

Investigation of infertility and making a diagnosis

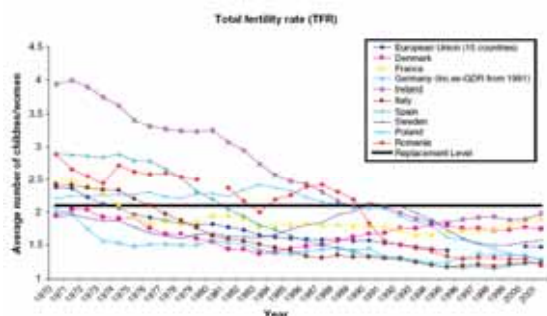
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Conflict of interest

None

Infertility – the issues

- 1 in 7 couples have difficulty conceiving
- This may be due to detectable causes or unexplained
- Patients suffer considerable psycho-social morbidity as a consequence of not having children
- There are consequences for society as a whole from fewer children being born



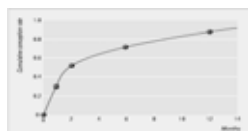
Courtesy RAND Europe

Definition of infertility

Inability to conceive after at least 1 year of regular unprotected intercourse

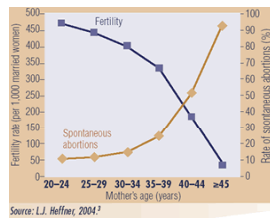
Spontaneous conception

- In the general population 84% women would conceive within 1 year of regular unprotected sexual intercourse. Of those not conceiving in the first year, half would conceive in the second year - a cumulative conception rate of 92% in 2 years



- Increasing female age is associated with reduced chance of conception: 94% of women of 35 years but only 77% of 38 year olds conceive over 3 years of trying

Effect of female age



Fertility declines and spontaneous miscarriage rates increase as the woman's age increases, with the effect becoming more marked after the age of 35

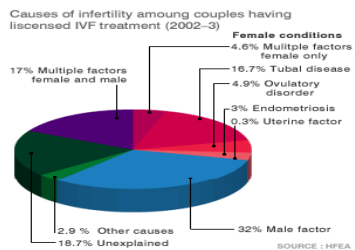
When to investigate

- Balance between couple's concerns and the risk of over-investigating couples who have a reasonable chance of spontaneous conception
- Reasonable to investigate all couples who have not conceived after 2 years of trying
- Where the woman is ≥ 35 , investigate after 1 year of trying
- Where there is a potential infertility factor in the history, investigate sooner
- Reasonable to start investigations whenever patients present?

Why make a diagnosis?

- To help couple understand
- To identify underlying or associated pathology
- To get a prognosis
- To plan treatment
- To advance knowledge

Good Medicine!



From the UK Human Fertilisation and Embryology Authority (HFEA)

Causes of Infertility

- Male
- Female
- Couple
- Unexplained

Male History and Examination

- Previous pregnancies
- Pyrexial illness within 6 months
- Orchitis, epididymitis, mumps or STD
- Torsion, maldescent or varicocoele
- Previous or current illnesses
- Habitus
- CVS and respiratory
- Testicular site and volume
- Varicocoele
- Epididymal thickening
- Scrotal swelling

Female History and Examination

- Menstrual cycle
 - Length, regularity, IMB, PCB
- Previous Gynae history
 - PID, Endometriosis
 - Pregnancy, post partum/abortal sepsis
- Previous surgery
 - Appendix, ovarian
- Ongoing systemic illness
- BMI
- Abdominal
- Pelvic
- Endocrine disorders
 - galactorrhoea
 - hirsutism
 - thyroid disease

Couple History

- Smoking and alcohol intake
- Coital frequency
- Dyspareunia
- Erectile or ejaculatory problems
- Understanding of fertile period
- Awareness of folic acid

Principles of Investigation

- Assessment of gamete production
 - sperm production
 - ovulation
- Assessment of possibility of fertilisation
 - Frequency of coitus
 - Knowledge of fertile period
 - Coital difficulties
 - Possibility of tubal disease

Lower reference values of semen parameters – WHO Manual 5th Ed

Parameter	Lower reference limit
Semen volume (mL)	1.5 (1.4–1.7)
Total sperm number (10 ⁶ per mL)	39 (33–46)
Sperm concentration (10 ⁶ per mL)	15 (12–18)
Sperm motility, progressive, %	42 (39–45)
Progressive motility (PM, %)	32 (29–36)
Abnormally shaped spermatozoa, %	54 (50–60)
Sperm morphology, normal, %	4 (3.5–5)
Semen characteristics, threshold values	
pH	≥7.2
Normalised positive acrosin test (10 ⁶ per mL)	≤1.0
Midl test double spermatozoa with normal peritene, %	≥50
Microfluidised test: spermatozoa with normal heads, %	≥60
Spermatozoa per spermatozoa	≥2.0
Spermatozoa per spermatozoa	≥1.0
Spermatozoa per spermatozoa per spermatozoa	≥1.0

These are 5th centile lower reference values from studies of men whose partners conceived within 12 months of stopping contraception
By definition, 5% 'fertile' men will have results below these values

Male subfertility - aetiology

Category	Frequency
• Seminiferous tubule dysfunction	60–80%
• Post-testicular abnormalities / defects	10–20%
• Primary hypogonadism	10–15%
• Secondary hypogonadism (Hypothalamic-pituitary disorders)	1–2%

Male subfertility - aetiology

Category	Examples
Primary gonadal disorders	<i>Congenital</i>
	<i>Acquired</i>
	<ul style="list-style-type: none"> • Y-chromosome abn. • Klinefelter syndrome • Cryptorchidism • Anorchia • Androgen insensitivity • 5α-reductase deficiency • Varicocele • Haemochromatosis • Viral orchitis • Epididymo-orchitis • Drugs / toxins • Radiation • Hyperthermia • Trauma / torsion • Immunological • Systemic illness

Male subfertility - aetiology

Category	Examples	
Hypothalamic-pituitary disorders	<i>Congenital</i>	<i>Acquired</i>
	<ul style="list-style-type: none">• Kallmann syndrome• IHH• Multi-system disorders:<ul style="list-style-type: none">- Prader-Willi syndrome- Laurence-Moon-Biedl syndrome• Haemochromatosis	<ul style="list-style-type: none">• Pituitary tumours• Hypothalamic tumours• Hormone-related:<ul style="list-style-type: none">- Hyperprolactinaemia- Androgen XS- Estrogen XS- Cortisol XS• Infiltrative disorders• Vascular• Drugs• Chronic illness• Nutritional deficiency• Obesity

Male subfertility - history

- Reproductive history:
 - duration of infertility
 - frequency / timing of coitus
 - previous partner(s) / pregnancies / fertility issues
 - genito-urinary infections (e.g. chlamydia, gonorrhoea)
- Sexual function
 - libido
 - erectile function
 - ejaculatory function
 - pubertal development
- Scrotal surgery / disorders
 - cryptorchidism
 - torsion
 - trauma
 - inguinal / scrotal / retroperitoneal surgery

Male subfertility - history

- Past medical history:
 - diabetes mellitus
 - neurological disease
 - cancer survivors
 - hypothalamic-pituitary disorders
 - viral orchitis
- Drugs
 - prescribed
 - illicit

Drugs impairing male fertility

Mechanism	Examples
Gonadotoxins (impair spermatogenesis)	<ul style="list-style-type: none"> • Sulfasalazine • Colchicine • Methotrexate • Nitrofurantoin • Cytotoxic chemotherapy
Erectile dysfunction	<ul style="list-style-type: none"> • Beta-blockers • Thiazide diuretics
Ejaculatory failure	<ul style="list-style-type: none"> • Alpha-blockers • Anti-depressants
Antiandrogenic	<ul style="list-style-type: none"> • Spironolactone • Cimetidine
Hypothalamic-pituitary suppression	<ul style="list-style-type: none"> • Testosterone • Anabolic steroids • Drugs → ↑ prolactin • GnRH analogues
Drugs of misuse	<ul style="list-style-type: none"> • Cannabis • Cocaine • Heroin

Male subfertility - history

- Alcohol / smoking
- Environmental factors
 - heavy metals
 - organic solvents
 - pesticides / herbicides
 - (phytoestrogens)
 - radiation
 - heat
- Family / social history
- Systems review
 - hyposmia / anosmia
 - headaches / visual disturbance
 - recurrent respiratory infections

Male subfertility - examination

- Hypoandrogenism / hypogonadism

Eunuchoidal proportions	Ante-dates puberty
↑fat mass	Current deficiency
↓ muscle mass	
↓ Body hair, Fine wrinkles	Long-standing deficiency
- Endocrine / genetic disorders
- Systemic disorders
- Genital abnormalities
 - penis
 - testes
 - size / volume
 - consistency
 - symmetry
 - masses
 - epididymides
 - vasa deferentia
 - varicocele
 - prostate



Male subfertility – genetic screening

- Genetic screening
 - karyotype analysis
 - screening for Y-chromosome abnormalities
 - screening for specific disorders:
 - cystic fibrosis
 - hypogonadotrophic hypogonadism
 - haemochromatosis

Male subfertility – endocrine assessment

- Serum testosterone
 - 09.00h (repeated on at least 1 occasion)
 - consider SHBG measurement (e.g. if borderline low level in obese subject)
- Serum LH/FSH
- Pituitary assessment
 - prolactin / FT4, TSH / 09.00h cortisol / IGF-1
 - dynamic endocrine testing
 - MRI pituitary
 - visual field assessment
- Inhibin B

Male subfertility – screening for other complications

- Complications
 - D(E)XA for hypogonadism
 - TFTs and fasting glucose / HbA1c in Klinefelter syndrome

Case 1 - Clinical vignette

28-yr-old male – nightclub doorman

PC Primary infertility

HPC Trying for family for 18 months
GP: semen analysis

Normal libido/erectile function
Normal pubertal development

PMH Nil of note

DH Multivitamins/protein supplements

F/SH Occasional cannabis use

SE Nil of note

Semen analysis	
Volume (>2mL)	2.1
number/mL (>20 million)	~1000
morphology (>15% normal)	na
motility (>50%)	na

Case 1 - Examination / Investigations

O/E

- Weight 112 kg
- Height 192 cm
- BMI 30.3 kg/m²
- Muscular build
- Mild bilateral gynaecomastia
- Normal secondary sexual characteristics
- Adult external genitalia
- Testes 15 mL - soft

Ix

Testo (8.0–29.0)	20.6
LH (1.5–6.3)	<0.1
FSH (1.0–10.1)	<0.3
Hb (13.0–17.0)	17.3
Hct (0.39–0.50)	0.54
IGF-1 (7.5–30.0)	38

Δ:

Case 2 - Clinical vignette

35-yr-old male – postman

PC Primary infertility

HPC Trying for family for 24 months
GP: semen analysis

Normal libido/erectile function
Normal pubertal development

PMH Nil of note

DH Nil

F/SH Nil of note

SE Nil of note

Semen analysis	
Volume (>2mL)	2.5
number/mL (>20 million)	nil
morphology (>15% normal)	na
motility (>50%)	na

Case 2 - Examination / Investigations

O/E

- Weight 92 kg
- Height 180 cm
- BMI 28.4 kg/m²

Ix

Testo (8.0–29.0)	8.9
LH (1.5–6.3)	11.3
FSH (1.0–10.1)	19.0
Karyotype	47XXY

- Bilateral gynaecomastia
- Normal secondary sexual characteristics
- Adult external genitalia
- Testes 6-8 mL - soft

Δ: Klinefelter syndrome

Case 3 - Clinical vignette

28-yr-old male – Iraqi student

PC Primary infertility

HPC Trying for family for 18 months
GP: semen analysis

Reduced libido/erectile function
Delayed puberty

PMH Nil of note

DH Nil

F/SH Nil of note

SE Nil of note

Semen analysis	
Volume (>2mL)	1.4
number/mL (>20 million)	nil
morphology (>15% normal)	na
motility (>50%)	na

Case 3 - Examination / Investigations

O/E

- Weight 65 kg
- Height 165 cm
- BMI 23.9 kg/m²

Ix

Testo (8.0–29.0)	0.8
LH (1.5–6.3)	0.2
FSH (1.0–10.1)	0.5
Anterior Pituitary f ⁿ	Otherwise normal
Pituitary MRI scan	normal

- Reduced facial and body hair

- Tanner stage 4
 - penile development
 - pubic hair
- Testes 4-5 mL – soft

- Normal visual fields
- No other endocrinopathy

Δ: Congenital hypogonadotropic hypogonadism
Previous exogenous testosterone therapy

Confirming Ovulation

- History of regular cycles
- Mid-luteal phase progesterone: 7 days from next period
- Detection of LH surge
- Temperature charts: not recommended

Clinical assessment of Anovulation

- History of oligo- or amenorrhoea
 - An absent or irregular cycle implies anovulation
- Any bleeding suggests adequate oestrogen levels
- Galactorrhoea suggests hyperprolactinaemia
- Hirsutism points towards elevated androgens

Tests in Anovulation

- Pelvic Ultrasound Scan
- FSH/LH
- Prolactin
- TSH
- Testosterone if hirsute or virilised
- ?AMH

Commonest cause of Anovulation is Polycystic Ovarian Syndrome

Definition of PCOS

- Any 2 of 3
 - **Oligo- or anovulation**
 - **Clinical/Biochemical hyperandrogenism**
 - **Polycystic ovarian morphology**
 - "12 or more follicles in each ovary measuring 2 – 9 mm and/or increased ovarian volume (>10ml)"
 - Not applicable to women on OCP
 - Follicle distribution not relevant
 - Stromal appearance not relevant
 - Unilateral appearance is sufficient
- **Plus** exclusion of other etiologies (HAIRAN, CAH, Cushings, tumours)



Assessment of Tubal Status

- Always do chlamydia screen first
- Hysterosalpingogram (HSG)
 - Screening test
 - For low risk women
- HyCoSy: using Ultrasound
- Laparoscopy and dye
 - More informative
 - More risky



HSG showing bilateral hydrosalpinges

