Overview

- Introduction
- Male infertility
- Female infertility
- Assisted reproductive technologies
Introduction

Following unprotected sex:
- 84% of couples conceive within 1 year
- 92% of couples conceive within 2 years

- failure of a couple to conceive after 12 months of regular unprotected intercourse
  - Primary = Never been pregnant
  - Secondary = previous pregnancies

- Infertility affects 1 in 7 couples

- Risk factors: Age, smoking, alcohol, weight, chronic disease (diabetes)
Male Infertility

- Male infertility occurs in 5% of men
- Major cause of infertility in 30% of couples and a contributory factor in a further 20%
- Only a small number have an identifiable treatable cause

Definitions:
- Oligozoospermia – low sperm count
- Asthenozoospermia – reduced sperm motility
- Azoospermia – absence of sperm in ejaculate
- Teratozoospermia – Abnormal morphology
Causes

- **Idiopathic oligo/ azoospermia** (16%) – testes often small + raised FSH
- **Asthenozoospermia/ teratozoospermia** (17%) – abnormal motility/morphology
- **Varicocele** (17%): controversial, 15% of male, most are fertility
- **Genital tract infection** (4%) – Chlamydia, gram –ve enterococci.
- **Sperm autoimmunity** (1.6%)

- **Congenital**: cryptorchidism, chromosome disorders (2%)
  - Klinefelters: 50% of chromosomal: 47 XXY, hypogonadism

- **Obstructive azoospermia** (1.8%):
  - congenital e.g. absence of vas deferens (Cystic Fibrosis)
  - vasectomy
  - Post-infection
  - Trauma

- **Systemic** (1.3%): iatrogenic e.g. chemo/radiotherapy, drugs e.g. cannabis

- **Gonadotropin deficiency** (0.6%)
Both partners should be involved in the assessment (both patients have factors in 35% of infertile couples)

Male:
- Previous children,
- Previous urogenital surgery/trauma (hernias, neck of bladder??)
- Genital pathology (e.g. infection: dysuria, frequent voiding, discharge, pain...etc)
- PMH (adult mumps, CF, Cancer, hep B + C)
- Occupation – (agricultural workers using pesticides, away a lot)
- Drug hx (prescription, over-the-counter and recreational drugs)
- Sexual habits (frequency, timing, problems - erectile dysfunction)
- Smoking, alcohol, weight....
- Family history of infertility
Examination

- **General**: Weight, height, scars...
- **Scrotum and testes**:  
  - Size (Prader oridometer – small testes, ?Primary testicular failure)
  - Tenderness
  - Abnormal masses (e.g., cysts, varicocele, hernia)
  - Have testes descended?
- **Epididymis**:  
  - Size
  - ? spermatocele
  - ? cysts
- **PR: Prostatitis**:  
  - size
  - shape (nodularity, irregularity)
  - tenderness
- **Vas deferens**: size, absent due to congenital malformation
- **Penile abnormalities**, including position or urethral meatus and structural abnormalities
- **Assess secondary sexual characteristics** (gynaeomastia - indicative of hypogonadism)
Investigations

- Minimum of 2 semen analysis, 3 months apart. If 1st is normal then leave it.
- Semen Analysis – 3-7 day abstinence
  - Volume, >2ml
  - Sperm count, >20million/ml
  - Motility, >50%
  - Morphology, >30% normal
- Blood Tests: Testosterone, Oestrogen, LH/FSH (e.g. klinefelter syndrome)
- Ultrasound/Doppler if clinically indicated
- Others: Anti-sperm antibody tests, Genetic tests
Management

General: Health weight, Stop smoking, limit alcohol

Medical:
- Men with hypogonadotrophic hypogonadism - gonadotrophin drugs
- Effectiveness of antisperm antibodies and systemic corticosteroids is unclear.
- Any infection, swabs + cultures, treat only if an identified infection (leucocytes in their semen alone, not enough)
- denafil (Viagra) – erectile dysfunction

Surgical
- Men **should not be offered** surgery for varicoceles because it does not improve pregnancy rates
- Obstructive causes of oligospermia may be correctable by surgery
- In-utero insemination (IUI) in cases of poor sperm quality or sexual dysfunction
- IVF techniques like Intracytoplasmic sperm injection (ICSI) are treatments of choice for severe oligospermia
Case 1

- Mr Zee, 33
- Referred from GP as he and his wife have been trying to get pregnant for 18 months
- Hx: generally fit and well only thing he can recall was about 2 years ago had a really bad infection. Fever, headache, fatigue and muscle aches For about 1-2/52
- Parotid glands were very swollen and tender to touch
- Noticed painful swelling of the testicle and reddening of the scrotal skin
- Went to his GP but was told not to worry
- Feels like his testes have since shrunk
- Rest of his history is unremarkable
Case 1

- Infertility secondary to mumps infection
- Orchitis develops with mumps in 20 to 30 percent of postpubertal males
- Research the infection causes inflammation and swelling that can increase pressure on the sperm-producing parts of the testis leading to damage and reduced sperm production.
- Complete infertility is unlikely and wife probably has some fertility issues as well
- Rare
Female Infertility

Causes
Investigation
Treatment
Causes

1. Fallopian Tube and peritoneal factors 20%
2. Ovarian dysfunction (anovulation) 20%
3. Uterus or cervical factor 10%
Causes 1

1. Fallopian Tube and peritoneal factors 20%
   - Pelvic adhesions (Hx of infection? Ectopic pregnancy?)
   - Endometriosis (Hx: 2y dysmenorrhea, pelvic pain, dyspareunia) (tube blockage, ?luteal phase defect)
   - Previous ruptured ectopic
   - Tx: IVF; surgery to repair Fallopian tubes

2. Ovarian dysfunction (anovulation) 20%

3. Uterus or cervical factor 10%
Causes 2

1. Fallopian Tube and peritoneal factors 20%
2. Ovarian dysfunction (anovulation) 20%
   - PCOS
   - Premature ovarian failure
   - Hypothalamic amenorrhoea
   - Hx: 2y amenorrhoea? Periods regular?
   - Examination: endocrine signs? Hirsutism? Galactorrhoea? obesity?
   - Tx: induction of ovulation
3. Uterus or cervical factor 10%
## WHO classification of ovulation disorders

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Causes 3

1. Fallopian Tube and peritoneal factors 20%
2. Ovarian dysfunction (anovulation) 20%
3. Uterus or cervical factor 10%
   - Congenital malformation
   - Cervical stenosis (cone biopsy, cautery)
   - Cervicitis
   - Hx: infection? Cervical surgery?
   - Tx: intrauterine insemination
History

- Age, occupation, contraception, sexual history
- Pregnancies, terminations, miscarriages, ectopics
- Menstrual Hx: age of menarche, cycle and duration, pain, recent changes?
- Vaginal discharge? Character, amount, irritation?
- Illnesses: PID, diabetes, renal disease
- Surgery – pelvis/abdomen
- Coitus frequency, relation to fertile days
  - Ovum released day 14
Examination

- Evidence of endocrine disorder
  - Obesity, acne, hirsuitism, thinning hair
- Physical development
- Abdominal examination
  - Scars, masses, pain, guarding
- Vaginal examination: uterus size, mobility, ovaries enlarged?
Investigations 1

For ovulation

- Detect LH surge in urine — ovulation within 36 hours (regular cycles only)

- Daily basal body temperature (before getting up in the morning)
  - Incr progesterone levels within 12hrs of ovulation – 0.4-0.6°C
  - Incr basal body temp (regular cycles only)
  - Unreliable!

- Luteal phase progesterone concentration
Menstrual cycle

- Menstrual cycle

- Ovarian cycle
  - Growing follicle
  - Ovulation
  - Corpus luteum
  - Corpus albicans

- Body temp.
  - 37°C
  - 36°C

- Anterior pituitary hormones
  - Luteinizing hormone (LH)
  - Follicle-stimulating hormone (FSH)

- Ovarian hormones
  - Estradiol
  - Progesterone

- Uterine cycle
  - Menses
  - Follicular phase
  - Luteal phase
  - Menses

- Timeline
  - 0 days
  - 14 days (Ovulation)
  - 28 days
Investigations 2

Hormone tests

- **Serum progesterone**
  - middle of luteal phase (days 21-23)
  - 10x rest of cycle (30ng/ml cf 3-6ng/ml) if ovulation occurred

- **LH, FSH, (testosterone if ?PCOS) days 3-8**

- **Prolactin**
  - ? Microadenoma of pituitary
  - Inhibits GnRH (so hypogonadotrophic hypogonadism and anovulation)
Investigations 3

For tubal patency

- Hysterosalpingography
  - Radio-opaque dye and x-rays:
  - Vagina – uterus – fallopian tubes – abdominal cavity?
  - Blockage, shape, polyps, fibroids?

- Laparoscopy and blue dye
  - Dye should spill from fimbrial end of tubes
  - Hydrosalpinx? Obstruction?
  - Possible to open fimbrial end
Investigations 4

Uterine or ovarian pathology

- Ultrasound with vaginal probe
  - PCOS
  - Normal ovary with small follicles
  - Normal uterus and endometrium
Treatment of female subfertility

1. Fallopian tubes
2. Ovarian dysfunction
3. Uterine lesions
Treatment 1

For lesions of fallopian tubes

- Laparoscopy
  - Salpingostomy – fimbrial end opened
  - Salpingolysis – dividing peritubal adhesions
  - Reanastomosis – remove blockage and anastamose
  - Removal or blockage of tubes for IVF to decrease ectopics

- Poor results, best for reanastamosis of sterilization 40-60%
Salpingostomy

A: Hydrosalpinx (laparoscopic image).

B, C: The hydrosalpinx is opened with the aid of special hooks and laser CO2 (laparoscopic image).

D: The opened distal ends are everted (cuff neostomy) with the aid of SwiftLase (laparoscopic image).

E: The final result, with methylene blue coming out freely towards the peritoneal cavity (laparoscopic image).
Treatment 2

For ovarian dysfunction (anovulation)

- Excess prolactin:
  - Bromocriptine (dopamine agonist) – successful, menstruation restarts, fertility restored

- Ovarian failure, primary or secondary
  - Oestrogen low, FSH high
  - No more oocytes, so no more ovulation
  - Oestrogen replacement
Treatment 3

For ovarian dysfunction, cont..

- Ovulation failure – low FSH and LH
  - Give FSH from day 2-3, incr dose weekly depending on # & size of follicles on US
  - Satisfactory response – give hCG (acts like LH surge)
  - Up to 6 treatment cycles
  - Ovarian hyperstimulation syndrome OHSS possible – high oestrogen, coagulation disorders and fluid/electrolyte imbalance – life threatening if severe
Treatment 4

Anovulation with PCOS

- Clomifene citrate
  - Inhibits oestrogen receptors in hypothalamus
  - So inhibits –ve feedback on GnRH/FSH/LH release, and so incr FSH
  - Monitor with US to prevent multiple pregnancies
## Treatment of ovulatory disorders

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Case 2

- Mrs X, age 35
- 14 months of unprotected, regular sex with husband
- Has been sexually active since a young age with multiple partners
- Previously had chlamydia (10 years ago), not sure how long she had it before it was treated. Recalls having very painful periods around the same time

Observation/Gynaecological History

- Previous cycles of 28 days with periods lasting for 7 days
- LMP: 16/02/2014
- Experiences heavy bleeding during periods
- Often experiences lower abdominal pain
- Used to be on the OCP
- Last smear was 2006 (normal)
- Has 1 child (15), 2 ectopic pregnancies (2007, 2011)
Case 2

- Infertility as a long term consequence of PID likely due to chlamydia.

- Injury and scarring to the fallopian tube resulting in tubal infertility.

- Management: ? Surgery or IVF
Assisted Reproductive Technologies

IVF
IUI
ICSI
Donors
Artificial fertilization

- Inability to transmit sperm or eggs along fallopian tubes (damage/absence of tubes, or abnormal sperm)
- First IVF baby 1978
- Conception rates 20-30% per cycle
IVF Step 1

Step 1: Controlled ovarian hyperstimulation (to maximise collection of oocytes)

1) GnRH agonist in late luteal phase – to prevent premature (natural) ovulation

2) hMG given IM daily – promotes follicular growth and development
   - hMG = human menopausal gonadotropins = purified LH & FSH from urine of postmenopausal women

3) hCG (substitute for LH surge)
   - Promotes maturation of oocytes before ovulation
   - Given once ovaries stimulation to the point where:
     - Lead follicle > 16mm diameter
     - 3-4 other follicles > 13mm
     - Serum oestradiol >=200pg/mL per large follicle
Step 2: Retrieval of oocytes

- US-guided
- Trans-vaginal
- 24-36 hrs after hCG
Step 3: Fertilization

- Semen collected same day as oocytes retrieved
  - Washed, incubated
- Each mature oocyte in petri dish with 50-150,000 motile sperm
IVF Step 4

Step 4: culture and transfer

- Fertilized oocytes put on growth medium
- Embryos graded (# cells, even growth?, fragmentation?)
- Embryos transferred to uterus in flexible catheter via cervix – 2 maximum
Step 5: Progesterone (luteal support)

- From day of transfer until placenta producing progesterone (8-10 weeks)
- Beta hCG 11-12 days after transfer – to confirm implantation
NB, Also: 1

- Pre-implantation genetic diagnosis
  - (CF, sickle cell)
- In-vivo fertilization:
  - Oocytes and sperm place in fallopian tube. Not in UK.
- ICSI: intracytoplasmic sperm injection
  - Sperm numbers low or unable to fertilize
- Cryo-embryo transfer
  - Avoids repeat ovarian stimulation
- IUI: In-utero insemination
  - Washed semen injected into uterus (after ovarian stimulation)
NB, Also: 2

- Donors
- Sperm donation
  - Each donor used with max 6 couples
  - Match height, hair colour and race
  - IUI
  - Children have the right to know identity of biological parent from age 18
- Egg donation
- Surrogate mothers
  - In UK, baby is legally the child of the woman who bears him or her
- Adoption
References

- Problem orientated obstetrics and gynaecology. I Symonds, P baker, L Kean
- Oxford handbook of clinical specialties. J collier, M Longmore, K Amarakone