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Multiple Gestations

Basics and Beyond

Federation of Obstetric & Gynaecological Societies of India

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3

Multiple Gestations: Classification, Etiology and Diagnosis

Anupama Rao

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INTRODUCTION

Of the spontaneously occurring multiple gestations, twins are the most frequent. Because of the increase in the use of assisted reproductive technologies, the frequency of multiple gestations has increased enormously over the past 20 years.[1] Multiple gestations currently account for 3% of all live births. Since monochorionic twins share a placenta they are likely to have interconnected circulations. Different combinations of shared and separate placentae occur in triplet pregnancies and other higher-order multiple pregnancies. Since twins make up >98% of all multiple pregnancies, most areas covered by this chapter are of twins and not higher order multiples.

CLASSIFICATION

Zygosity, Amnionicity and Chorionicity

Zygosity refers to the number of fertilized eggs that result in a multiple gestations. If one egg is fertilized and divides into two embryos, the pregnancy is described as monozygous, whereas if two eggs are fertilized and result in separate embryos, the pregnancy is described as dizygous.

The number of amnions (inner membranes) that surround babies in a multiple pregnancy decideds *amnionicity*. Pregnancies with one amnion (so that all babies share an amniotic sac) are described as monoamniotic; pregnancies with two amnions are diamniotic; and pregnancies with three amnions are triamniotic.

The number of chorionic (outer) membranes that surround babies in a multiple pregnancy would decide *chorionicity*. If there is only one common membrane, the pregnancy is described as monochorionic; if there are two, the pregnancy is dichorionic; and if there are three, the pregnancy is trichorionic.

Types of Twin Pregnancy

- *Dizygotic twins,* or binovular twins result from fertilization of two ova, which have mostly ruptured from two follicles, either from same ovary or rarely one from each ovary, by two sperms, during a single ovulatory cycle. This is called superfecundation, where fertilization of two ova occurs within the same menstrual cycles but not necessarily by the same act of coitus, and not necessarily by the sperm of same male. Other type, superfetation, where fertilization and implantation of two ova occur in two different menstrual cycles, does not seem to happen in human race.
- *Monozygotic twins or* uniovular twins result from the division of single fertilized ova. The

outcome of monozygotic twins depends upon when the division has occurred **(Figure 3.1)**. The underlying mechanism of its development is poorly understood.

Types of Triplet Pregnancy

Trichorionic triplets: Each baby has a separate placenta and amniotic sac.

Dichorionic triamniotic triplets: One baby has a separate placenta and two of the babies share a placenta. All three babies have separate amniotic sacs.

Dichorionic diamniotic triplets: One baby has a separate placenta and amniotic sac and two of the babies share a placenta and amniotic sac.

Monochorionic triamniotic triplets: All three babies share one placenta but each has its own amniotic sac.

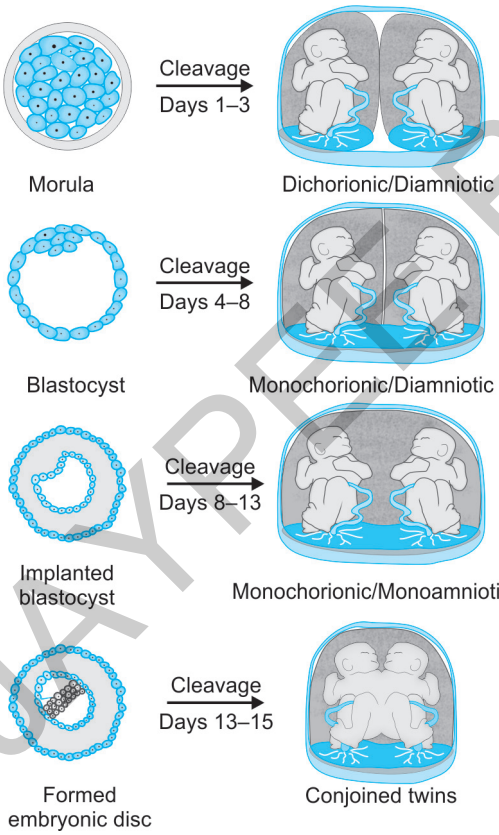

Fig. 3.1 Outcome of monozygotic twinning [Retrieved from http//commons,Wikimedia.org/wiki. File-placentation(Dufendach K,2008,Placentation,Web)]

Monochorionic diamniotic triplets: All three babies share one placenta. One baby has a separate amniotic sac and two babies share one sac.

Monochorionic monoamniotic triplets: All three babies share a placenta and amniotic sac.

Monochorionic twin pregnancies and dichorionic triplet pregnancies carry higher risks because the babies share a placenta.

ETIOLOGY

Spontaneous Twinning

Multiple gestations arise more frequently from fertilization of two separate oocytes [1.2% dizygotic (DZ) twinning], than from a single fertilized oocyte that subsequently divides into two identical structures [0.4%; monozygotic (MZ) twinning] **(Table 3.1)**.[1]

Monozygotic Twinning (MZ)

There is a genetic component to the increased likelihood of an embryo to divide. Though frequency of monozygotic twin is more or less constant, there is familial predisposition in occurrence of monozygotic twins. History of

Table 3.1 | Difference between monozygotic and dizygotic twins

Feature	*Monozygotic*	*Dizygotic*
Type	Identical	Fraternal
Fertilization	Single ovum by single sperm	Two ova by two sperms
Genotype	Same	Different
Phenotype	Identical	Different/ Fraternal
Placenta	Single or separate	Separate
Connecting vessels	Present	Absent
Inter-twin membrane	May be absent in Mono-Mono types	Always present
Thickness of inter-twin membrane	Thinner	Comparatively thicker
Twin peak sign	Absent	Present

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twinning on maternal side is more likely, whereas there is no evidence for a paternal effect on monozygotic twinning.[2] An excess of monozygotic twins occurs in mothers who are themselves one of monozygotic twins. However, some other factors may be of importance as reflected in the recently reported increased incidence of MZ twinning as a consequence of ovarian stimulation[3] and following the transfer of blastocysts after in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI).[4]

Dizygotic Twinning (DZ)

Fertilization of two simultaneously ovulated oocytes results in dizygotic twinning. The DZ twinning rate is affected by race, genetic factors, maternal age and parity, endogenous gonadotropins and fertility enhancing drugs. The DZ twinning rate is related to a wide variety of endogenous and exogenous factors and appears to be mediated by pituitary FSH release.

Dizygotic twinning is associated with increased basal follicle-stimulating hormone (FSH) concentrations and excessive follicular recruitment. Mothers of DZ twins have significantly higher basal FSH concentrations and FSH pulse frequency[5] with consequent elevation of follicular phase estradiol, inhibin and luteinizing hormone (LH) concentrations.[6] This suggests that the primary cause of multiple ovulation causing DZ twinning is increased secretion of FSH and LH in response to elevated secretion of, or sensitivity to, GnRH.

Also this hypothesis of extragonadally determined DZ twinning is supported by the finding that the basal FSH concentration in women is significantly higher in populations with high twinning rates (e.g. Western Nigeria: 50/1000 maternities) compared to that in women from populations with low twinning rates.

Also some seasonal variation in occurrence of twinning has been found, with slightly more tendency for twins in women conceiving during summer.

Iatrogenic Twinning

The significant increase in the incidence of multiple gestations is almost entirely the result of the use of gonadotropins and other agents for induction of ovulation or assisted conception. Multiple gestation, as a result of ovarian hyperstimulation, occurs in three circumstances:

Induction of Ovulation

During ovulation induction, the ovaries are stimulated to produce several follicles, thus increasing the risk of multiple oocytes being released and subsequently fertilized. The first-line treatment of women with normogonadotropic anovulation, including polycystic ovarian syndrome (PCOS), is clomiphene citrate or other anti-estrogens. The incidence of twins is increased to 10% and that of triplets is 1%. Treatment with gonadotropins should be confined to those who are resistant to clomiphene, i.e. remain anovulatory, because the risk of multiple gestations is as high as 25%.

In Vitro Fertilization

In *in vitro* fertilization, multiple gestations rates are increased by the transfer of excess embryos in the hope of improving pregnancy rates. Increased maternal age and more number of embryos transferred contribute significantly to risk of multiple gestation in IVF cycles. The risk of a multiple gestations when 2 embryos were transferred was found to be 22.7% and 19.7% for women aged 20–29 years and 30–34 years, respectively. This risk increased to 45.7% in women aged 20–29 years and 39.8% for women aged 30–34 years, if 3 embryos were transferred.[7]

Significant diminution in the expected pregnancy or birth rates is not seen with transfer of only two embryos. The transfer of embryos should be limited to 2 or 3 in order to reduce the risk of multiple gestations.[8] The remaining 'spare' embryos are cryopreserved and can be used in subsequent cycles, if pregnancy does not occur.

Strict guidelines for embryo transfer can prevent risk of multiple gestations in ART cycles. Better recognition of high quality embryos with improved technology; delaying implantation to the blastocyst stage when fewer but healthier embryos are available, will also help in reducing the multiple gestations rates.

Intrauterine Insemination in Combination with Ovulation Induction

Ovarian stimulation along with intrauterine insemination in couples with unexplained infertility and male subfertility increases the risk for multiple gestations (ESHRE Workshop,

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1996). The larger number of oocytes available for fertilization can be a factor resulting in increased risk.[9]

DIAGNOSIS

History

Though, in majority of women having multiple pregnancies, no specific causative history is found; in few women, there will be history of infertility treatment with or without assisted reproductive technology with ovulation-inducing drugs. Family history of twinning may be found in few cases. History of taking OC pills in recent past may be there in few cases.

Most women carrying multiple gestations have normal symptoms and signs (e.g. breast tenderness, fatigue, nausea, vomiting) of pregnancy in first trimester. Few of them may have increased nausea/vomiting or features suggestive of hyperemesis gravidarum.

In third trimester, women may feel excessive enlargement of abdomen. Symptoms—because of excessive enlargement of uterus like discomfort, breathlessness, orthopnea are more evident in late third trimester. Multiparous woman may experience excessive fetal movements.

Other minor ailment of pregnancy like hemorrhoides, varicose veins, constipation and edema feet are often exaggerated.

Symptoms related to development of anemia or pregnancy-induced hypertension (PIH) can appear early in pregnancy and are likely to be severe.

Examination

On general examination, apart from unusual weight gain tachycardia, tachypnea, pallor and edema feet may be noted.

Abdominal Examination

These findings are evident in third trimester.

Inspection: Excessive enlargement, stretched glossy skin, enlarged veins, stretched umbilicus can be seen. Abdomen is more barrel shaped; sometimes, situation is aggravated by the presence of hydramnios.

Palpation: Fundal height and abdominal girth are often more than period of gestation by dates, Palpation of too many fetal parts with feeling of more than two fetal poles should raise suspicion of multiple gestations.

Auscultation: Simultaneous hearing of two distinct fetal heart sounds located at two different spots heard simultaneously by two observers, with difference in heart rate of more than 10/min.

Occasionally, clinical examination fails to diagnose twins in antenatal period and may get detected in labor only after delivery of first of the twins.

INVESTIGATIONS

Laboratory

Beta HCG levels are significantly higher than singleton. But cannot be used for definitive diagnosis.

Sonography

Ultrasound examination remains the most reliable method for diagnosis of multiple gestations. Pregnancy risks, clinical management and subsequent outcomes are very different for monochorionic and dichorionic twin gestations (and monochorionic, dichorionic and trichorionic triplet gestations). Early and accurate determination of amnionicity and chorionicity is critical in the antenatal management of twins. The optimal time for diagnosis is in the first trimester or early second trimester.[10]

Determination of gestational age by sonography is important in future management of multiple gestations. In twins, there is expert consensus that first trimester ultrasound dating is preferable. There is a need for larger prospective studies to examine the use of singleton charts in twin and triplet pregnancies. Due to the problem of discordance, several studies have cited the need to use the larger twin for dating purposes to minimize the chance of missing a fetus that might present with IUGR.[11]

First trimester sonography can determine chorionicity with almost 100% sensitivity. The chorionity in first trimester can be determined by sonography in first trimester by checking number of placental masses, the lambda or T-sign and membrane thickness.

Screening for and identification of aneuploidy, determination of the etiology of discordance, early

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diagnosis of twin-to-twin transfusion syndrome, and the management of a surviving twin following intrauterine demise are examples of clinical management depending on chorionicity. The high mortality and morbidity of monoamniotic twins is well-documented, and early and intensive monitoring and intervention may improve the outcomes.[12]

Radiography

X-ray for diagnosis of twin pregnancy is not common practice nowadays. It is, sometimes, done in or just before labor to assess relative position of twins with each other. Also, it may help in evaluation of suspected case of conjoined twins. Rarely MRI may be required, if there is suspicion of conjoined twins.

DIFFERENTIAL DIAGNOSIS

- *Hydramnios:* Fundal height more than expected, difficulty in palpating fetal parts, changing lie and, sometimes, external ballotment felt even up to late second trimester.
- *Big baby*: Only two fetal poles and single heart sound.
- *Ascites*: More fullness in flanks, difficulty to feel uterine contour.
- *Ovarian tumor or fibroid with pregnancy*: Uneven bulging over the uterus, sometimes, groove between uterine contour and mass, two fetal poles and single heart sound.

Ultrasonography will help to make the final diagnosis.

SUMMARY

All patients, who are suspected to have a twin pregnancy on first trimester physical examination or who are at risk (e.g. gestations resulting from assisted reproductive technologies), should have first trimester ultrasound performed. Every attempt should be made to determine and report amnionicity and chorionicity when a twin pregnancy is identified. Perinatal outcome in multiple pregnancy is largely driven by chorionicity, the accurate assignment of which is therefore of critical importance. Although the accuracy in confirmation of gestational age at the first and second trimester is comparable, dating should be done with first trimester ultrasound. When twin pregnancy is the result of in vitro fertilization, accurate determination of gestational age should be made from the date of embryo transfer. There is insufficient evidence to make a recommendation, of which fetus (when discordant for size) to use to date a twin pregnancy. However, to avoid missing a situation of early intrauterine growth restriction in one twin, most experts agree that the clinician may consider dating pregnancy using the larger fetus.

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