



Indian FERTILITY Society

SYNAPSES

MULTIPLE PREGNANCY AND REPRODUCTIVE MEDICINE

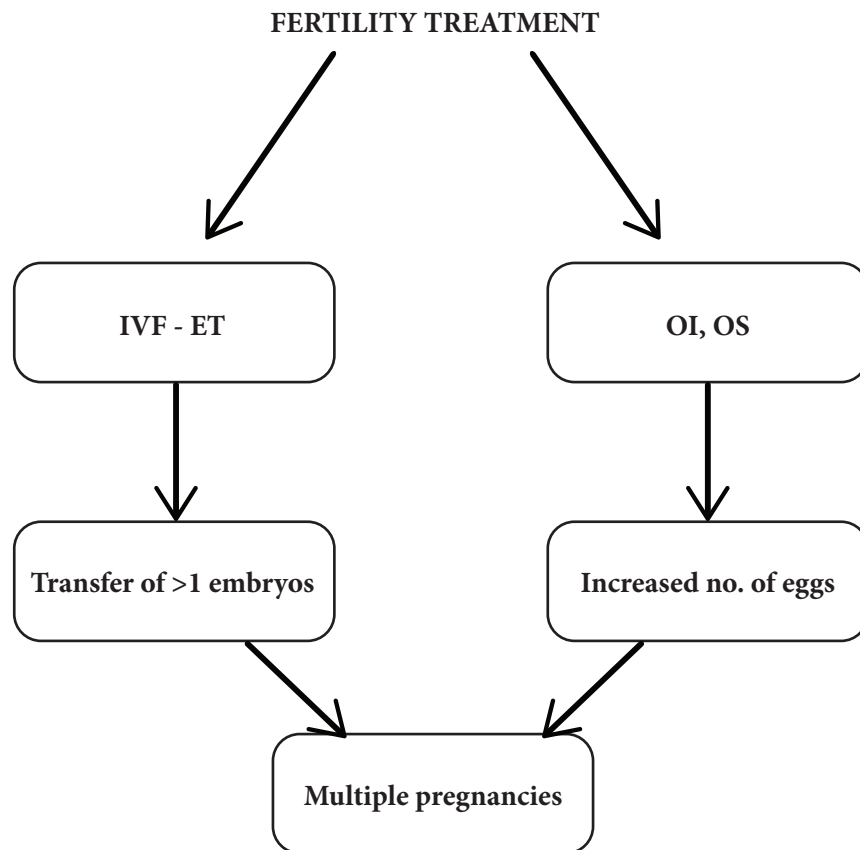
Definition

It refers to twins, triplets and higher number of foetuses(quadruplets, quintuplets).

Incidence

The incidence of monozygotic twins is constant (4 per 1000 births).It is the incidence of dizygotic twins that varies and depends on ethnicity, maternal age, parity, use of fertility treatments etc. African countries have reported the highest incidence of dizygotic twins , while Asia has the lowest.¹ Naturally occurring triplets births occur in 1 per 7000 to 10,000 births and naturally occurring quintuplets births occur in 1 in 600,000 birth.² In India , incidence of twins is around 2 per 1000 births.³

Fig. 1: Multiple births and fertility treatments



ART : Assisted Reproductive Techniques
IVF : In Vitro Fertilization
OI : Ovarian Induction
OS : Ovarian Stimulation

Etiology

Advanced age and parity

Race and ethnicity : Dizygotic twins are common in the Africans than Asians.

Genetics

Use of fertility drugs

ART

Types

- ▶ **Dizygotic twinning** : Twinning which occurs because of fertilization of two separate ova is called as dizygotic twinning (1.2 %) [Fraternal twins]
- ▶ **Monozygotic twinning** : Twinning in which a single fertilized ova subsequently divides into two identical structures is known as monozygotic twinning (0.4%) [Identical twins]

Outcome and incidence of the monozygotic twinning depends **on the timing of division.**

- 0-72 hrs- Diamniotic Dichorionic twins, occurs in 29% of cases
- 4-7 days - Diamniotic Monochorionic twins, occurs in 70% of cases
- 8 -12days-Monoamniotic Monochorionic twins, occurs in 1% of cases
- 13 days-16 days (Incomplete division) -Conjoint Twins, extremely rare

Pathogenesis

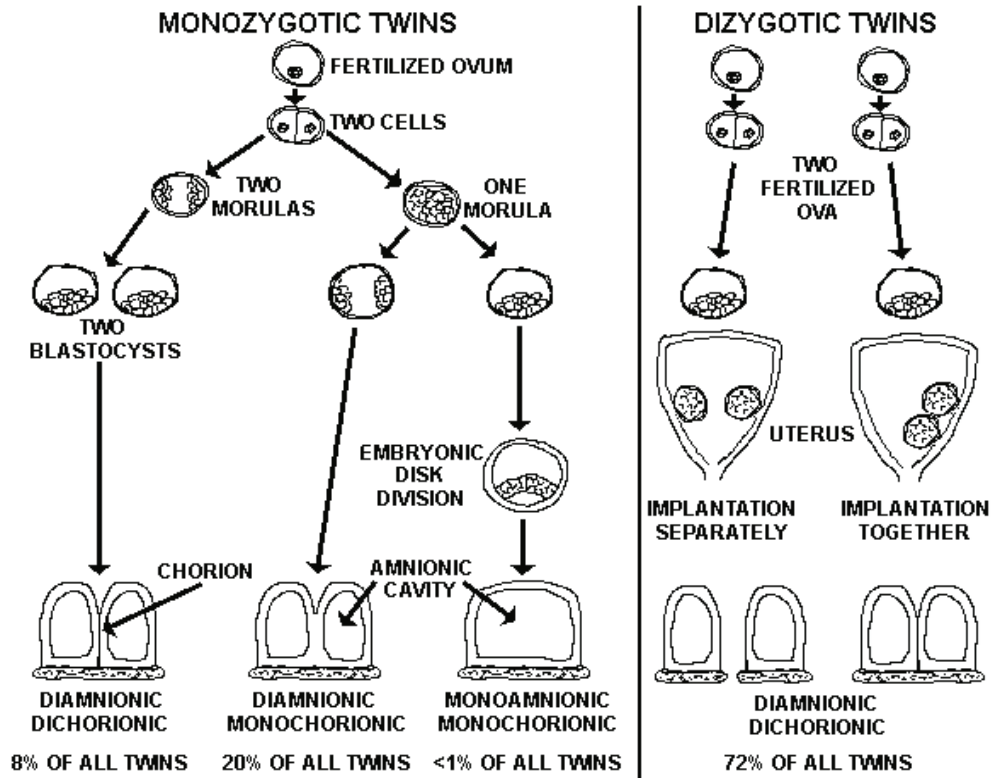


Fig. 2: Pathogenesis of twins¹⁴

Diagnosis

History	Examination	Investigation
<ul style="list-style-type: none"> • Age • Parity • H/O Fertility • Treatment • Genetic • Race • Exaggeration of common symptoms of pregnancy 	<ul style="list-style-type: none"> • Uterine height more than the period of gestation • Multiple fetal parts • Multiple fetal heart sounds • Striae gravidarum and Cholasma may be severely increased 	<p>Role of Ultrasound</p> <ul style="list-style-type: none"> • Diagnosis • Antenatal surveillance • Determines amnionicity, chorionicity and zygosity. • Chorionicity : Can be done as early as at 10 -14 weeks <p>Monochorionic : 'T' sign</p> <p>Dichorionic : lambda sign 'γ'</p> <p>Dichorionic Twins (80%) (Two placentas) Lambda sign</p> <p>Monochorionic Twins (20%) (One placenta) T sign</p> <p>ABOUBAKR ELNASHAR</p>

History	Examination	Investigation
		<ul style="list-style-type: none"> • Measurement of membrane thickness & counting the number of layers of the intertwin membrane – visualisation of intertwin membrane is a reliable sign of diamnionicity. • Well defined hyperechoic membrane of > 2 mm thickness and 4 layers (amnios- chorion-chorion –amnios) - predictor of dichorionicity, more reliable at less than 26 weeks of period of gestation. • In monochorionic twin, the inter twin membrane is <2mm and 2 layers only (aminos-aminos).

Management

- Early registration.
- Routine investigations.
- Early scan for dating and Chorionicity.
- Combined screening should be offered.
- **Detailed anomaly Ultrasonography at 18-20 weeks.**
- **Fetal echocardiography at 19-21 weeks** (risk of cardiac anomalies is higher in Monochorionic twins (2% in uncomplicated, 5% in TTTS).
- **Cervical length-by TVS at 20-24 weeks** of gestation to evaluate the risk of spontaneous preterm delivery. Cut off value at this gestation is 25mm.
- Growth scan 4 weekly in Dichorionic twin and 2 weekly in Monochorionic twin .
- Regular ANC visits- 4 weekly till 28 weeks followed by 2 weekly from 28 weeks till 34 weeks and then followed by weekly visits (can be individualized according to complication).
- Antenatal steroids at 34 weeks.
- Biophysical profile:
 - Twice a week after 30 weeks for monochorionic monoamniotic twins.
 - Weekly from 34 weeks onwards for monochorinic diamniotic twin pregnancy.
 - 36 weeks onwards for dichorionic diamniotic twin pregnancy (can be individualized according to complication).
- Management of complications.

Problem statement

- The incidence of multiple pregnancy and delivery has increased dramatically over the past decades. In IVF, the usual practice of transferring two or more embryos to achieve higher pregnancy rates results in a high incidence of multiple births.
- In the World Collaborative Report on IVF figures for 2000 showed conventional IVF and ICSI twin rates were 26.9% and 26.2%, respectively, and triplet rates were 2.8% and 2.9%, respectively, for an estimated total of approximately 197,000 to 220,000 babies worldwide.⁵
- Twin gestation carry additional risks for both mother and offspring and extensive monitoring is required. [Table 1]
- Despite the substantial risks associated with multiple pregnancy, double embryo transfer (DET) during IVF treatment continues to be widely practiced.⁶ The embryo transfer practices differ worldwide due to variation in IVF regulation.
- IVF clinics in private sector are in a competitive environment. It means the perceived reputation of the clinic became closely related to its success rate per fresh IVF cycle.
- There is a common understanding among patients and health professionals that transfer of more than one embryo improves the success rate of IVF. Hence they neglect the harmful consequences of Twins.⁷

- Another factor is the higher cost of IVF cycles which makes patient and her spouse reluctant to go for multiple IVF cycles so as to promote single embryo transfer.
- The cost of care for children born prematurely as a result of multiple births is also considerable. According to one study, the estimated neonatal cost to the UK's National Health Service (NHS) for a twin is 16 times higher than that for a singleton baby.

Table. 1: Maternal, fetal, Neonatal Risks

Maternal	Fetal	Neonatal
Preeclampsia	IUGR	Prematurity
Eclampsia	Prematurity	LBW
Preterm labor, PROM	TTTS	Birth Asphyxia and RDS
APH	Conjoined Twins	Metabolic Complications
Anemia	Congenital malformation	NICU admissions
Surgical and Assisted delivery	Acardiac twin	Cerebral palsy and mental retardation
PPH	Vanishing twin(common with ART procedure)	
Failed Lactation		
Placenta previa		
Maternal death if associated with other comorbid conditions.		

Strategies to reduce multiple births

1. **eSET (Elective Single Embryo Transfer):** In good prognosis women, the cumulative live birth rate after eSET, followed by the transfer of a thawed embryo in a subsequent frozen embryo transfer cycle is comparable to that after DET, but with a significantly lower risk of multiple pregnancy.⁸

Table. 2: ASRM Guidelines on Number of embryos to be transferred⁹

Recommendations for the limit to the number of embryos to transfer.				
Prognosis	Age (y)			
	< 35	35–37	38–40	41–42
Cleavage-stage embryos ^a				
Euploid	1	1	1	1
Other favorable ^b	1	1	≤3	≤4
All others	≤2	≤3	≤4	≤5
Blastocysts ^a				
Euploid	1	1	1	1
Other favorable ^b	1	1	≤2	≤3
All others	≤2	≤2	≤3	≤3

^a See text for more complete explanations.
^b Other favorable = Any ONE of these criteria: *Fresh cycle*: expectation of 1 or more high-quality embryos available for cryopreservation, or previous live birth after an IVF cycle; *FET cycle*: availability of vitrified day-5 or day-6 blastocysts, euploid embryos, 1st FET cycle, or previous live birth after an IVF cycle.
Please note: Justification for transferring additional embryos beyond recommended limits should be clearly documented in the patient's medical record.
ASRM. Limits on number of embryos to transfer. *Fertil Steril* 2017.

Other Scenarios

1. An additional embryo may be transferred if a patient with a favourable prognosis fails to conceive after multiple cycles with high quality embryo(s).
3. One embryo should be transferred in patients with coexisting medical condition to which multiple gestation can be an additional morbidity .
4. In case of transfer of embryos more than the recommended limits, counselling and justification must be documented on patient's permanent records.
5. There is insufficient data to recommend number of embryos transferred when the patient age > 43 yrs using her own oocytes. Caution should be exercised as the risk of multiple pregnancy is dramatically increased with advancing age.
6. Age of the donor should be used to determine the appropriate number of embryos to be transferred in donor cycles. For example, when the donor is <35 yrs of age ,single embryo transfer should be planned.

How to promote eSET?

1. To select the embryo with maximum implantation potential by Preimplantation Genetic screening, Blastocyst culture and Time lapse.¹⁰
3. Appropriate counselling about the health risks of multiple pregnancy and the merits of eSET.
4. **IVF funding policies** that support access to several fresh and frozen IVF cycles. In Europe, countries with higher rates of eSET, such as Belgium, Norway and Denmark, have generous IVF state funding arrangements.⁶
5. Setting a multiple birth rate target for the IVF clinics as done in UK.
6. The laboratory conditions and techniques should be continuously refined to allow selection of a single developmentally-competent embryo more easily.
7. Birth per embryo transferred' : this term should be given the status of 'the criterion of ART excellence'.¹¹

2. Embryo/Fetal reduction,

It is used to reduce the number of multiple births worldwide. The collaborative data have reported satisfactory outcome for the children and limited risks for the mother¹² but this kind of intervention raises serious ethical and psychological problems.¹³ It may be indicated in cases of particularly high order multiple pregnancies but can never be justified as a method for reduction of twins.

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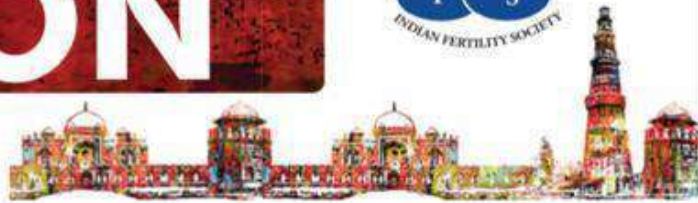
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