Implantation/Placentation and Early Pregnancy

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What is implantation

• The attachment of the fertilized egg or blastocyst to the wall of the uterus

• Involves penetration of the embryo into uterine epithelium into the circulatory system, to form the placenta
Embryo transfer

Maximal chance of normal implantation is only about 40% per cycle under optimal conditions.

Macklon et al Human Reprod Update 2009
Follicular phase

Luteal phase

PROGESTERONE
Progesterone

- Induces secretory changes in the endometrium
- Receptivity (pinopodes) - Surface epithelial cells undergo loss of microvilli & develop smooth protrusions, appearing and regressing during the window of receptivity
- Upregulates HOXA genes
- Promotes local vasodilation
- Promotes uterine myometrial quiescence and immunomodulation
Key ingredients

- Good embryo / hatched blastocyst
- Receptive endometrium (hormonal milieu)
- Dialogue and synchrony between the two
Pre-implantation signaling

![Diagram of pre-implantation signaling process](image)

Key terms:
- DAY 1: Fertilization, Fertilized egg (zygote)
- DAY 2: First cleavage, 2-cell stage
- DAY 3-4: 4-cell stage, 8-cell uncompacted morula, 8-cell compacted morula
- DAY 4: 8-cell compacted morula
- DAY 5: Trophectoderm, Early blastocyst
- DAY 6-7: Late-stage blastocyst (hatching), Blastocoel, Inner cell mass
- DAY 8-9: Epiblast, Implantation

EPF, HCG
Preparation for implantation

- Endocrine  – progesterone; secretory endometrium; nourishment
- Prostaglandins/ vasculogenesis
- Window of implantation (opportunity) – days 16-22
Markers of implantation

- Integrins
- LIF
- HOXA 10/11
- Progesterone
Hatching
3 stages of implantation

- Apposition
- Adhesion
- Invasion
STAGES OF IMPLANTATION

1 Apposition  2 Adhesion  3 Invasion
Trophoblastic invasion

- Lipids
- Cytokines
- Growth Factors
- Modulated by hormones i.e. progesterone
2\textsuperscript{nd} week after ovulation

- Invasion of maternal blood vessels begins and placenta starts to form.
Limitation of Invasion

• To confine the placenta to its intrauterine location.

• Invasion of the trophoblast is limited by the formation of the decidual cell layer.

• Natural killer cells – cytokines
Normal (Decidua)

Stratum basalis of endometrium

Myometrium

Accreta (75-78%)

Increta (17%)

Percreta (5%)
Problem placentation

- Pre-eclampsia
- Placenta accreta, increta, percreta
Restraining factors: PAI; TIMPS

Promoting factors: MMPS
Causes of implantation failure

- Maternal
- Paternal
- Embryo
- Interface
Endometriosis

- Prevalence – 6 – 10% in the general reproductive age female population and up to 25 – 50% in women with infertility
- Proposed mechanisms - altered folliculogenesis, impaired fertilization, defective implantation and poor oocyte quality, with decreased ability to implant
Hydrosalpinx
Hydrosalpinx

- Toxic effect of the fluid on the embryo
- Mechanical embryo washout
- Oxidative stress
- Altered gene and integrin expression
- Reverse peristalsis phenomenon
Polyps

- Mechanism by which polyps may adversely affect fertility is poorly understood, but may be related to mechanical interference with sperm transport, embryo implantation or aberrant expression of implantation markers.
Fibroids

- Anatomical distortion of the cervix, uterine cavity or tubal ostia – altered likelihood of sperm entering the uterus, migrating through the uterus and entering the proximal fallopian tube.
- Altered tubo-ovarian anatomy may hinder ovum retrieval and transport by the fallopian tube.
- Alter implantation potential by promoting abnormal uterine contractility, altering endometrial blood supply and localized endometrial inflammation or secretion of vasoactive substances.
Adenomyosis

- It is likely to reduce endometrial receptivity in a manner similar to endometriosis.
PCOS

- Ovulation is readily obtained with medical induction, implantation rates remain lower than fertile controls and early pregnancy loss rates are increased.
- Regulatory roles of progesterone are suboptimal or absent, and this results in relatively constant unopposed action of estrogen in the endometrium (Giudice, 2006).
- Increasing evidence of dysregulated expression of markers of uterine receptivity in endometrium of women.
Acute/ Chronic Endometritis

- Possible action of microbial products on the endometrial receptivity
- Acute endometritis - most commonly caused by bacteria, usually responds well to treatment and is only rarely associated with long-standing infertility.
- Chronic endometritis – can be bacterial, viral or parasitic. There is a strong relationship between genital tuberculosis and infertility.
Ovarian stimulation
Therapy

• Tailored to the cause

• Empirical forms of treatment – Progesterone, LMW heparin, Steroids, Intralipid, GM-CSF etc.
Gamete and Embryo factors

- Chromosomal abnormality
- Zona hardening
- Embryo transfer
Other factors in RIF

- Obesity
- Smoking
- Thyroid disease
- Immune factors
- Male factors
qBHCG

- **When is a urinary bhcg first positive?**
  - 3 days before the period is due

- **When is the blood test bhcg positive?**
  - 8 days after ovulation
  - 1 day after implantation

- **When is the trigger hcg out of the patients system?**
  - By day 10 post injection.
QBhcg

- Doubles every 48 hrs
Medications used to support a pregnancy

- Luteal support
  - Progesterone
  - HCG (recombinant; urinary)
Options

- Depend on:
  - Country
  - Clinic
  - Patient – cycle
  - Doctor
Australia

– Progesterone
  • Crinone gel (8%) - 1-2 vaginal application daily
  • Progesterone pessaries (200mg) – 3 vaginal tables per day

(IM Injections)

– HCG injections (Ovidrel, Pregnyl)
  • Pregnyl 1500IU/ Ovidrel Day 2 and Day 6
Early pregnancy

- Biochemical pregnancy
- Clinical pregnancy
- Ongoing pregnancy
- Ectopic pregnancy
- Pregnancy of unknown location
- Blighted ovum
- Miscarriage
• Biochemical pregnancy

  – When the urinary or blood hcg is initially positive, but then it declines and no sac is seen on USS.

  – Probably occurs in close to 30% of pregnancies if early bhcg monitoring were done.

  – No curette is usually needed, and a period usually follows a few days later.
Clinical pregnancy
Ectopic pregnancy
Ruptured ectopic
Pregnancy of unknown location
Blighted ovum
• Miscarriage
  
  – (Complete/inevitable/missed)

  – Options: spontaneous, medical, surgical (D&C)

  – 3 consecutive miscarriages constitutes “recurrent miscarriage” and needs to be appropriately investigated.
• What is the single biggest risk of fertility treatment?
Multiple Pregnancy/ Twins
• **Dizygotic** – from two eggs.
  – Race (eg. Nigerian > Japanese)
  – Age
  – Parity
  – Taller and heavier women
  – Number of embryos transferred: If replace two embryos and have a positive pregnancy test – 30% chance of a twin pregnancy.
  – OI – FSH; Clomid

• **Monozygotic** – (identical twins)
  – Stable across populations
  – ? Higher in ART but not conclusively shown by studies.
  – Risky pregnancies – shared placenta/amniotic cavity
Summary

- Knowledge regarding implantation is evolving
- Recurrent implantation failure v/s recurrent miscarriage – opposite ends of the spectrum
- Management depends on the cause, very few empiric therapies are justified
- Important to have an awareness of complications of early pregnancy
- Field of medicine undergoing rapid change with continuing focus on R&D to achieve BESST (Birth Emphasizing successful singleton at term) outcome
• Comments, Questions?
• Thank you