Management of Female infertility

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Assess and manage as a couple because:

- 30% infertility male factor related
- emotional support

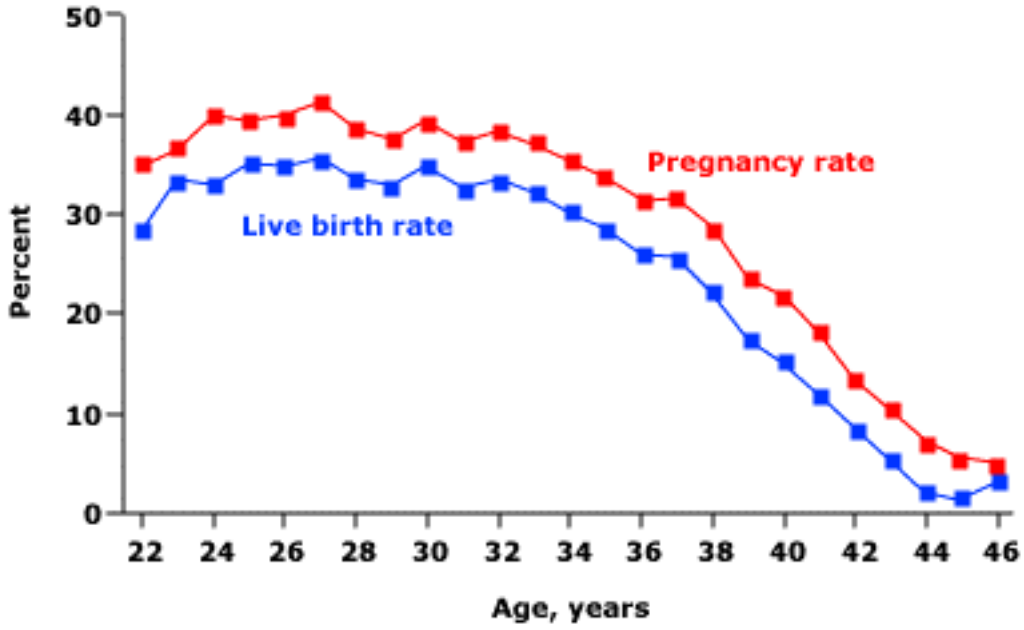
Role of the physician

1) diagnose and treat the medical problems
2) counselling :provide patients with correct information and dispel myths
3) emotional / psychological support
   extremely stressful event for couples
4) determine the optimal time to stop treatment and consider adoption etc.

(NB) important to stress there are no guarantees with infertility treatment and failure is always possible

Prognosis dependent on

1) ***age of patients*** especially female >35
2) duration infertility
3) time left for conception
4) cause of infertility
5) previous infertility treatments



Usually assess / investigate after 12 months of unprotected intercourse, however may investigate earlier if:

- obvious problem eg. Amenorrhoea / oligomenorhoea
- IMB
- Pelvic pain / dyspareunia
- History of PID /ruptured appendix/ peritonitis
- age ≥ 35 years

months	% conceiving	fecundability
0		0.2
3	50%	0.17
6	70%	0.1
12	85%	0.05
24	92%	0.03
36	95%	0.01

Lifestyle factors affecting fertility

note most studies are observational, epidemiological and retrospective, and therefore subject to bias

1) smoking
   women smoking > 10/cigarettes per day → reduced fertility.
   Related to: oocyte aging
   Tubal / cervical factors
   Inconclusive data on smoking and male fertility
   Suggested reduced fertility in female offspring exposed to in-utero tabacco
2) weight
   BMI > 30 }
   < 20 } → reduced fertility
3) alcohol
   ≥ 4 drinks per week leads to reduced fertility secondary to anovulation / endometriosis
4) caffeine
   250mg / day (2 cups coffee) leads to:
   - reduced fertility RR 1.2-2.5
   - increased M/C RR 2.2

History

age of both partners

menstrual history (including LMP)

- menarche
- regularity / premenstrual molimina
- dysmenorrhoea / pelvic pain / dyspareunia

obstetric history

- previous conception
- same relationship / previous relationship

gynaecological history

- contraception history
- hirsutism / acne / excessive oily skin
- galactorrhoea
- cervical surgery / TOP / cone biopsy / diathermy to cervix etc.

sexual history *(enquire at the end, once rapport is established)*

- coital frequency & timing during the menstrual cycle
- lubrication
- erection / penetration / ejaculation etc
- sexual douching as may have spermicidal action

medical / surgical history

- PID / appendicitis / pelvic surgery
- others e.g. D/M, thyroid

drug history

- smoking ↓ fecundability proportionate to amount of smoking
- ETOH
- Caffeine intake
- Marijuana → ↓ GnRH secretion
- Cocaine → ↓ spermatogenesis

psychological & social history

- exercise
- excessive weight change (> 10% within 12 months)
- stress
- occupation of both partners
- response to infertility
- quality of the relationship etc

history in male partner:

- erection / ejaculation difficulties
- trauma to testes
- infection to testes e.g. mumps, UTI
- history of undescended testes

Examination

- height : weight
  - obesity → weight loss essential (aim BMI 20-30)
  - anorexia
- BP
- Visual field assessment
- thyroid assessment
- galactorrhoea + breast assessment (lumps)
- hirsutism & hair distribution
- abdominal examination for masses / tenderness
- vaginal examination for:
  - uterine size
  - adnexa masses
  - uterus direction (A/V or R/V)
  - utero-sacral nodularity / tenderness
- speculum
  - papsmear
  - endocervical / HVS swabs (if required)

Investigations

Aims

1) assess ovulation
2) sperm production
3) female anatomy
4) ensure adverse treatable factors during pregnancy are recognized

Initial tests

- FBC / ESR / EUC / LFT / blood group and AB screen / rubella / VDRL / HbsAg / hep C / HIV
- D3 LH / FSH / oestradiol
  FSH < 10 iu/ml
  E2 < 275 pmol/L and ideally < 150 pmol/L
- D21 progesterone
- TFT / PRL / antithyroid hormones
- androgens especially if hirsutism / irregular cycles:
  FAI / testosterone / SHBG
  DHEAS / androstenedione
  17 (OH) progesterone
- chlamydia Antibody titre (sensitivity 70%)
- semen analysis / IBT
- pelvic and TV ultrasound D8-14
  - endometrial lining
  - ovarian volume / antral follicle count
  - follicle size
  - uterine abnormalities
- Hy-Co-Sy
  - Sensitivity 90%
  - Less discomfort compared HSG
  - Expensive and requires expertise

- HSG performed early follicular phase
  if performed luteal phase - radiation exposure
  - endometrium may occlude ostia

  Sensitivity 70% with F(+) up to 50%
  Painful
  Oil versus water based
  Useful in the younger couple, before endoscopy to assess uterus and tubes.
  For the older couple or if there is any significant pain, endoscopy would be 1st line.

Secondary tests

- **endoscopy**
  - laparoscopy dye }
  - hysteroscopy } ideally done follicular phase

  after a normal HSG, defer endoscopy >3 months to allow for the therapeutic effects
- **endometrial biopsy**
  D21-26 or 7-12 days after LH surge
- **PCT**
  intercourse 2-8 hours prior to assessment around time LH surge
  (1) normal ≥ 5 motile sperm / HPF
  (2) good quality mucus

  useful for:
  - assess sexual intercourse adequacy
  - cervical mucus } interaction
  - sperm function }

  If abnormal → often ill-timed ∴ repeat PCT.
  The significance of PCT results debatable as:
  normal PCT - good sign
  abnormal PCT - does NOT preclude pregnancy

Further investigations (usually when there is abnormal previous investigation)

1) Sperm / cervical mucus interaction testing (if abnormal PCT)
   treatment of abnormal cervical mucus:
   - estrogens (0.625 – 5mg Premarin) / mucolytics
   - A/B if chlamydia infection
   - IUI
   - superovulation + IUI
   - IVF

2) C/T / MRI brain if hyperprolacinaemia

Management

depends on:

- ***Female age***
- Duration of infertility
- Time left for conception
- cause of infertility
- previous infertility treatments

10% - 15% unexplained i.e no abnormality detected after standard infertility investigations possibly caused by subtle problems in:

- Oocyte
- sperm dysfunction
- fertilization problems
- implantation

Treatment options

- observation : after 12 months infertility MFR = 5% after 24 months MFR = 1-3%
- specific treatment for the cause
- ART

General advice

- folic acid
- eliminate / reduce smoking , alcohol. Caffeine and illicit drug use
- optimize weight

Anovulation

- clomiphene in increasing doses (maximum 6 ovulatory cycles). See appendix for instructions.
  if anovulation detected in 1st line investigation may treat for 3 cycles empirically before further investigations
- gonadotrophins
  requires full infertility workup prior to initiation
- Pulsatile GnRH pumps
- hyperprolactinaemia Rx bromocryptine / cabergoline
- increased androgens PCOS Rx
  - clomiphene / ovulation induction agents
  - metformin
  - dexamethasone if ↑ DHEAS
  - ovarian drilling

Endometriosis

- surgical ablation / excision of endometriotic implants / reconstructive tubal surgery followed by clomid / superovulation ± IUI
- ART

ART vs surgery depends on :

- Severity
- Symptoms
- patients age
- other infertility factors

Tubal disease

(a) proximal tubal disease
- falloposcopic dilatation
- microsurgical excision & reanastomosis

ART vs surgery depends on:
(1) extent of tubal disease
(2) age patient e.g. younger patient may opt for surgery
(need to exclude distal co-existent disease)
(3) other infertility factors

(b) distal tubal disease (1) salpingolysis
(2) neosalpingostomy
(3) IVF

(with severe adhesions, IVF better options as conception rate < 20%)

Cervical factor (see previously)

Treatment of choice inadequate mucus = IUI ± ovarian hyperstimulation

other Rx - estrogen } unproven RCT
- mucolytics }

Uterine factors

hysteroscopic treatment of submucous fibroids / intra-uterine adhesions / polyps is the preferred technique and has replaced most abdominal procedures

Male factors (see notes on male infertility)

Unexplained infertility (fecundability 1-5% per month)

Management:	fecundability
• IUI (after 4 cycle cumulative PR plateaus)	4%
• Clomiphene ± IUI results in double the fecundability rates Useful to try for up to 6 cycles	6-8%
• Controlled Ovarian Hyperstimulation (COH) + IUI	10-15%
• ART IVF / ET	20-40%

  - ➢ PR plateaus after 6 cycles
  - ➢ After failed IVF therapy, up to 15% may conceive naturally up to 5 years (depending on duration of infertility)

Intrauterine insemination

AIH
- cervical factor
- sperm unable to be deposited into vagina

AID always frozen 6/12 to prevent HIV

IUI alone has been shown to marginally improve pregnancy rates in unexplained infertility especially if there are subtle male defects

indications for IUI
1) male mechanical problems eg. retrograde ejaculation
2) female mechanical problems eg. vaginismus
3) cervical hostility
4) mild semen abnormalities

APPENDIX 1

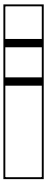
Instructions on the use of Clomiphene

(Clomid or Serophene)

Clomiphene is known as the fertility pill. It is used to promote ovulation (releasing an egg)

- You should take clomiphene from day **2 to day 6 or 5 to 9** your next menstrual cycle.
- You will also be given a temperature chart to document your temperature every day. Take your temperature first thing in the morning and mark this down on the chart.
- You will also need to obtain a ovulation testing kit (eg **clearplan**) to test for ovulation. You should start performing the ovulation test 2 to 5 days after completing the course of Clomid (I will instruct you) and perform this every day until the ovulation test becomes positive. Once the ovulation test becomes positive you may have to come in and have a blood test to confirm the result. I may also ask you to have an ultrasound to assess your ovaries. Once the ovulation test becomes positive this indicates that YOU WILL ovulate in the next 24 hours and therefore you should have sexual intercourse every/other day for the next four days.

negative



positive

- You will also need to have a **blood test approximately one week after the positive ovulation test** to check that you have ovulated.
- If your next period does not come 3 weeks after the urine test, then you should have a pregnancy test to determine if the cycle has been successful or not.

Generally I will see you every month after a period to check your progress. Clomiphene is given for up to 6 ovulatory cycles. If, after a maximum of 6 cycles you have not fallen pregnant, then we shall move on to other treatment options. Often this involves advanced reproductive technique e.g. IVF and you will need to have injections and more complex tests and ultrasound monitoring. I will discuss this with you if this is required.