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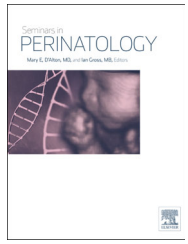

Examination of the twin placenta

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ABSTRACT

Twin birth rates have increased dramatically over the past three decades, and twins currently account for 3% of all pregnancies. Twin pregnancies of any type are at risk for prematurity. In addition, monochorionic twin pregnancies (25–30% of all twin pregnancies) are predisposed to a specific set of complications, including twin-to-twin transfusion syndrome (TTTS), twin reversed arterial perfusion syndrome (TRAP), malformations, and intertwin growth discordance. This article reviews the basic mechanisms underlying the twinning process, the relationship between zygosity and chorionicity, and the various types of twinning. We describe the major complications of monochorionic twinning in association with their reported placental characteristics (or lack thereof). Finally, a rational, evidence-based approach to examination of the twin placenta is presented. It is essential for the pathologist to understand the value, strengths, and limitations of examination of the twin placenta in order to provide a meaningful clinicopathological correlation in complicated (monochorionic) twin pregnancies.

Introduction

The incidence of multiple births has increased sharply over the past three decades. In the United States, the twin birth rate rose more than 75% from 1980 to 2009 to reach 33 per 1000 total births in 2010.[1] This dramatic increase in twin births has been attributed to two related factors: older maternal age distribution and expanded use of fertility enhancing therapies (assisted reproductive technologies (ART) and non-ART treatments such as ovulation stimulation).[1]

The perinatal mortality of twins is about five times that of singletons,[1] in large part because of increased prematurity rates. In 2010, more than 5 in every 10 twins were delivered preterm, compared with about 1 in 10 singletons.[1] In addition, monochorionic twins (25–30% of all twins) are susceptible to a specific set of complications, including twin-to-twin transfusion syndrome, discordant growth restriction, and malformations.

A basic understanding of the mechanisms underlying the twinning process, the relationship between zygosity and chorionicity, and the different types of twinning may contribute to accurate clinicopathological correlation in cases with atypical pregnancy outcome and/or discordant twin phenotypes.

Relationship between zygosity and chorionicity

Twins and twin pregnancies can be categorized according to zygosity or chorionicity. Zygosity refers to the type of conception. Dizygotic (non-identical, fraternal) twins (70%) result from multiple ovulation with (near-)synchronous fertilization of two ova by two sperm cells. Monozygotic twins (so-called "identical" twins) (30%) result from division of a zygote originating from the fertilization of one ovum by one sperm cell. The mechanism underlying this division involves either splitting of a single cell mass (splitting theory) or the

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development of more than one organizing axis (co-dominant axis theory).[2]

The causes of dizygotic twinning are multifactorial; maternal family history, ethnicity, age, gonadotropin levels, use of artificial conception technology, and dietary factors all likely play a role.[3,4] The stimulus for monozygotic twinning is less well understood but may be related to environmental influences, demonstrated by the increased rate of monozygotic twins in ART pregnancies.[5] In addition, genetic factors are implicated in monozygotic twinning, supported by the higher prevalence of females in many monozygotic twinning disorders and the abnormally high monozygotic twinning rate in some genetic syndromes, such as Opitz G/BBB and Beckwith–Wiedemann.[4] Monozygotic twins are generally assumed to be genetically identical. However, it is now well established that phenotypic and genotypic differences between monozygotic twins are common, attributable to a range of genetic and epigenetic processes and further confounded by environmental influences.[3,6]

Chorionicity refers to the type of placentation and is closely related to zygosity. In dizygotic pregnancies, each zygote develops its own amnion, chorion, and placental circulations. Dizygotic twins therefore (virtually) always have a dichorionic placenta. The appearance of the dichorionic placenta depends on the sites of blastocyst implantation. Distant implantation sites are more likely to result in separate placentas; when the blastocysts implant close to each other, the placentas may be fused as a single placental mass (with separate fetoplacental circulations).

In monozygotic twin pregnancies, the type of placentation depends primarily on the timing of division of the zygote. Early division, within the first three days post-fertilization (70% of monozygotic twins), usually will result in dichorionic placentation. Division between three and nine days post-fertilization (25%) will result in diamniotic-monochorionic placentation. Late division (8–12 days post-fertilization; 2%) leads to monoamniotic-monochorionic placentation, whereas even later zygotic splitting (13–16 days; 1:100,000) results in conjoined monoamniotic-monochorionic twinning.

The relationship between chorionicity and zygosity is traditionally summarized with the following general rules. First, dizygotic twins are dichorionic. Second, monozygotic twins can be either monochorionic or dichorionic. Third, a monochorionic placenta is diagnostic of monozygosity. The validity of the first and third rules has been challenged recently by several well-documented reports describing the unequivocal existence of dizygotic monochorionic (diamniotic) twins, usually, but not always, in the context of assisted reproductive technology.[7,8]

Determination of zygosity and chorionicity

Knowledge of chorionicity is important for optimal prenatal management of twin pregnancies, as monochorionic twins are notoriously at risk for specific complications such as twin-to-twin transfusion, fetal growth discordance, and malformations. Chorionicity is usually determined early in pregnancy by ultrasound examination between 10 and 14 weeks of gestation. Ultrasound clues to chorionicity include gender (fetal gender discordance indicates dichorionicity), placental site (two clearly distinct placental sites indicate dichorionicity), thickness and layering of the dividing membrane (thick, four-layered dividing membrane indicates dichorionicity), and shape of the junction between dividing membrane and placenta. The "lambda" or "twin peak" sign, a triangular projection of echodense chorionic villi and trophoblast extending up to the base of the dividing membrane, reflects dichorionicity. The "T-sign," created by the dividing membrane approximating the placenta at a 90° angle, suggests monochorionicity. Postnatally, the onus is on the pathologist to determine or confirm chorionicity by examination of the placenta, as described below.

While chorionicity is important for the course of the pregnancy, accurate zygosity diagnosis mainly has implications for postnatal and lifelong health care of twins. Zygosity is particularly important for medical reasons, such as organ transplantation and inheritance of specific genetic diseases. Accurate determination of zygosity is therefore indicated in all multiple gestations. Twins of different sex are always dizygotic. In spite of well-documented sporadic exceptions of dizygotic monochorionic twinning,[7,8] monochorionicity remains an excellent proof of monozygosity. If the twins are of the same sex and either dichorionic or of unknown or uncertain chorionicity, zygosity diagnosis depends on genetic markers such as blood group testing (a difference in blood groups is proof of dizygosity) or, preferably, DNA studies using skin biopsy, umbilical cord tissue, or a buccal smear.

Complications of (monochorionic) twinning and corresponding placental characteristics

Twin-to-twin transfusion syndrome (TTTS)

Twin-to-twin transfusion syndrome is a complication of monochorionic twinning, characterized by a shift of blood volume from one twin (donor) to the other (recipient) through placental vascular communications, resulting in hemodynamic imbalance. Severe, chronic TTTS complicates 9–15% of all monochorionic twin pregnancies and, if left untreated, is associated with mortality rates exceeding 70%.[9] TTTS is a complex and multifactorial condition, with both placental and fetal contributions (reviewed by De Paepe and Luks[10]). Adverse placental choriovascular and other anatomic factors, in combination with various maladaptive responses in one or both twins, are believed to result in a series of hemodynamic, hematologic, and hormonal imbalances, culminating in the development of oligohydramnios/polyhydramnios and other features of fully established TTTS (reviewed by De Paepe and Luks[10]).

The diagnosis of TTTS relies on strict perinatal ultrasound criteria based on detection of asymmetric distribution of amniotic fluid across the intertwin membrane (oligohydramnios/polyhydramnios).[11] Additional ultrasound findings corresponding to increasing stages according to the Quintero staging system of severe TTTS include non-visualization of the (donor) bladder, critically abnormal Doppler studies, fetal hydrops, and (impending) fetal demise.[11] In recent years, more detailed description and staging of TTTS has included a variety of cardiac and hemodynamic indices.[12]