis group than in the controls, and an apparent increase in respiratory difficulties at birth and orthopedic postural deformities in the newborn, and a higher incidence of abruptio placentae, premature rupture of membranes, and postpartum hemorrhage. These discrepancies between the British study and both the United States and Canadian collective studies and the follow-up study quoted above[17] may be due to a number of differences in design and perhaps mostly to the fact that the British study group contained 41% of cases with elevated maternal serum AFP as the indication for amniocentesis. There is increasing evidence that elevated AFP in the maternal serum may be an indicator of a variety of pregnancy problems, including intrauterine growth retardation, prematurity, and intrauterine death.

AMNIOCENTESIS FOR GENETIC DIAGNOSIS

Midtrimester amniocentesis is currently done for four groups of congenital disorders, namely chromosomal aberrations, sex-linked disorders, inborn errors of metabolism, and neural tube defects. During the last decade the use of genetic amniocentesis increased dramatically, and in the last couple of years, surveys have been published on cases from the United States and Canada[19] and from Europe,[20, 29] each comprising more than 10,000 cases (Table 1.2).

It is seen that the distributions in the four main groups and the percentages of abnormal findings are strikingly similar. The same applies to reports from individual centers, including our own.[15] Chromosomal aberrations and neural tube defects are the two most important indications in terms of numbers. Most laboratories now perform chromosome studies and AFP determination on all amniotic fluid samples received for genetic diagnosis, although the yield of affected fetuses through the added test is quite low.

Chromosome Aberrations

Modern tissue culture methods have been developed to the point that with a single sample of 10 ml or more of amniotic fluid,[21] successful cultivation can be achieved in more than 98% of the cases. Once a sufficient population of fetal cells can be harvested, it

Table 1.1
Results of a Follow-up Study of 2,000 Midtrimester Amniocenteses[17]

	No. (%)	Control Groups*	
		1 (%)	2 (%)
Outcome known	1,943	2,000	2,000
Therapeutic abortion	51 (2.6)		
Lost to follow-up	57		
Spontaneous abortion	25 (1.3)	23 (1.1)	
Stillbirth and neonatal death	27 (1.4)	23 (1.1)	27 (1.3)
Premature (<2,500 gm)	67 (3.6)	75 (3.7)	79 (3.9)
Congenital malformations	31 (1.6)	25 (1.2)	39 (1.9)

* Control group 1 includes women in an AFP screening program with exclusion of abnormal levels; group 2 includes women who delivered at UCLA and who did not have high-risk pregnancies. There were no significant differences between the study group and the two control groups in regard to outcome.

Table 1.2
Summary of Two of the Largest Surveys of Prenatal Diagnosis of Congenital Disorders, as Modified from Galjaard[29] (1980)

	United States & Canada*	Europe & Israel†
Chromosome aberrations	6,523	9,864
Abnormal	157 = 2.4%	292 = 3%
Maternal age	3,012	7,549
Abnormal	79 = 2.6%	224 = 3%
Previous trisomy	1,924	1,811
Abnormal	23 = 1.1%	21 = 1.2%
Parental translocation	293	504
Unbalanced	29 = 9.9%	47 = 9.3%
Miscellaneous	1,294	
Abnormal	26 = 2.0%	
Sex-linked disorders	433	280
Male fetuses	195 = 45%	123 = 44%
Metabolic diseases	522	632
Affected	126 = 24%	148 = 23%
Neural tube defects	6,600	838
Abnormal	165 = 2.5%	29 = 3.5%
Total amniocenteses	14,078	12,614
Affected	643 = 4.6%	592 = 4.7%

* Based on data from Epstein and Golbus[19] (1977).
† Based on data from Murken et al.[20] (1979).

is possible to assess the fetal karyotype and to identify any fetal chromosome abnormality. Some 80–90% of all pregnancies which have been monitored by midtrimester amniocentesis have been at risk for fetal chromosome abnormalities. Fetal chromosome studies are today considered indicated in the following situations:

1. When a previous pregnancy has resulted in the birth of a chromosomally abnormal infant or conceptus.
2. When a chromosomal abnormality is known to exist in one of the parents, including balanced translocation, mosaicism of two or more karyotypes, and aneuploidy (i.e. abnormal chromosome numbers).
3. History of a chromosomal abnormality in a close relative.
4. Pregnancies following multiple spontaneous abortions.
5. When a previous pregnancy has resulted in a child with multiple malformations in

which no cytogenetic studies were performed.

6. When there is increased risk of chromosomal abnormalities due to advanced maternal age.

The last indication is by far the most frequent. Its frequency depends on the age limit chosen. At the time when most laboratories had a low capacity, amniocentesis was usually only recommended for women 40 years or older. Only in this age group does the risk of having a child with Down's syndrome exceed 1% which is commonly considered to be the risk of a miscarriage as a result of the procedure[22] (Fig. 1.1). But Down's syndrome (trisomy 21) only constitutes about 60% of the chromosomal anomalies found at amniocentesis for maternal age. The empirical probability of an excess or deficit of chromosomes being found at amniocentesis is higher, but many of these fetuses will be aborted spontaneously. With easier access to genetic amniocentesis, the trend has been to lower the age limit for amniocentesis, on the basis of maternal age alone, to 35 years. Most parents are unwilling to equate the risk of losing the pregnancy with the risk of having an abnormal child, since it is possible to attempt another pregnancy after a loss caused by the procedure.

Chromosome studies on amniotic fluid cells require special cytogenetic facilities and expertise. The culture techniques have gradually been perfected, and the average time required to harvest sufficient cells in metaphase has gradually been reduced to 15 days on the average. For the karyotyping, both fluorescent methods and permanent staining with one of several banding procedures can be used. The banding techniques permit identification of individual chromosomes and a more accurate classification of chromosomal aberrations. In some laboratories a number of metaphases are analyzed directly under the microscope, whereas others make

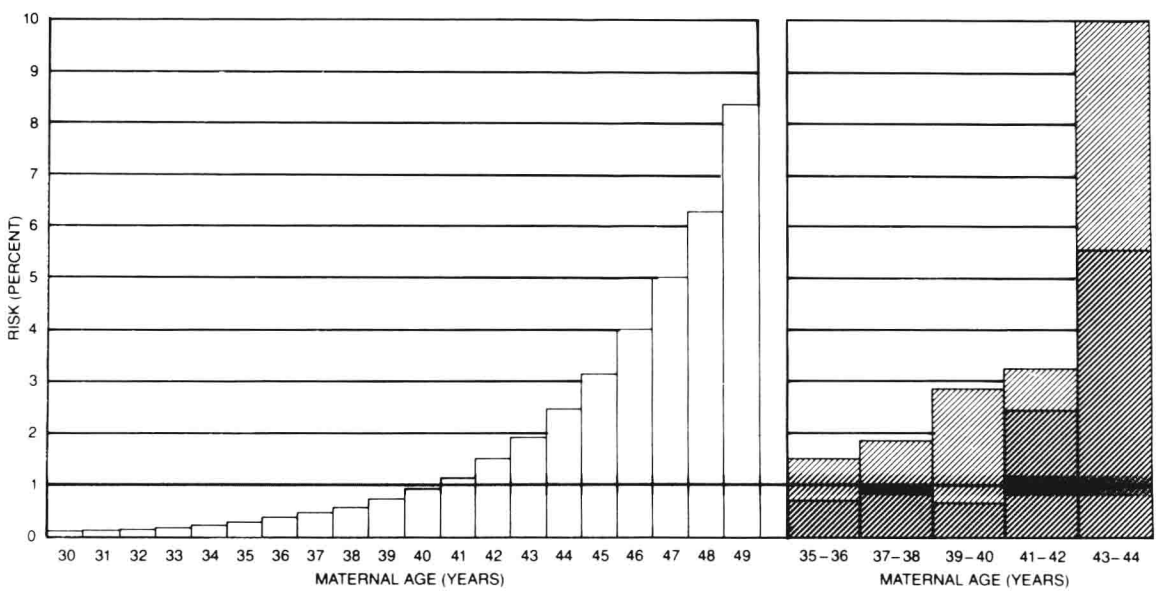

Figure 1.1. Risk of chromosomal abnormality in a fetus in relation to maternal age. The *graph* to the *left* shows the empirical risk of giving birth to an infant with trisomy 21 (Down's syndrome). On the *right* the *darkest bars* show the probabilities of finding trisomy 21 by amniocentesis. Some fetuses with this anomaly are aborted. The *full bars* indicate the probabilities of finding any abnormal number of chromosomes at amniocentesis. (Reproduced with permission from F. Fuchs, Genetic Amniocentesis, *Scientific American 242*(6): 53, June 1980.[22])

a number of microphotographs for detailed studies. The individual chromosomes are cut out and arranged in numerical sequence, after which they are photographed again to provide a permanent record of fetal karyotype. With this technique the average time for reporting the results is 17 days in our laboratory.

Failure to obtain growth of the amniotic fluid in culture occurs in 1–3% of the cases. This can be very traumatic to the parents, heightened by the fact that the mother will usually have experienced quickening while waiting for the results. In such instances we recommend repeat amniocentesis, since the New York State law permits abortion up to 24 weeks.

Not all abnormal karyotypes are associated with abnormal phenotypes. Thus, balanced translocations in one of the parents can result in unbalanced translocations with abnormal phenotype in the offspring, or the same balanced translocation and normal phenotype as in the parent, or no abnormalities at all. Occasionally, mosaicism and abnormal cell lines are encountered, probably due to artifacts or viral contamination[15] or inversions which usually are inherited from one of the parents. In such instances it is essential for the obstetrician to consult with the geneticist before reporting the results to the parents.

Sex-Linked Disorders

Sex chromatin was the first genetic marker found in amniotic fluid cells, and sex-linked disorders were the first for which midtrimester amniocentesis was performed.[6] Sex-linked diseases are recessive disorders linked to an X chromosome, and it only manifests itself if the other sex chromosome is a Y, i.e. in males. The disease is only found in a female if she is the result of a marriage between a female carrier and a male suffering from the disease. The most important sex-linked disorders are hemophilia and Duchenne's form of muscular dystrophy. As a rule, no specific antenatal diagnosis can yet be made of such disorders; what can be diagnosed is the sex at risk.

The presence of affected brothers or uncles or the birth of a son with the disease to a sister or aunt may raise the suspicion that a woman is a carrier of a sex-linked disease, i.e. she is a heterozygote for the disorder before she has given birth herself. Methods are available to permit the detection of heterozygotes of hemophilia, whereas in Duchenne's progressive muscular dystrophy, heterozygosity can be demonstrated in only 60–75% of the possible carriers. With early diagnosis in affected males, investigation of carrier status of female relatives, genetic counseling of those at risk, amniocentesis, and interruption of gestations with male fetuses, a considerable reduction of the incidence of sex-linked disorders can be achieved.

A diagnosis of the fetal sex can be made on the basis of the presence or absence of sex chromatin in the nuclei of uncultured amniotic fluid cells. Although this method is rapid and simple and has a high degree of accuracy, many laboratories prefer to verify the diagnosis by karyotyping the cells after culture.

In sex-linked recessive disorders, half of the male offspring will be affected. The percentage of affected offspring is thus much higher than in cases at risk for other genetic disorders (cf. Table 1.2). But in the absence of a specific diagnosis, selective abortion must include all pregnancies with male fetuses. For some parents the fact that only half of the male fetuses will be affected is disturbing and makes it very difficult for them to decide whether to have an abortion or not. Efforts are therefore being made to identify specific markers for each of the sex-linked disorders, and some progress in regard to hemophilia has recently been reported,[23] but it does require fetal blood sampling by fetoscopy.

Biochemical Abnormalities

It was Brock and coworkers[24, 25] who discovered the relationship between elevated levels of AFP in the amniotic fluid and anencephaly and open spina bifida. As mentioned earlier, AFP had been detected in fetal blood in 1956; its function and purpose have not been clarified and remain unknown. But the use of AFP determinations to discover these malformations, which can be grouped together as the neural tube defects, received additional impetus when the development of very sensitive assays for AFP made it possible

to measure this specific protein in the maternal plasma in early pregnancy.[26] This permitted the development of screening tests based on maternal blood levels around the 15th week of gestation. In open neural tube defects and a few other congenital malformations, the level of AFP is greatly increased in the amniotic fluid, and this is reflected in the maternal blood, although the maternal levels are 100-fold lower than those in amniotic fluid and 100,000-fold lower than those in fetal blood.

The levels of AFP in maternal and fetal bloods and in amniotic fluid vary with gestational age but not in parallel fashion. When abnormally high maternal values are encountered, it is therefore essential to verify the gestation age by sonography. Equally important is to determine whether the fetus is alive and whether it is a singleton or multiple gestation because intrauterine death and multiple gestation are associated with elevated levels, as is placenta previa[27] (Fig. 1.2). The use of screening tests is therefore dependent upon the availability of sonography. Table 1.3 shows the results obtained in the first 4,220 patients screened at the New York Hospital-Cornell Medical Center (L. Cederqvist, personal communication). There were 63 cases with elevated values for the calculated age of gestation; these cases were studied with sonography and amniocentesis, and only 7 cases of neural tube defects were detected. In all other cases with elevated maternal levels, an explanation was provided by the work-up, and no pregnancies were interrupted on the basis of a false positive value, nor was any case of open neural tube defect missed.

Inborn Errors of Metabolism

Although the number of genetic metabolic diseases which can be diagnosed from amniotic fluid constituents is remarkably high,[28, 29] the practical application of amniocentesis for this purpose is limited by the great rarity of these diseases. As seen in Table 1.2, these disorders only accounted for 3.7 and 5.0% of the American and European materials, respectively. On the other hand, the chance of finding an affected fetus in cases at risk is about 1:4, and for families in whom one of these often severe, debilitating diseases occurs, prenatal diagnosis represents an important advance. It has become almost impossible to keep track of the more than 70 metabolic disorders in which prenatal diagnosis has been made or is potentially possible, and since most obstetricians will never encounter more than a few, Table 1.4 is not exhaustive but shows the best known examples of each of the major groups. For details of methodology and references, see Galjaard (1980).[29]

A reliable prenatal diagnosis of a genetic metabolic disease is generally based upon biochemical assay of cultured amniotic fluid cells. Only in rare instances can the diagnosis be made by assay of the amniotic fluid supernatant, which of course is time-saving, since it does not require growing of cells in culture. There is probably no laboratory in the world which masters the enzyme assays for all diagnosable metabolic diseases and has determined the ranges for normal values, and international collaboration and centralization has therefore been established, particularly in North America and Europe. In order to gain sufficient experience with the often complicated and time-consuming assays of enzyme activities, it is essential that this work be concentrated in a few centers. However, any hospital offering prenatal diagnosis of genetic disorders must establish the necessary referral lines and follow the development of new diagnostic methods.

DISORDERS OF LIPID METABOLISM

The best known and most frequent of the disorders of lipid metabolism is *Tay-Sachs disease* which is a G_{M2} gangliosidosis, an infantile form of amaurotic familial idiocy. It is a fatal degenerative disease of the nervous system, characterized by progressive accumulation of G_{M2} ganglioside in central and peripheral neurons. While the rate in the general population is very low, the disease has a high incidence among Ashkenazi Jews. It is autosomal recessive, and in this population group the carrier rate may be as high as 1:30. The biochemical cause is a deficiency of an isoenzyme of hexosaminidase, hexosaminidase A. Since it is possible to identify heterozygotes, amniocentesis needs only to be applied if the parents, by screening of Jews, have been found to be heterozygotes.