

# Contents

**Preface: Prenatal Screening and Diagnosis** **xv**

Anthony O. Odibo and David A. Krantz

**Preimplantation Genetic Testing: Indications and Controversies** **519**

Amber R. Cooper and Emily S. Jungheim

In the last two decades, the use of preimplantation genetic testing has increased dramatically. This testing is used for identifying single-gene disorders, chromosomal abnormalities, mitochondrial disorders, gender selection in non-Mendelian disorders with unequal gender distribution, aneuploidy screening, and other preconceptually identified genetic abnormalities in prospective parents. Genetic testing strategies and diagnostic accuracy continue to improve, but not without risks or controversies. In this review the authors discuss the techniques and clinical application of preimplantation genetic diagnosis, and the debate surrounding its associated uncertainty and expanded use.

**An Update on Cystic Fibrosis Screening** **533**

Katherine R. Goetzinger and Alison G. Cahill

Cystic fibrosis (CF) is a monogenic, autosomal recessive disorder, which ultimately leads to multisystem organ dysfunction and a subsequent decrease in life expectancy. Because of the sizeable number of disease-causing mutations (>1000) and expansive ethnic and racial distribution, CF has presented a challenge for prenatal diagnosis. This article aims to review the genetics of CF, its spectrum of genotypic-phenotypic variations, current prenatal carrier screening and diagnostic recommendations, ultrasonographic markers of CF, and available reproductive options for carrier couples.

**An Overview of First-Trimester Screening for Chromosomal Abnormalities** **545**

Ray O. Bahado-Singh and Pedro Argoti

The last decade has witnessed the transformation of first-trimester Down syndrome screening from an aspiration to a clinical reality. First-trimester screening now equals or exceeds the diagnostic accuracy of conventional midtrimester screen while realizing an important desire of pregnant women for early diagnosis. Beyond the obvious benefits to individual patients, this accomplishment emphatically affirms the centrality and value of clinical research.

**First-Trimester Genetic Counseling: Perspectives and Considerations** **557**

Eugene Pergament

As first-trimester screening has assumed an increasingly dominant role in the obstetric care of prospective parents, the need for genetic counseling

has also increased. There are several challenges related to first trimester screening; foremost among them is the need to distinguish between screening and diagnosis. Additional challenges include the need to discuss not only Down syndrome but cardiac defects, developmental/genetic syndromes, adverse pregnancy outcomes, and preeclampsia. In the future, counseling will involve specific risk assessment for a broad range of chromosome abnormalities. This article provides a framework for providing genetic counseling to prospective parents undergoing first trimester screening. However, the counseling session has to be individualized based on the counselor's approach and unique issues and concerns related to the pregnancy.

### **First-Trimester Screening for Chromosomal Abnormalities: Advantages of an Instant Results Approach**

565

Mary E. Norton

Protocols that include first trimester screening for fetal chromosome abnormalities have become standard of care throughout the United States. Earlier screening allows for first trimester diagnostic testing in cases found to be at increased risk. However, first trimester screening requires coordination of the nuchal translucency ultrasound screening (NT) and biochemical screening, during early, specific, narrow, but slightly different gestational age ranges. Instant results can often be provided at the time of the NT ultrasound if preceded by the programs that perform the biochemical analyses; this optimizes the benefits of the first trimester approach while improving efficiency and communication with the patient. This article discusses the benefits and logistics of such an approach.

### **Additional First-Trimester Ultrasound Markers**

573

J. Sonek and K. Nicolaides

The first trimester (11–13 +6 weeks) ultrasound examination is useful for several reasons: determination of an accurate date of confinement, diagnostic purposes, and screening for fetal defects. Nuchal translucency measurement combined with maternal serum markers (free b-human chorionic gonadotropin and pregnancy-associated plasma protein A) is the mainstay of first-trimester screening for chromosomal defects. However, over the past decade additional ultrasound markers have been developed that improve the performance of this type of screening. The novel markers include evaluation of the nasal bone, fronto-maxillary angle measurement, and Doppler evaluations of the blood flow across the tricuspid valve and in the ductus venosus.

### **Monitoring Quality Control of Nuchal Translucency**

593

Howard Cuckle

Nuchal translucency is the single most discriminatory marker for screening Down syndrome. When this marker is combined with concurrent maternal serum markers, the model-predicted performance is greater than for all second-trimester serum-only combinations. However, quality results for

the marker are more difficult to achieve than for serum markers. Monitoring of images and proper training are essential, but the ongoing use of epidemiologic indicators is the only way to assure quality. The positive rate in the screened population may indicate a problem, but the average multiple of the normal median values and the standard deviation of the logarithm (base 10) of these values are the key indicators for the markers. If there is a 10% shift in the median or a 0.02 change in the standard deviation, the results will be compromised.

## **Clinical Implications of First-Trimester Screening**

605

Stephen T. Chasen

First-trimester aneuploidy screening is associated with very high detection rates for Down syndrome and other chromosomal abnormalities. The clinical implications of early screening relate to prenatal diagnosis of chromosomal abnormalities and important information obtained at screening. Early screening can change the rate of invasive prenatal diagnosis and the gestational age of prenatal diagnosis and abortion, and lead to earlier prenatal diagnosis of certain major structural abnormalities. The detection of biochemical abnormalities associated with obstetric complications, such as low pregnancy-associated plasma protein A, could also affect the management and outcomes of some pregnancies.

## **Adverse Pregnancy Outcomes After Abnormal First-Trimester Screening for Aneuploidy**

613

Laura Goetzl

Women with abnormal results of first trimester screening but with a normal karyotype are at risk for adverse pregnancy outcomes. A nuchal translucency of greater than 3.5 mm is associated with an increased risk of subsequent pregnancy loss, fetal infection, fetal heart abnormalities, and other structural abnormalities. Abnormal levels of first trimester analytes are also associated with adverse pregnancy outcomes, but the predictive value is less impressive. As a single marker, pregnancy-associated plasma protein (PAPP)-A level less than 1st percentile has a good predictive value for subsequent fetal growth restriction. Women with PAPP-A level less than 5th percentile should undergo subsequent risk assessment with routine maternal serum afetoprotein screening with the possible addition of uterine artery pulsatility index assessment in the midtrimester.

## **Cost-Effectiveness of Down Syndrome Screening Paradigms**

629

Aaron B. Caughey, Anjali J. Kaimal, and Anthony O. Odibo

Methodologic and ethical concerns in the area of prenatal diagnosis include whether the effects of such testing on individuals other than patients are considered, what assumptions are made regarding termination of pregnancy following a diagnosis, whether the redundancy of screening and diagnostic methods is considered, and how the impact of positive or negative screening results on patient experience and anxiety can be

quantified. Several studies have examined the cost-effectiveness of screening for Down syndrome (DS). Given the current test characteristics, screening for DS is cost-effective across a wide variety of clinical situations. In fact, contingent screening is potentially a dominant strategy (costs less and leads to better outcomes). Understanding the methodology and salient issues of cost-effectiveness analysis is critical for researchers, editors, and clinicians to accurately interpret results of the growing body of cost-effectiveness studies in prenatal diagnosis.

### **Screening and Testing in Multiples**

643

Mark I. Evans and Stephanie Andriole

The same principles for diagnosis and screening in singleton pregnancies apply to multiples. However, there can be significant differences in the safety and efficacy of all approaches with multiple gestations. This article deals with specific aspects of screening in multiple pregnancies.

### **Noninvasive Prenatal Diagnosis: 2010**

655

Mark I. Evans and Michael Kilpatrick

Looking for fetal cells and now nucleic acids has been the holy grail of prenatal diagnosis for more than a century. The use of noninvasive diagnostics has potential far beyond aneuploidy; in fact, its use for Rhesus disease is already commonplace in Europe. Accurate segregation of fetal cells from maternal cells or identification of cell-free fetal (cff) DNA or RNA is critical to the development of fetal cells as a screening or diagnostic prenatal technique. The large number of approaches that have been used is testimony to the fact that none of them have been particularly successful. This article discusses the current status and challenges of noninvasive prenatal diagnosis.

### **The Role of Second-Trimester Serum Screening in the Post–First-Trimester Screening Era**

667

Alireza A. Shamshirsaz, Peter Benn, and James F.X. Egan

Considerable advances have been made in identifying women whose pregnancies are at the greatest risk for fetal Down syndrome and other aneuploidies. Maternal serum tests and ultrasonography in either the first or second trimester provide effective prenatal screening. However, the most efficacious protocols are based on the combination of first- and second-trimester tests. In this article the advantages and best strategies in providing these sequential screening protocols are discussed.

### **Modifying Risk for Aneuploidy with Second-Trimester Ultrasound After a Positive Serum Screen**

677

Diane Timms and Winston A. Campbell

Prenatal diagnosis for aneuploidy (primarily Down syndrome) has evolved over the past 4 decades. It started as a screening process using maternal

age of 35 years or older as a risk factor to offer patients the option for prenatal diagnosis. The actual diagnosis used an invasive procedure (amniocentesis) to obtain fetal cells for processing to determine fetal karyotype. This had a potential risk for miscarriage. The development of noninvasive prenatal screening to better identify pregnant patients at high risk for Down syndrome improved the ability to detect cases of aneuploidy and limit amniocentesis to only patients considered at high risk. This approach has a higher detection rate and a lower procedure-related rate of fetal loss than use of maternal age of 35 years or older alone. This article presents an overview of how prenatal diagnosis has evolved and then focuses on the current status of using ultrasound to evaluate patients considered to be screen-positive for Down syndrome based on first-trimester screening (10–14 weeks) or second-trimester (15–22 weeks) maternal serum analyte screening.

### **Biophysical and Biochemical Screening for the Risk of Preterm Labor**

693

Joseph R. Wax, Angelina Cartin, and Michael G. Pinette

Preterm birth is the leading cause of perinatal morbidity and mortality in developed nations. The heterogeneous causes of spontaneous preterm birth make prediction and prevention difficult. Recently developed biochemical and biophysical tests add significantly to clinicians' ability to evaluate and treat women at risk for spontaneous preterm birth. The primary importance of transvaginal cervical sonography and cervicovaginal fetal fibronectin lies in the high negative predictive values of the tests for reducing preterm delivery risk. Cervical length may be useful in identifying women who are candidates for cervical cerclage or progesterone therapy for preterm birth prevention. Together, cervical length and fibronectin can be used in the triaging of women symptomatic for preterm labor.

### **Toxoplasmosis, Parvovirus, and Cytomegalovirus in Pregnancy**

709

Deborah M. Feldman, Diane Timms, and Adam F. Borgida

Several infections in adults warrant special consideration in pregnant women given the potential fetal consequences. Among these are toxoplasmosis, parvovirus B19, and cytomegalovirus. These infections have an important effect on the developing fetus depending on the timing of infection. This article reviews the modes of transmission as well as maternal and neonatal effects of each of these infections. In addition, recommended testing, fetal surveillance, and treatment where indicated are outlined.

### **Screening for Open Neural Tube Defects**

721

David A. Krantz, Terrence W. Hallahan, and John E. Sherwin

Maternal serum screening for congenital anomalies began over 30 years ago with the advent of alpha-fetoprotein (AFP) screening for open neural tube defects. It was from these screening programs that the more complex multiple marker Down syndrome screening programs developed. However, today open neural tube defect screening remains a relatively simple

approach. In recent times, questions arise about the validity of the risk assessment associated with neural tube defect screening because of the impact of folate acid enrichment in diets and lack of outcome ascertainment. However, it still remains true that those with elevated AFP levels are at higher risk for having a pregnancy affected with open neural tube defect.

**First- and Second-Trimester Screening for Preeclampsia and Intrauterine Growth Restriction**

727

Methodius G. Tuuli and Anthony O. Odibo

Preeclampsia and intrauterine growth restriction are major contributors to perinatal mortality and morbidity. Accurate prediction is important for identifying those women who require more intensive monitoring, permitting earlier recognition and intervention, and allowing targeting of potential preventive measures to those at risk. Although different measures of placental dysfunction have been associated with increased risk adverse pregnancy outcomes, the ability of any single one to accurately predict these outcomes is poor. Attempts to use predictive models combining analytes and measurements of placental structure and blood flow have so far produced mixed results. The use of first- and second-trimester biochemical markers in combination with uterine artery Doppler screening shows promise as potential screening tools. Large prospective studies are needed to further evaluate the choice of parameters and strategies of combination to achieve the best predictive models.

**Prenatal Screening for Thrombophilias: Indications and Controversies**

747

Jeanine F. Carbone and Roxane Rampersad

A thrombophilia is defined as a disorder of hemostasis that predisposes a person to a thrombotic event. Data suggest that at least 50% of cases of venous thromboembolism in pregnant women are associated with an inherited or acquired thrombophilia, which can lead to an increased risk of maternal thromboembolism and adverse pregnancy outcomes such as recurrent pregnancy loss, intrauterine fetal demise, preterm preeclampsia, and intrauterine growth restriction. Inherited and acquired thrombophilias have different indications for testing. This article examines screening procedures for thrombophilias in the setting of adverse pregnancy outcomes.

**Index**

761