Screening for Aneuploidy in Multiple Gestations

The Challenges and Options

Whitney Bender, MD[a], Lorraine Dugoff, MD[b,*]

KEYWORDS

• Multiple gestation • Aneuploidy • Nuchal translucency • Serum screening
• Cell-free DNA • Noninvasive prenatal testing

KEY POINTS

- Although the incidence of multiple gestations has increased greatly over the last several decades, the data regarding aneuploidy screening in twins are limited.
- Screening for aneuploidy in twins using serum-based approaches is complicated because an unaffected twin may mask an affected twin. This possibility may be associated with decreased test performance compared with screening in singletons.
- Combined nuchal translucency and first-trimester serum screening with pregnancy-associated plasma protein A and beta–human chorionic gonadotropin is associated with a sensitivity and specificity of 87.4% (95% confidence interval [CI], 52.6–97.7) and 95.4% (95% CI, 94.3–96.3) in monochorionic twins and 86.2% (95% CI, 72.8–93.6) and 95.2% (95% CI, 94.2–96.0) for dichorionic twins.
- Although the data are limited, preliminary studies indicate that cell-free DNA screening may prove to be the optimal aneuploidy screening strategy for twins.
- Maternal age and nuchal translucency measurement are the only methods that can be used currently to screen for aneuploidy in higher-order multiple gestations.

INTRODUCTION

Over the past few decades, the incidence of multifetal gestations in the United States has increased markedly. Twins account for 1 in 30 live births in the United States.[1] The twinning rate increased 76% from 18.9 per 1000 births to 33.3 per 1000 births between 1980 and 2009.[1] Higher-order multiples increased by more than 400% during the same time period.[2] These trends are likely secondary to the increased use of assisted reproduction technology (ART) as well as the trend toward an older maternal age at conception.[2,3]

[a] Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA; [b] Reproductive Genetics Division, Maternal Fetal Medicine and Reproductive Genetics University of Pennsylvania Perelman School of Medicine, 2 Silverstein Building, 3400 Spruce Street, Philadelphia, PA 19104, USA
* Corresponding author.
E-mail address: Lorraine.DugoffDr@uphs.upenn.edu

Obstet Gynecol Clin N Am 45 (2018) 41–53
https://doi.org/10.1016/j.ogc.2017.10.004
obgyn.theclinics.com

This article reviews the incidence of aneuploidy in twins and aneuploidy screening options for twin gestations as well as higher-order multiples. The unique challenges of aneuploidy screening in multiple gestations are also discussed.

FACTORS ASSOCIATED WITH ANEUPLOIDY IN TWIN GESTATIONS

Zygosity

Zygosity refers to the genetic makeup of the pregnancy; chorionicity, in contrast, refers to the placentation. Zygosity determines the degree of risk for chromosomal anomalies and whether or not the fetuses are concordant or discordant with regard to these risks. Monozygotic twins result from the splitting of a single fertilized ovum and, therefore, share their genetic material. Dizygotic twins result from the fertilization of 2 separate ova by 2 separate sperm, resulting in genetically distinct fetuses.

In clinical practice, the determination of zygosity is usually made from chorionicity on ultrasonography. This ultrasonography is best performed in the first trimester when the identification of the lambda or twin peak sign has been shown to be 100% accurate.[4] This sign is diagnostic of a dichorionic pregnancy. In contrast, the T sign on ultrasonography is suggestive of monochorionicity. With rare exceptions, monochorionic twins are monozygotic. From 80% to 90% of dichorionic pregnancies are dizygotic. Less than 10% arise from a single zygote that divided within 3 days postfertilization.[4–6]

Monozygotic twins

The frequency of spontaneous monozygotic twins is constant at 4 per 1000 births.[2] Monozygotic twins comprise one-third of all spontaneous twin pregnancies.[2] Because the rate of dizygotic twins increases secondary to ART, this proportion of spontaneous twin pregnancies that are monozygotic may be as much as 10 times greater.[7,8] The risk of chromosomal abnormalities in monozygotic pregnancies has historically been considered to be the same as in singleton pregnancies given the shared genetic material between the 2 fetuses. Rarely, monozygotic twins may be discordant for genetic anomalies secondary to postzygotic nondisjunction.

Dizygotic twins

The incidence of dizygotic twins varies with race, maternal age, parity, and the use of fertility treatment.[2] In dizygotic pregnancies, each fetus has an independent aneuploidy risk. Historically, it has been reported that the maternal age–related risk for each individual twin is the same as for a singleton pregnancy; therefore, the chance of 1 twin being affected for a genetic anomaly is twice that of the singleton risk. The risk of both twins being affected is the risk of the singleton squared. This risk estimation is likely oversimplified given that 10% to 20% of dichorionic twins are monozygotic.[6–8]

More recent data indicate that the incidence of aneuploidy in twins is lower than was originally reported. In a retrospective review of 77,279 twin pregnancies, including 182 with at least 1 fetus affected with Down syndrome, Sparks and colleagues[9] reported a significantly lower than expected Down syndrome incidence in women 25 to 45 years old with both monozygotic and dizygotic pregnancies. This decreased incidence of Down syndrome was most notable in monozygotic pregnancies and with increasing maternal age. The observed to expected incidence of Down syndrome per pregnancy was 33.6%, 75.2%, and 70.0% for monozygotic, dizygotic, and all twins, respectively ($P<.001$ for all comparisons).[9] Similar results were reported by Boyle and colleagues[10] in a retrospective study of 14.8 million births, including 427,720 multiple births. The investigators observed an adjusted relative risk of Down syndrome per fetus from