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Infertility

Evening News

Meet Louise, the world's first test-tube arrival

SUPERBABE

Wide-eyed Louise Brown pictured in hospital 18 hours after she was born. Today she's doing well. See Page Three

- Infertility is a problem through out history, however increasing rates noticed, esp. male factor..... Environmental!!!!!!!
- The first successful birth of a "test tube baby“, Louise Brown occurred in 1978 in Oldham General Hospital, U.K.
- Robert G. Edwards; the physiologist who developed the treatment, was awarded the Nobel Prize in Medicine in 2010.

Definition

- Inability of the couple to conceive after 1-2 years of regular unprotected sexual intercourse.
- “A woman of reproductive age who has not conceived after 1-2 years of unprotected vaginal sexual intercourse. *NICE guideline,*
- Primary infertility; couple have failed to conceive before.
- Secondary infertility; woman has previously been pregnant regardless of the outcome of the pregnancy and now unable to conceive.

Chances of conception

- People who are concerned about their fertility should be informed that 85% of couples in the general population will conceive within 1 year if:
  - the woman is aged under 35 years
  - they do not use contraception and have regular sexual intercourse.

- Half of those who do not conceive in the first year will do so in the second year
  (cumulative pregnancy rate over 92%)

Factors affecting Fertility

- **Frequency/Timing of sexual intercourse:**
  - Every 2 to 3 days optimises the chance of pregnancy

Frequency of intercourse	Probability of conception (within 6 months)
1 time per week	17 %
3 times per week	50 %

- **Obesity:**
  - Women who have BMI of over 30 should be informed that they are likely to take longer to conceive and will affect treatment success rates.

Factors affecting Fertility

- **Low body weight**
  - Women with BMI less than 19 and irregular menstruation should be counselled to gain weight.

- **Smoking**
  - Strong association between smoking and fertility in both partners.
  - Affects success rates of ARTs.

Factors affecting Fertility

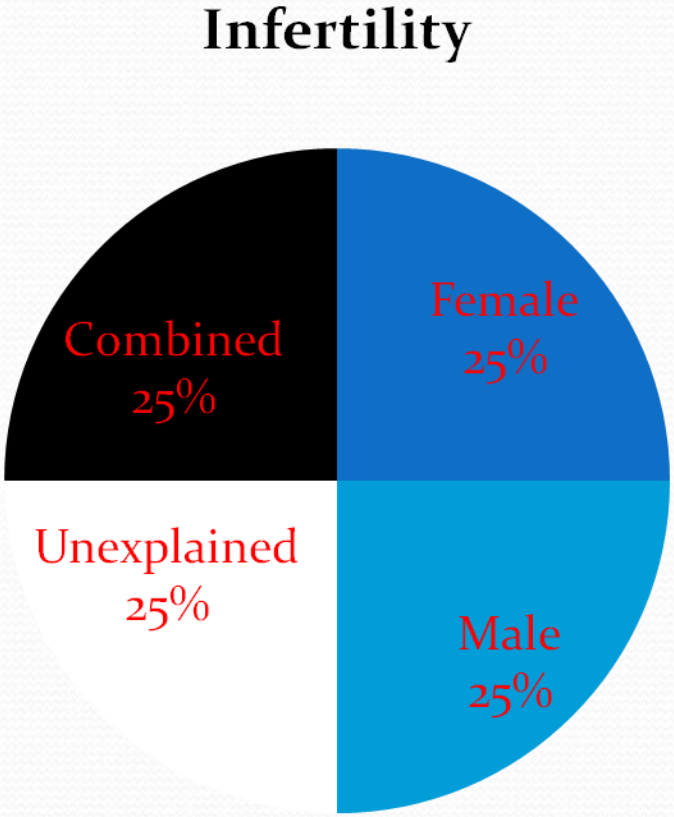
- **Caffeinated beverages**:
  - No evidence on effect of caffeine on fertility.

- **Alcohol**
  - Female patients should be informed that 1 or 2 units of alcohol once or twice per week reduces risk of harming a developing fetus.
  - Intoxication may affect semen quality.

Factors affecting Fertility

- **Prescribed, over-the-counter and recreational drug use**
- **Occupation**
- **Tight underwear**
  - There is an association between elevated scrotal temperature and reduced semen quality

Causes: It is estimated that infertility affects 1 in 7 couples, women's age ≤35 yrs .



Basic Work-up for Infertility

- **Carried out by the GPs and should be offered to:**
  1. A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility.
  2. A woman of reproductive age who is using artificial insemination to conceive after 6 failed trials.

- **Consider earlier referral to infertility specialists where:**
  - the woman is aged 36 years or over.
  - there is a known clinical cause of infertility or a history of predisposing factors for infertility.
  - treatment is planned that may result in infertility (such as treatment for cancer).
  - People who are concerned about their fertility and who are known to have chronic viral infections such as hepatitis B, hepatitis C or HIV.

Basic Work-up for Infertility

- Detailed history and physical examination.
- Semen analysis.
- Evidence of ovulation.
  (Day 2-3 gonadotrophins, Day 21 progesterone)
- Susceptibility to rubella
- Cervical smear screening
- Screening for Chlamydia trachomatis
- Serum prolactin
- Thyroid function tests

Basic Work-up for Infertility

- **Semen analysis: (WHO 2010)**

  - semen volume: 1.5ml or more
  - pH: 7.2 or more
  - sperm concentration: 15 million spermatozoa per ml or more
  - total sperm number: 39 million spermatozoa per ejaculate or more
  - total motility: 40% or more motile
  or 32% or more with progressive motility
  - vitality: 58% or more live spermatozoa
  - sperm morphology (percentage of normal forms): 4% or more

Basic Work-up for Infertility

- **Evidence of ovulation:**

  1. Menstrual history of regular cycles.
  2. serum progesterone in the mid-luteal phase of their cycle (day 21 of a 28-day cycle) even if they have regular menstrual cycles.
  3. Serum gonadotrophins (follicle-stimulating hormone and luteinising hormone) on Day2-3 especially in irregular periods.

Further investigations

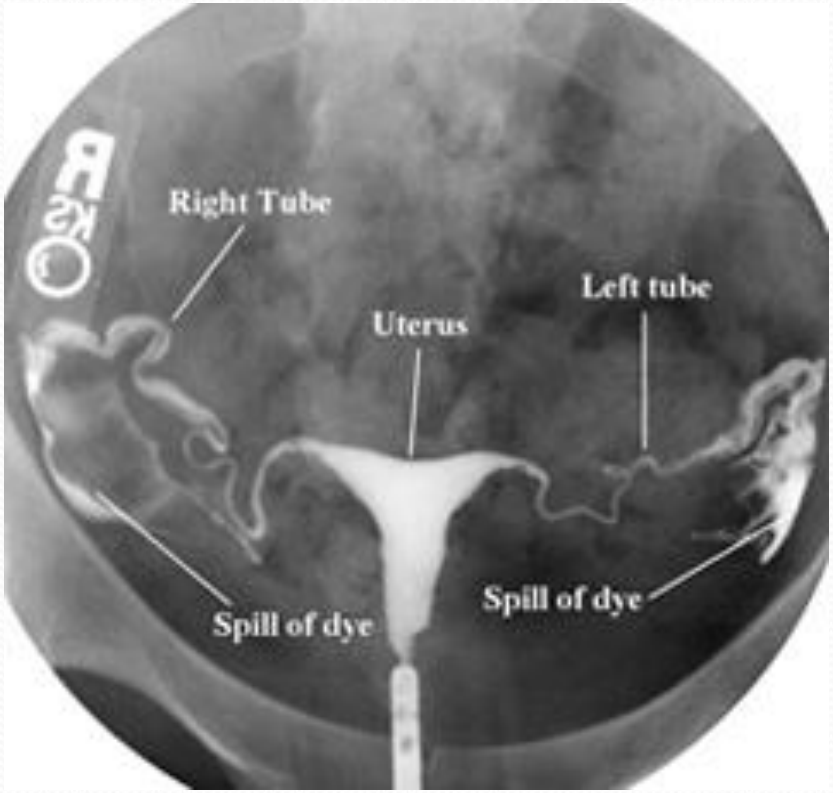
- **Ovarian reserve**
  -More important in >35 years old, suspected ovarian failure and to detect response to ovulation induction.

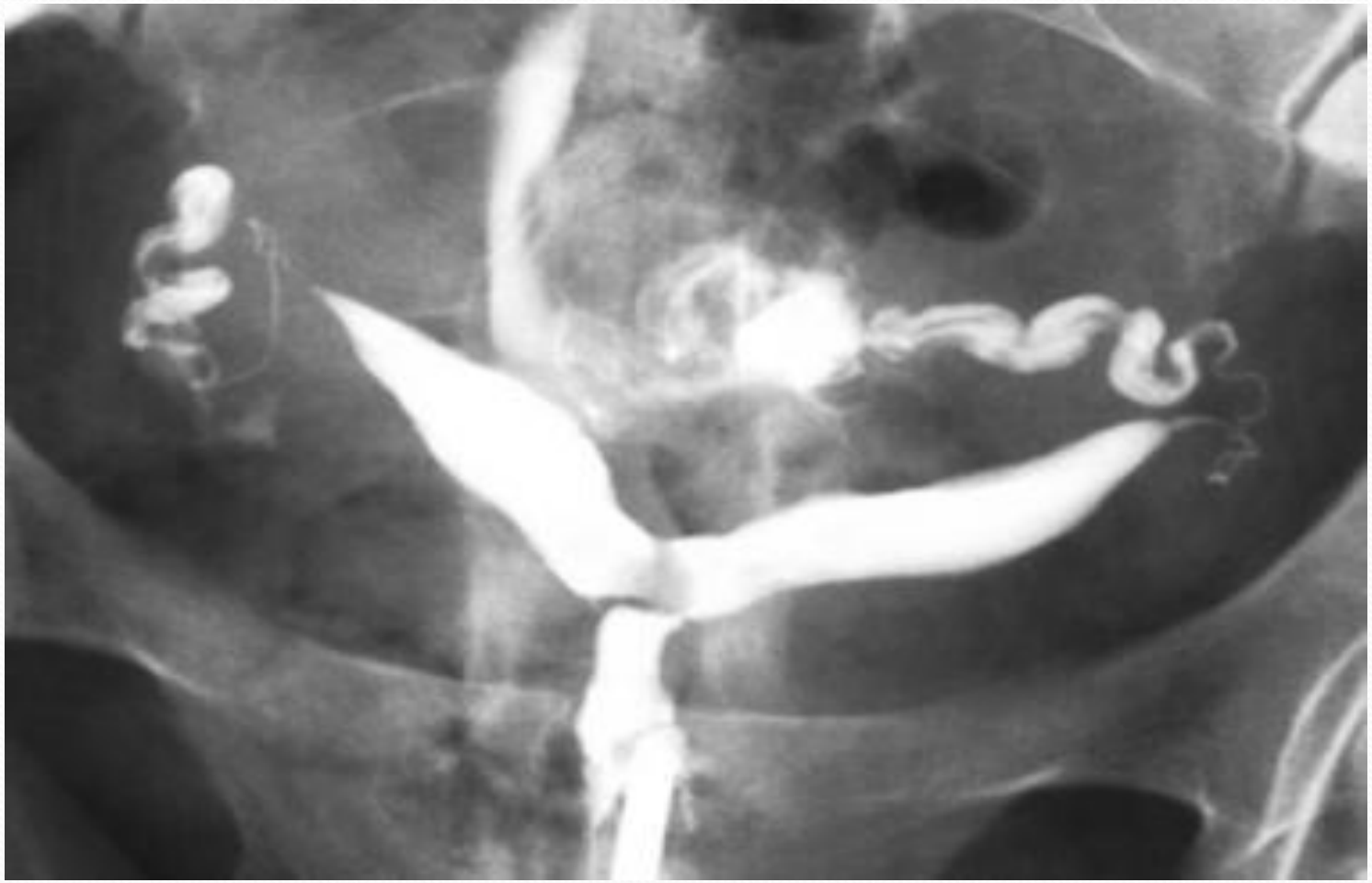
  1. Total antral follicle count. (AFC)
  2. Anti-Müllerian hormone (AMH) of less than or equal to 5.4 pmol/l for a low response and greater than or equal to 25.0 pmol/l for a high response
  3. Follicle-stimulating hormone greater than 8.9 IU/l for a low response and less than 4 IU/l for a high response.

- **No evidence for:**
  - ovarian volume
  - ovarian blood flow
  - inhibin B
  -oestradiol (E2)

Further investigations

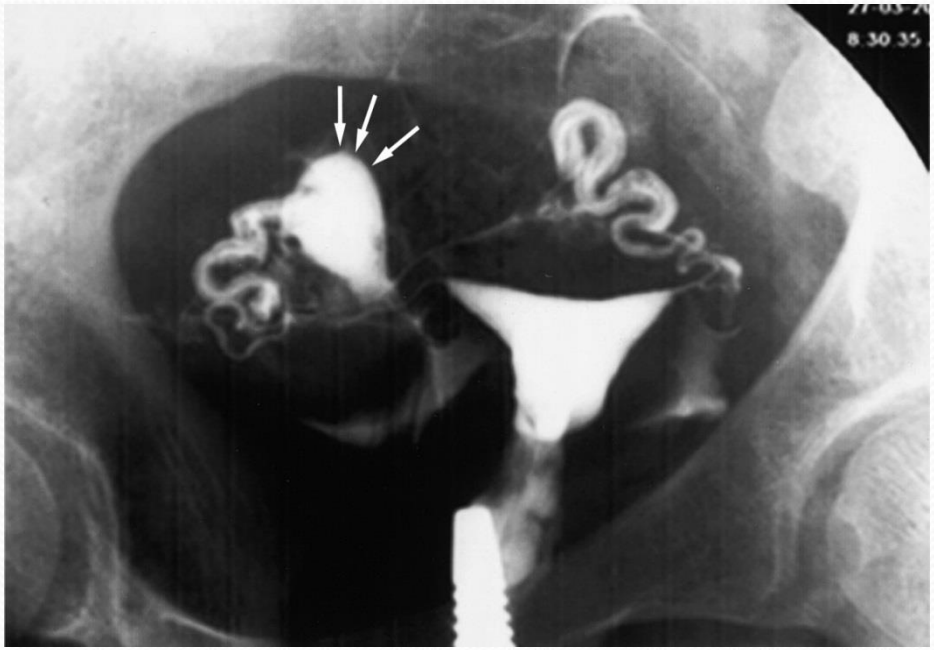
- **Investigation of suspected tubal and uterine abnormalities:**
  1. Hystersalpingography (HSG):
  - usually after failed successive cycles of ovulation induction, and in some centres after failed IUI.
  - good predictive but requires expertise.

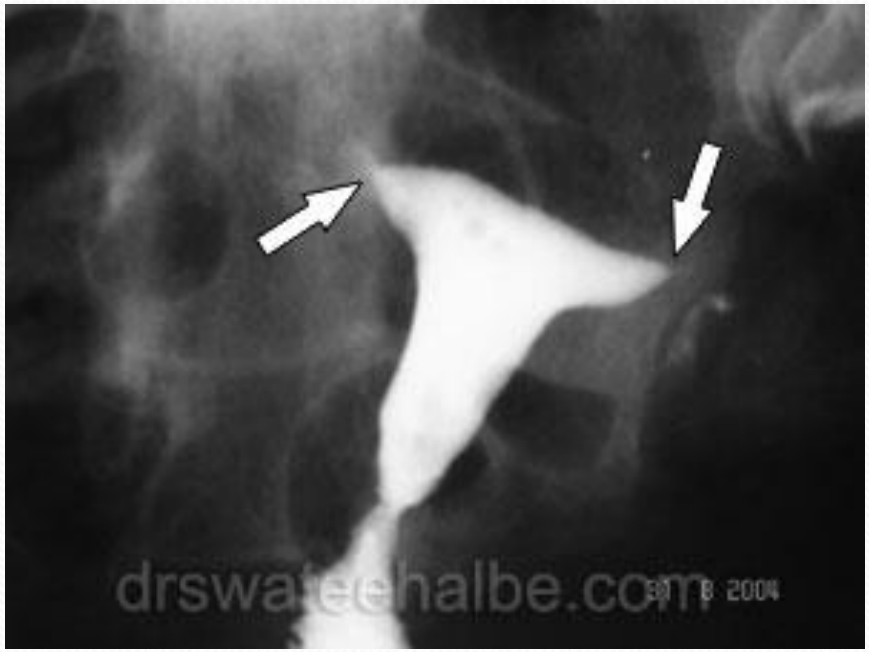




Further investigations

1. Hysterosalpingography (HSG):

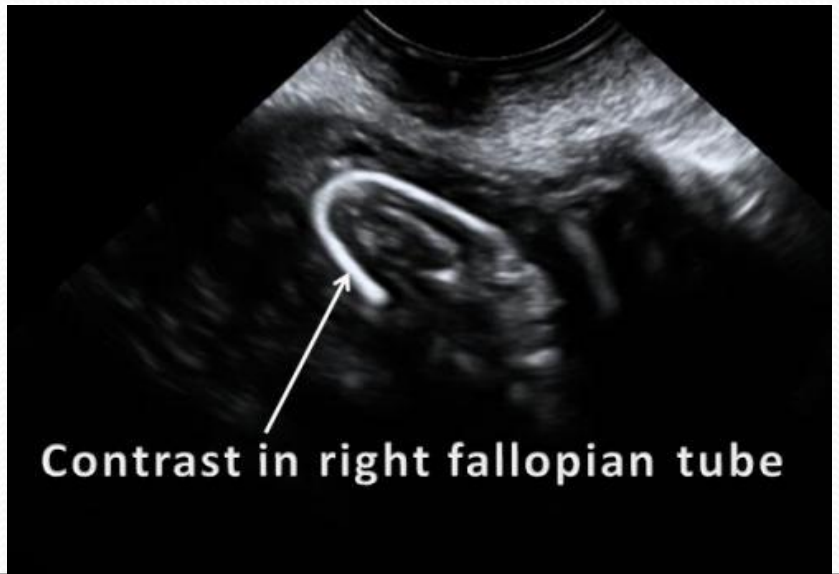


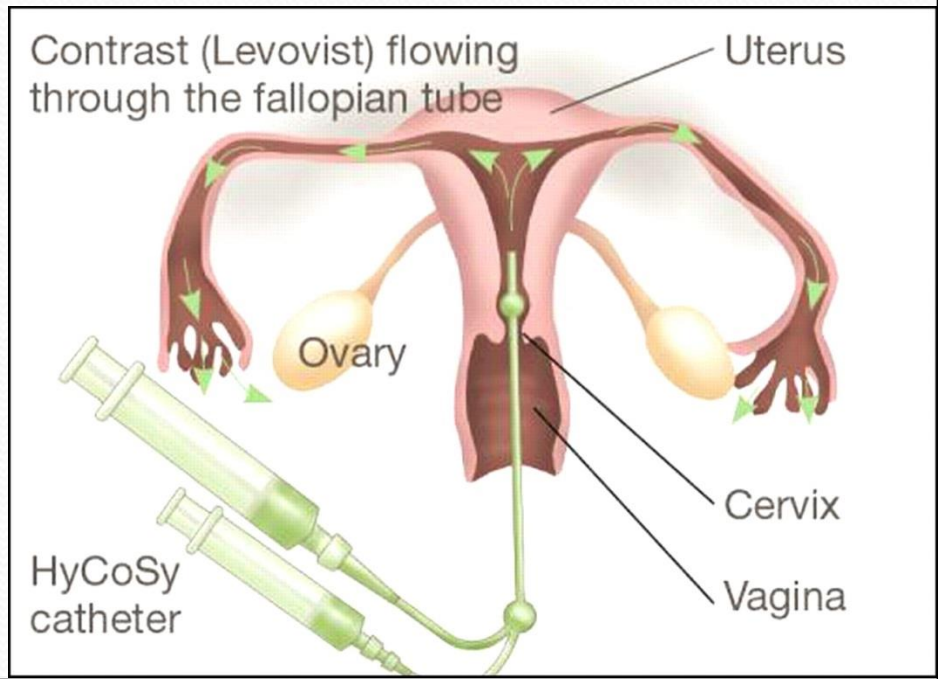


Further investigations

2. **Hysterosalpingo-contrast-Sonography (Hy-Co-Sy)**

- TVS scan during which air and saline or a solution of D-galactose is infused into the uterine cavity and observed to flow along the fallopian tubes..... Consider before IUI
- Requires more expertise.
- Less invasive.

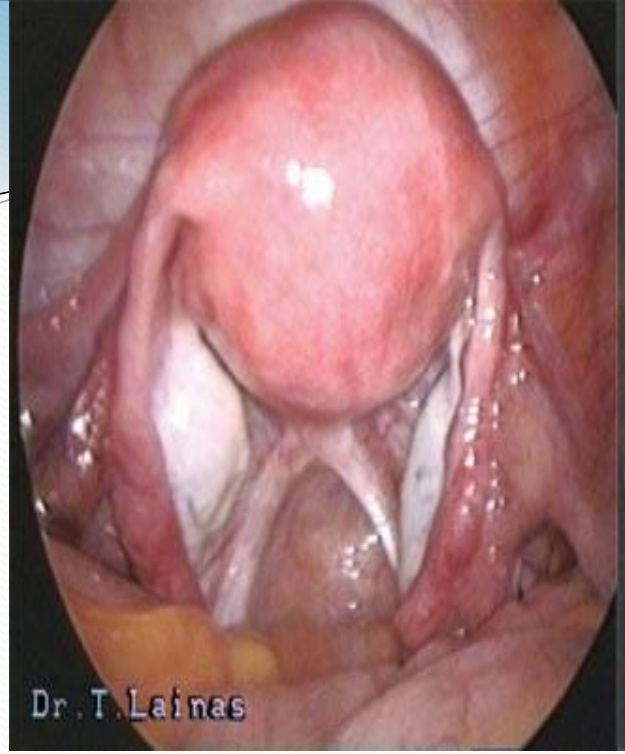




Further investigations

- **Laparoscopy:**
  - Invasive procedure.
  - to check for pelvic disease; such as endometriosis and to check tubal patency.
  - therapeutic as in laparoscpic myomectomy , LOD and tubal surgery.

- **Hysteroscopy:**
  - to evaluate uterine cavity.
  - In case of repeated failed IVF cycles.
  - therapeutic as in intrauterine septum.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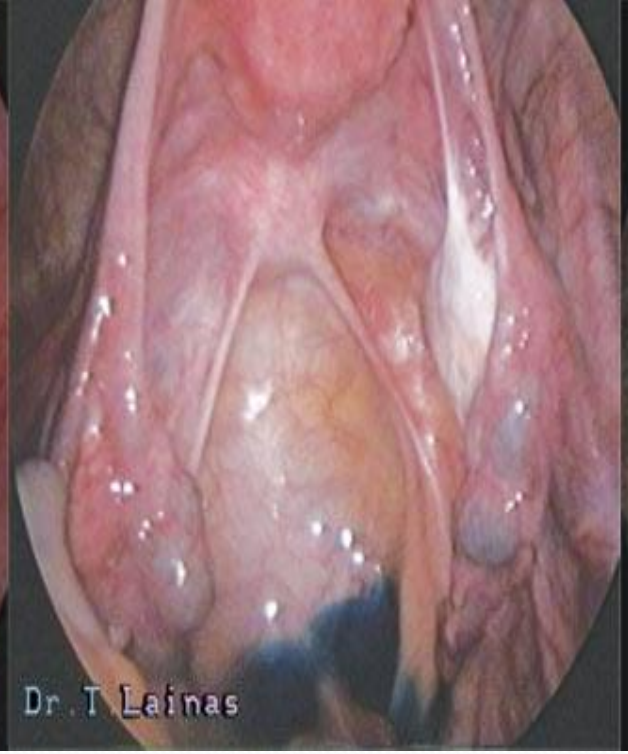
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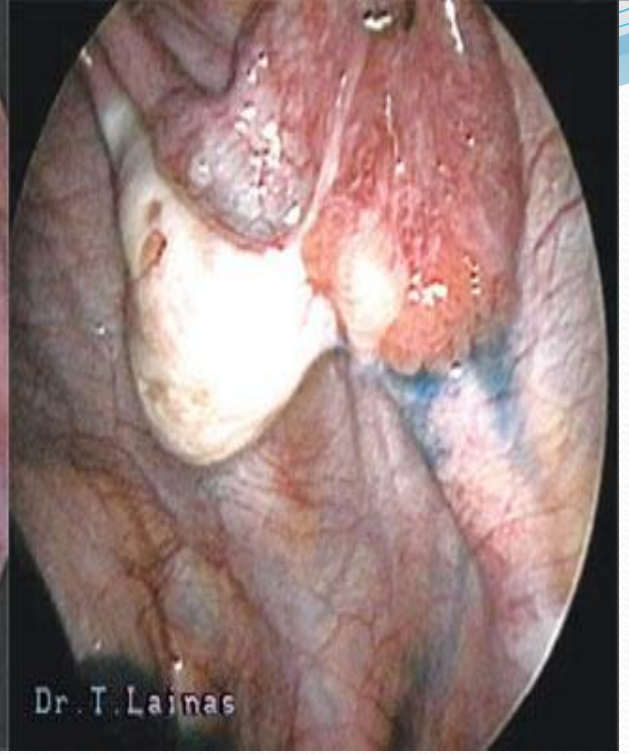
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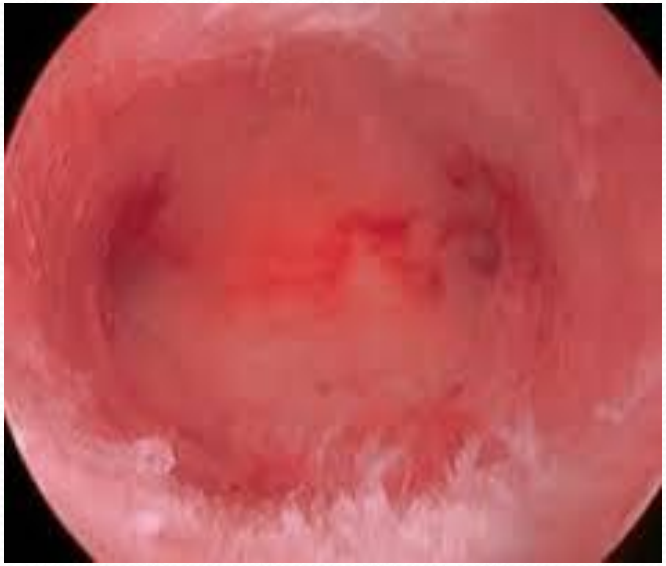
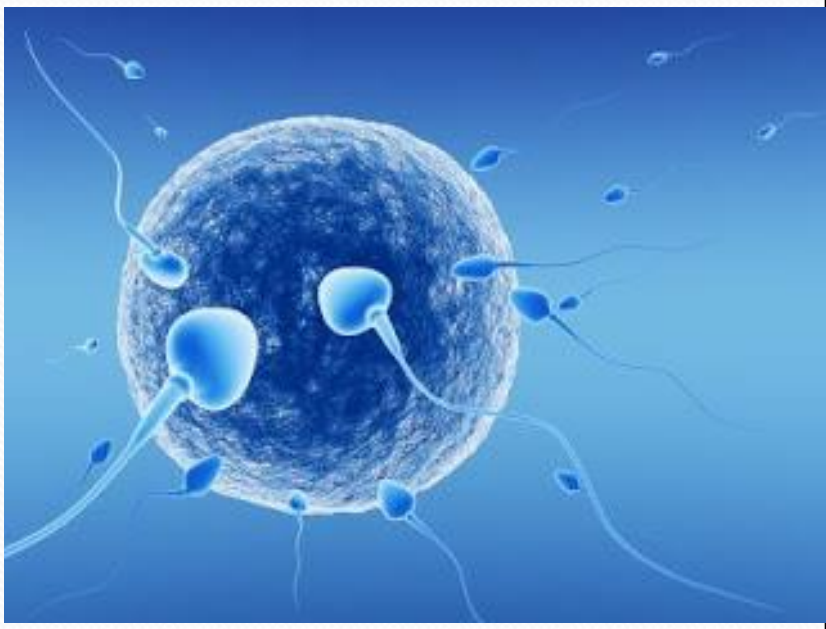


Management

1. Counseling.
2. Treatment of the cause.
3. Ovulation induction.
4. Artificial insemination (IUI)
5. IVF/ICSI

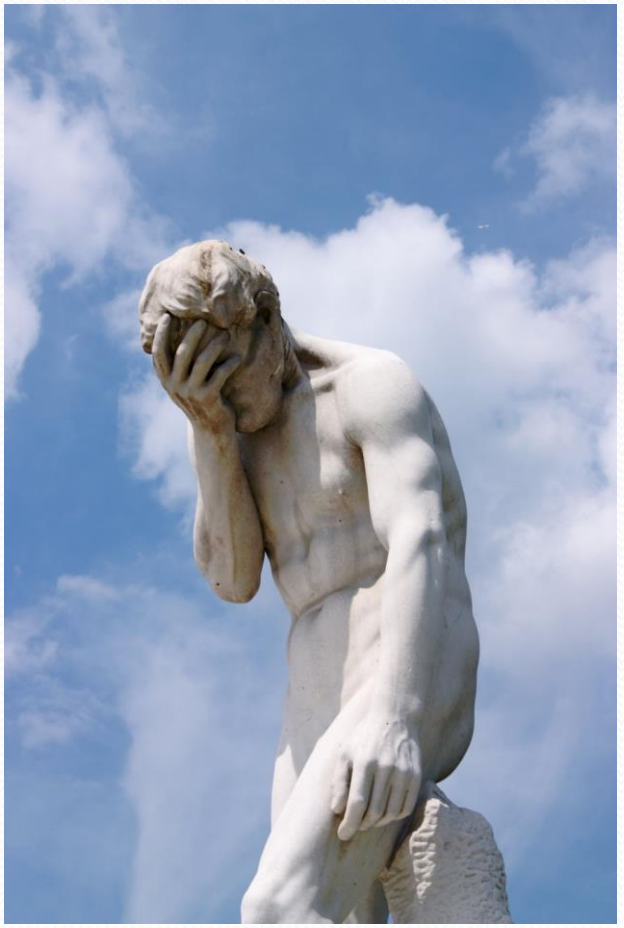


Treatment of the cause:

- **<u>Male Factor:</u>**
  (Liaise with the andrologist)

  1. Medical management:
  - Men with hypogonadotrophic hypogonadism should be offered gonadotrophin drugs.

  - Men with idiopathic semen abnormalities should not be offered anti-oestrogens, gonadotrophins, androgens, bromocriptine



Treatment of the cause:

- **Male Factor:**

2. Surgical management:

- Surgical correction of epididymal block in obstructive azoospermia.
- No evidence for surgical treatment of varicocele in infertility. (remains an area of debate)
- SSR(PESA,TESA and TESE)...then ART

3. Management of ejaculatory failure:

- Can be of great value as in retrograde ejaculation.

Treatment of the cause:

- **<u>Ovulation disorders:</u>**
  The WHO classifies ovulation disorders into 3 groups:

  1. Group I: hypothalamic pituitary failure (hypothalamic amenorrhoea or hypogonadotrophic hypogonadism).

  2. Group II: hypothalamic-pituitary-ovarian dysfunction (predominately polycystic ovary syndrome).

  3. Group III: ovarian failure.

Treatment of the cause:

- **<u>Ovulation disorders: (Group I)</u>**

  - Weight gain if BMI less than 19.

  - pulsatile administration of gonadotrophin-releasing hormone or gonadotrophins with luteinising hormone activity to induce ovulation.

Treatment of the cause:

- **<u>Ovulation disorders: (Group II “PCO”)</u>**

  1. Weight loss to BMI <30
  2. Clomiphene citrate and/or Metformin.
  - folliculometry via TVUSS should be done to avoid multiple pregnancies and risk of OHSS.
  - Not for more than 6 months.
  3. If resistant to the above, offer:
  - laparoscopic ovarian drilling, or,
  - ovulation induction via gonadotrophins.

  N.B.:
  - GnRHa should not be offered with ovulation induction for risk of OHSS.
  - No evidence for the role of adjuvant growth hormones.

Treatment of the cause:

- **<u>Ovulation disorders: (Hyperprolactinaemic amenorrhoea)</u>**

  - Women with ovulatory disorders due to hyperprolactinaemia should be offered treatment with dopamine agonists such as bromocriptine.

  - Consideration should be given to safety for use in pregnancy and minimising cost when prescribing.

Treatment of the cause:

- **Tubal and uterine factors:**

  1. Tubal microsurgery and laparoscopic tubal surgery:
  - May be more effective than no treatment.
  - No strong evidence. (e.g.: fimbrial end dilatation)

  2. Tubal catheterisation or cannulation:
  - With proximal tubal obstruction, selective salpingography plus tubal catheterisation, or hysteroscopic tubal cannulation, may be treatment options.

  3. Uterine surgery:
  - Women with amenorrhoea who are found to have intrauterine adhesions should be offered hysteroscopic adhesiolysis because this is likely to restore menstruation and improve the chance of pregnancy.

Treatment of the cause:

- **Tubal and uterine factors:**

  4. Surgery for hydrosalpinges before in-vitro fertilization treatment:

  Laparoscopic salpingectomy or disconnection of both tubes improve IVF/ICSI success rates(↑ pregnancy rate by 50%).

Treatment of the cause:

- **Endometriosis:**

  1. Medical management:

  - Ovarian suppression of minimal and mild endometriosis diagnosed as the cause of infertility in women does not enhance fertility and should not be offered.

  2. Surgical ablation:

  - In minimal or mild endometriosis; surgical ablation or resection of endometriosis plus laparoscopic adhesiolysis improves the chance of spontaneous pregnancy.
  - Laparoscopic resection of endometriomas may be beneficial, however recent RCTs suggest intervention only in endometriomas > 4cm.
  - In moderate or sever endometriosis; surgical treatment should be offered. (Debatable)
  - Post-operative medical treatment does not improve pregnancy rates.

Treatment of the cause:

- **Unexplained infertility:**

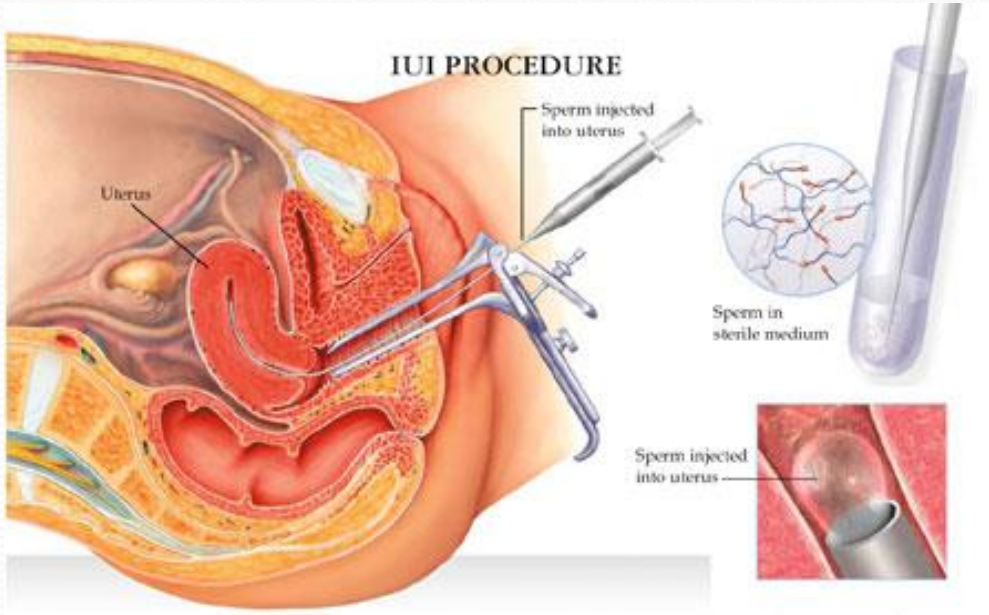
  - Ovarian stimulation should not be considered as does not improve pregnancy or birth rates.

  - Advise to try to conceive for two years of unprotected sexual intercourse before other options(Fecundity is 3-5%).

  - After two years of failure to conceive, consider IVF/ICSI.

Intrauterine insemination

- It is artificial introduction of semen inside the female's uterus.
- Success rate varies, lie between 8-12% per cycle.
- 50% of women will conceive after 6 cycles.
- Half of the unsuccessful ones, will conceive with further 6 cycles.



Intrauterine insemination

- Consider un-stimulated intrauterine insemination as a treatment option in the following groups as an alternative to vaginal sexual intercourse:
  - people who are unable to, or would find it very difficult to, have vaginal intercourse
  - people with conditions that require specific consideration in relation to methods of conception (for example, after sperm washing where the man is HIV positive)

- Do not offer IUI for people with unexplained infertility, mild endometriosis or mild male factor.!!!!!!!!!!!!!!!!!!!!!!!!!!!

- Always take in consideration the ages of the couple.

IVF/ICSI

- is a process by which the oocyte is fertilized by a sperm outside the body: *in vitro*, and then a gamete retransferred intrauterine.

IVF/ICSI

- In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles.

- In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI.

IVF/ICSI

- IVF/ICSI cycle consists of:
  1. Down-regulation of gonadotrophins.
  2. Controlled ovarian stimulation.
  3. Maturation of oocytes.
  4. Oocytes retrieval.
  5. Fertilization and incubation of the gametes.
  6. Embryo-transfer.
  7. Luteal phase support.

  (and cryopreservation choice offered if good quality embryos are available)

IVF/ICSI

- Down-regulation:
  - to avoid premature LH surge and spontenous ovulation.

  - either GnRH agonist protocol or GnRH antagonist protocol.

  - always use GnRH antagonist protocol in women with high risk of OHSS.

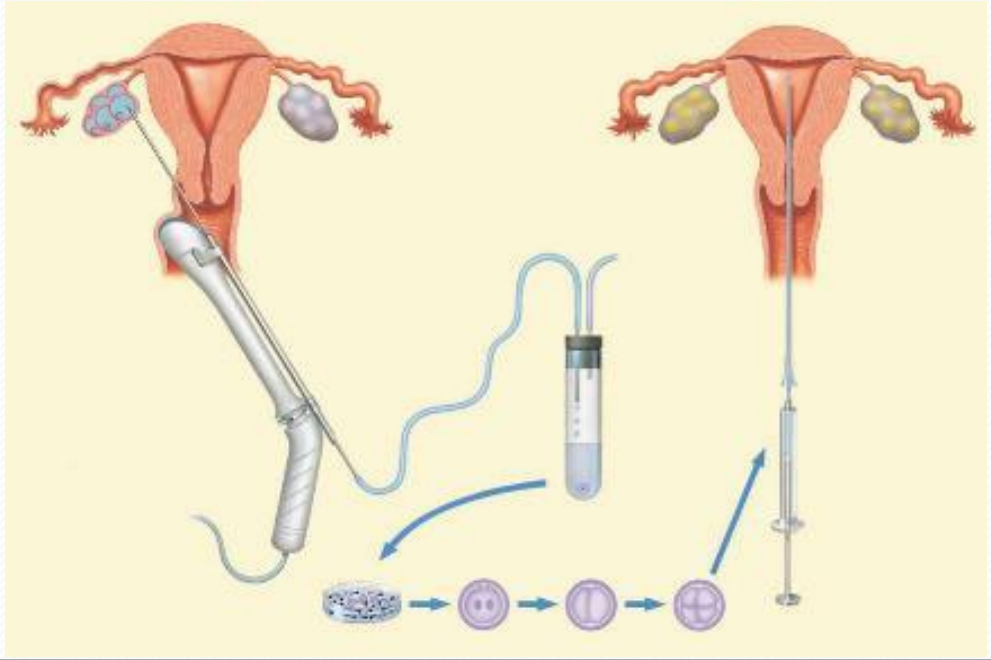
IVF/ICSI

- Controlled ovarian stimulation:
  - By urinary or recombinant FSH and/or HMG.
  - Dose depends on age, BMI, presence of PCO and ovarian reserve.
  - Monitoring of folliculometry by USS and E2.

- Triggering of ovulation:
  - By urinary of recombinant HCG, 36 before oocyte retrieval.

IVF/ICSI

- Oocyte retrieval:
  - ultrasound-guided oocyte retrieval.
- Fertilization and incubation.
- Embryo-transfer.
  - SET or DET.



IVF/ICSI

- Luteal phase support:

  - Should be offer luteal phase support with progesterone till 8 weeks of gestation.

  - Different form of progesterone with different routes of administration are available, RCT are taking place comparing efficacy of different forms.

- Generally, success rates lie between 40% and 60% per cycle.

Cryopreservation:

- Cryopreservation of semen, oocytes or embryos should be offered to anyone who may undergo treatment that may affect his/her fertility. (e.g.: chemotherapy for cancer).

- For cancer-related fertility preservation, do not apply the eligibility criteria used for conventional infertility treatment.

- Do not use a lower age limit for cryopreservation for fertility preservation in people diagnosed with cancer.

Summary

- Infertility is a significant medical and social problem affecting couple worldwide.
- It is a sensitive issue that should be handled with great care with continuous professional counselling.
- Most young couples will conceive naturally within 2 years.
- Evaluation of both partners for causes is essential.
- Treatment depends on the cause, and varies from medical treatment to surgery to ART.

References

1. Nice guideline, CG156, February, 2013.
2. The Human Fertilization and Embryology Authority, HFEA website.
3. ESHRE recommendation, ESHRE conference 2012.

Good Luck!