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Contraception

Combined hormonal contraception

- **Administration:**
  - Before initiation of combined hormonal contraception (CHC), complete medical history, medications and family history are reviewed. Recent blood pressure and body mass index are checked. However, no pelvic examination, labs or screening are needed
  - Standard preparation to start with is combined oral contraceptives containing ethinyl oestradiol ≤ 30 mcg, and levonorgestrel or norethisterone
  - CHC can be given in the first 5 days of the cycle without additional contraception
  - If given after day 5 of the cycle, additional contraception for 7 days OR pregnancy test may be done immediately and after 21 days
  - CHCs are prescribed for 12 months, routine annual review is recommended to assess blood pressure, body mass index, change to medical history or medications and compliance

- **Regimen:**
  - Tailored (combined hormonal contraception) CHC regimens may be superior to traditional cyclic regimen:
    - **Advantages:** Tailored regimens reduce withdrawal bleeding frequency and side effects
    - **Disadvantages:** unscheduled bleeding is common with tailored regimens
  - Examples to tailored regimens are shortened hormone-free interval, extended 9 weeks, continuous, and flexible extended

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- **Side effects:**

  Breakthrough bleeding is indicative for low oestrogen dose in CHC formula. Therefore, preparations with high oestrogen may be used. Up to 70 mcg may be used for a short term after expert advice is obtained

- **Effectiveness:**
  - **Overall effectiveness:**
    - All CHCs are comparable in effectiveness and are less effective than long acting reversible contraceptives (LARC) specially with typical use
    - Perfect-use failure rates are less than 1% (0.3%). However, typical-use failure rate of combined oral contraceptives is 9%
  - **Effect of obesity:**
    - Oral contraceptives are not affected by weight. However, effectiveness may be reduced by bariatric surgery (absorptive effect)
    - Contraceptive patches are less effective if women weight is 90 kg or above
  - **Effect of enzyme inducing drugs:**
    - Enzyme inducing drugs reduce CHC effectiveness for up to 28 days after stopping these drugs. An effective alternative should be used during this window
    - Use of lamotrigine with CHC should be avoided as it impacts seizure control and increases the risk of lamotrigine toxicity
    - Non-enzyme inducing antibiotics → no precaution
  - **Effect of ulipristal:**

    If ulipristal is used for emergency contraception, use of CHCs should be postponed for 5 days and another contraception is used till CHC is effective
  - **Effect of gastrointestinal symptoms:**

    Effectiveness of COC is reduced by vomiting or severe diarrhea

- **Non-contraceptive benefits:**
  - CHC improves heavy menstrual bleeding, dysmenorrhea, and premenstrual syndrome
  - CHCs reduce the risk of recurrence of endometriosis postoperatively (continuous regimen)
  - CHC improves polycystic ovary syndrome-related symptoms (acne, hirsutism, menstrual irregularities)
  - CHC reduces risk of certain cancers:
    - Endometrial cancer

- Ovarian cancer (risk is reduced by 40-50% after 10 years of use, the benefit persists for 30 years) and colorectal cancer (20%)
- Up to the age of 50, CHCs can be used for contraception, management of menopausal symptoms and prevention of bone loss

- **Side effects:**
  - Headache and dizziness
  - Nausea
  - Breast tenderness
  - Bloating. Better with tailored regimen
  - Unscheduled bleeding
    - These women should be advised to wait for 3 months before seeking medical advice
    - It is less observed with transdermal or vaginal preparations
    - It is less observed with oestradiol dose of 30 compared to 20 mcg
    - It is not related to progestin type
  - Mood changes

    In these cases, an alternative may be used or another CHC with a different progestin may be tried
  - Decrease in libido (unlikely with 20 mcg of oestradiol)
  - Slight delay in return of fertility

    However, return of ovulation occurs within 1 month in most women

- **Adverse effects:**
  - **Venous thromboembolism (VTE):**
    - CHCs increase the risk of VTE. Magnitude of risk is related to oestrogen dose & progestin type (the risk is least with first and second generation progestins and norgestimate)
    - Absolute risk of VTE is very small (5-12:10000 vs 2:10000 as a baseline)
    - Reduce immobility during travelling while on CHCs is associated with significant risk (VTE is 1:500 after an 8-hour flight)
    - Because of the risk of VTE, women should be switched to another contraception 4 weeks prior to surgery
    - The risk is the highest after initiation, and then decreases after 1 year of use

- **Vascular occlusion:**
  - CHCs are associated with very small increase in risk of myocardial infarction (1:10,000) and ischemic stroke (2:10,000) but not haemorrhagic stroke
  - The risk is greater with higher doses of oestrogen
- **Gynaecologic cancers:**
  - CHCs is associated with small increase in breast cancer risk (relative risk is 1.2). The risk decreases after discontinuation and normalizes after 10 years
  - CHC is associated with small increase in cervical cancer risk after 5 years of use (relative risk is 2). Risk is normalized after 10 years of use

- **Absolute contraindications (UKMEC category 4):**
  - Smoking (≥15 cigarettes/day) in women aged ≥35 years
  - Uncontrolled hypertension
  - Multiple risk factors of atherosclerotic cardiovascular disease
  - Current or history of venous thromboembolism/pulmonary embolism
  - Major surgery with prolonged immobilization
  - History of or current ischemic heart disease
  - Known thrombophilia
  - History of cerebrovascular accident
  - Complicated valvular heart disease, e.g., pulmonary hypertension, atrial fibrillation, or subacute bacterial endocarditis
  - Migraine with aura
  - Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies
  - Current breast cancer
  - Complicated or uncontrolled diabetes (with nephropathy, neuropathy, retinopathy)
  - Viral hepatitis (active or flare)
  - Severe (decompensated) cirrhosis
  - Hepatocellular adenoma and hepatoma

  Family history of breast cancer or positive BRCA are not contraindications to CHC

- **Incorrect use:**

  Incorrect use or missed pills more than 24 hours from the due time should be managed by:
  - If one pill is missed (> 24 hrs of due time), missed pill should be taken and the rest of pills are taken as scheduled (patch effect extends for 3 days, ring effect extends for 2 days)

- If 2 or more pills (72 hours since last pill) are missed, the last pill is taken, a backup method is used for 7 days and if a pill is missed in the first week, emergency contraception is used, while if the pill is missed in the third week of the cycle, pill free interval should be cancelled

Progestin only pills (POPs)

POPs are commonly used during breastfeeding or when oral contraception is preferred and there is a contraindication to oestrogen

- **Types of POPs:**
  - **Conventional POPs:** containing levonorgestrel. They act primarily by affecting cervical mucous permeability, endometrial changes and alteration of tubal mobility. Their effect on ovulation is variable
  - **New POPs:** containing desogestrel. These pills prevent ovulation more reliably (97%) and thereby, they are more effective than old-type POPs

- **Contraindications:**

  The only absolute contraindication (category 4) to POPs is current breast cancer

- **Side effects:**
  - Menstrual disorders: complete amenorrhea to unpredictable bleeding (main cause of discontinuation)
  - Development of functional ovarian cysts
  - Headache, dizziness, nausea, weight gain, bloating, acne, and mood changes

- **Incorrect use:**
  - **Older-type POPs:**

    A pill is considered missed if it is not taken within 3 hours of the due time, women should take the missed POP as soon as possible, take the next POP as scheduled, use additional contraception, or abstain from intercourse for 48 hours
  - **Desogestrel-containing POP:**

    A pill is considered missed if it is not taken within 12 hours of the due time, women should take the missed POP as soon as possible, take the next POP as scheduled, use additional contraception, or abstain from intercourse for 48 hours If the woman is breastfeeding

Long acting reversible contraception (LARC)

- **Methods:**

  LARC refers to intrauterine device (IUD), levonorgestrel-releasing intrauterine system (LNG-IUS) subdermal implants (Nexplanon), and contraceptive injectables

- **Mode of action:**
  - IUD is the only non-hormonal LARC and it acts mainly be alteration of the endometrium, tubal motility, and uterine contractions
  - Hormonal methods act by inhibition of ovulation through suppression of the hypothalamic/pituitary/ovarian axis. Secondary mechanisms of action include endometrial suppression and increased cervical mucus thickness

- **Effectiveness:**
  - LARC is more cost effectiveness even after 1 year of use compared to COCs
  - LARC reduces the rate of unintended pregnancy
  - IUD and LNG-IUS are more cost effective than injectables
  - Implants are highly effective. Failure rate is 0.1%

- **Administration:**
  - Pregnancy should be excluded before initiation of these methods
  - Informed consent is required. If a woman has difficulties with counselling, discussion should be made with the careers/other parties
  - For girls younger than 16, consider child protection issues and Fraser guidelines before initiation
  - For IUDs and LNG-IUSs, provider skills should be maintained by placing at least one IUD/month

- **Contraindications:**

  The only absolute contraindication (category 4) to POPs is current breast cancer

Intrauterine device (IUD)	▪ **Side effects:** □ Heavy menstrual bleeding □ Dysmenorrhea □ Increased vaginal discharge ▪ **Complications:** □ Vasovagal reaction □ Uterine perforation (1:1000) □ Failure of insertion □ Contraceptive failure (0.5%) □ Ectopic pregnancy (IUD prevents intrauterine pregnancy rather than extrauterine pregnancy because it does not prevent ovulation. Therefore, it does not increase risk of ectopic pregnancy but if pregnancy occurs, it is likely ectopic pregnancy) □ Pelvic inflammatory disease: the risk increases by 6 folds in the first 3 weeks after insertion. IUD has been linked actinomycosis infection, which is generally rare □ Expulsion (risk is 5%, mainly in the first 3 months) □ IUD displacement ▪ **Contraindications (category 4):** □ Pregnancy □ Current pelvic inflammatory disease □ Gestational trophoblastic disease with persistently elevated β-hCG □ Pelvic tuberculosis □ Immediate post-septic abortion □ Postpartum genital infection □ Unexplained vaginal bleeding before assessment □ Endometrial cancer □ Cervical cancer awaiting treatment □ Distorted uterine cavity ▪ **Follow-up:** A 3-6 week visit is recommended after insertion to confirm correct placement and absence of infection. No further follow-up is required if there are no concerns

levonorgestrel-releasing intrauterine system (LNG-IUS)	▪ **Indications:** □ Long term reversible contraception □ Treatment of heavy menstrual bleeding □ Treatment of dysmenorrhea □ Treatment of endometriosis-related pain □ Treatment of endometrial hyperplasia □ As a progestin component of hormonal replacement therapy (endometrial protection) ▪ **Contraindications:** □ Pregnancy □ Current breast cancer □ Distorted uterine cavity □ Current pelvic inflammatory disease □ Current purulent cervicitis/pelvic inflammatory disease □ Gestational trophoblastic disease with persistently elevated β-hCG □ Pelvic tuberculosis □ Immediate post-septic abortion □ Postpartum genital infection □ Unexplained vaginal bleeding □ Cervical cancer
subdermal implants (Nexplanon)	▪ **Failure rate:** is 0.1% ▪ **Duration of action:** Nexplanon is effective for 3 years ▪ **Side effects and complications:** □ Complications of insertion and removal e.g. broken or damaged implant, and difficult localization, difficult removal (formation of a fibrous band) *Nexplanon can be visualized by X-ray (radio-opaque) or ultrasound if not palpable* □ Abnormal bleeding patterns e.g., prolonged irregular bleeding □ Weight gain
contraceptive injectables	▪ **Failure rate:** is 0.3% with perfect use, 4% with typical use ▪ **Non-contraceptive advantages:** □ It may improve premenstrual symptoms and dysmenorrhea □ It reduces frequency of sickle cell crisis in affected women

	◻ It reduces frequency of epileptic seizures ◻ It may relieve endometriosis-related pain ▪ **Side effects:** ◻ Disturbances in menstrual pattern ◻ Weight gain ◻ Bone loss (reversible) ◻ Progestogenic side effects, e.g., bloating, breast pain, headaches, acne, and decrease in libido ◻ Delay in return of fertility (up to 9 months from the last injection) ▪ **Incorrect use:** Injectables should be given every 13 weeks. If the next dose is not given within 1 week of the due date, pregnancy should be ruled out, injection is given, and an additional method should be used for 7 days

Emergency contraception

- **Indications:**
  - Unprotected intercourse at any day of the cycle
  - Unprotected intercourse 21 days or more postpartum, 5 days or more after miscarriage, ectopic pregnancy, or gestational trophoblastic disease (GTD)

  Emergency contraception does not protect against further unprotected intercourse, and it should be repeated if necessary

- **Administration:**

  Oral levonorgestrel (1.5 mg), IUD, and ulipristal can be used:
  - IUD and ulipristal can be used up to 5 days. Levonorgestrel is used for up to 72 hours
  - Unlike IUD, oral medications do not work if ovulation occurred
  - In women who had unprotected intercourse early in the cycle, and recently has a second unprotected intercourse, levonorgestrel or ulipristal can be offered. They will not result in pregnancy disruption or foetal anomalies
  - IUD can be offered to adolescents if indicated

- After emergency contraception is administered, discuss immediate use of maintenance contraception with these women. If ulipristal was used, combined hormonal contraceptives should be delayed for 5 days and abstinence or barrier method is used for 7 days

- **Effectiveness:**
  - IUD is the most effective, followed by ulipristal and then oral levonorgestrel
  - Women weight affects effectiveness of levonorgestrel
  - Enzyme inducing drugs may reduce effectiveness of ulipristal and levonorgestrel. Therefore, IUD should be considered. The use of higher doses of levonorgestrel (3 mg) is of uncertain effectiveness. Do no repeat the course
  - Ulipristal effectiveness may be reduced if:
    - Progestin is given in the first 5 days after ulipristal administration
    - Progestin is given in the last 7 days before ulipristal administration

    Therefore, if emergency contraception needs to be repeated within the same cycle, levonorgestrel should not be used within 5 days of ulipristal use and ulipristal should not be used if levonorgestrel was used in the last 7 days

- **Contraindications:**
  - IUD contraindications are the same regardless of the indication (see before)
  - Ulipristal is contraindicated in women with severe asthma (managed by oral steroids)

- **Precautions:**
  - Breastfeeding increases the risk of IUD perforation. However, the absolute risk is remains low
  - Ulipristal should not be used with breastfeeding. If ulipristal is given, breastfeeding should be stopped, and breast milk should be discarded for 1 week after administration
  - Levonorgestrel can be used safely with breastfeeding

Postpartum contraception

- **Initiation of contraception:**
  - Contraception should be initiated by day 21 postpartum
  - Although it is not indicated in the first 3 weeks postpartum, contraceptive methods can be started safely immediately after birth if desired except COCs

- Immediate postpartum placement of intrauterine contraceptive methods or subdermal implants is recommended because it is associated with high acceptance and continuation rate and lower risk of unintended pregnancy
- Contraception should be available to provide to women prior to discharge. If the woman-preferred method cannot be provided immediately, a bridging method should be provided
- Women who start LARC immediately after abortion have lower chance to have another abortion within 2 years versus other methods

Back-up plans

- Additional method (barrier methods or abstinence) is required if hormonal contraception is started at or after 21 days postpartum (or 5 days after abortion, methotrexate treatment or treatment of gestational trophoblastic disease 'GTD')
- If unprotected intercourse occurred beyond 21 days postpartum, emergency contraception using levonorgestrel 1.5mg or ulipristal 30mg can be used after 21 days, or copper IUD can be used safely after 28 days

- **Contraceptives options:**
  - **Progestin only contraception:**
    - These options are safe to use at any time postpartum and has no adverse effects on lactation
    - In women receiving mifepristone for medical management of abortion, Implants can be used safely initiated at time of mifepristone administration. However, administration of injectables at time of mifepristone administration may increase incidence of failed abortion and the decision should be discussed with the patient
    - If there is absent or scant bleeding with medical management of abortion, this should not be attributed to hormonal contraception
  - **Combined hormonal contraception (CHC):**
    - In breastfeeding women, it should not be started earlier than 6 weeks postpartum
    - In non-breastfeeding women, CHC can be initiated 3 weeks postpartum if there is no increased risk of venous thromboembolism (VTE)
    - Regardless of breastfeeding status, CHC should not be used within 6 weeks postpartum if there is higher risk of VTE e.g. immobility, transfusion, body mass index ≥ 30, postpartum haemorrhage, caesarean delivery, preeclampsia, smoking

- CHC can start immediately after abortion. In women with recurrent miscarriage, antiphospholipid antibody syndrome should be ruled out before CHC is initiated. Otherwise, contraception should not be postponed to complete work-up
- Hormonal contraception may start immediately after treatment of GTD
- **Lactational amenorrhea method (LAM):**
  - LAM is efficient in the first 6 months if women are amenorrheic and exclusively breastfeed
  - Under these circumstances, LAM success if 98%
- **Intrauterine device (IUD):**
  - IUD can be placed either immediately after birth (10 minutes after delivery of the placenta) or within 48 hours postpartum. Otherwise, IUD placement should be delayed after 4 weeks
  - IUD can be placed immediately after expulsion of products of conception following medical treatment of abortion or at the time of surgical evacuation
- **Permanent sterilization:**
  - Both Flishie clips and modified pomeroy techniques may be used
  - This method should not be decided at delivery because there is high risk of regret
  - Consent of elective sterilization at time of caesarean delivery should be signed at least 2 weeks in advance
  - In case of abortion, an immediate decision of sterilization may be associated with high risk of regret. The procedure can be done at the same time of surgical abortion
  - Sterilization may start immediately after treatment of GTD
- **Barrier methods:**
  - Male and female condoms can be used safely immediately postpartum or after abortion
  - Diaphragm use should be delayed to 6 weeks postpartum after delivery, second trimester abortion or GTD to allow genital involution
- **Fertility awareness methods:**

  These methods may be difficult to use due to bleeding irregularities and breastfeeding

- **Special considerations:**
  - Women who are interested in conception after abortion, should be recommended to try to conceive immediately. Pregnancy outcomes are more Outcomes are more favourable if pregnancy occurs within 6 months of miscarriage compared to more than 6 months

- Women treated with methotrexate should receive highly effective contraception for at least 3 months. If unprotected intercourse occurred after 5 days of treatment, emergency contraception should be considered
- After complete molar pregnancy is surgically managed, pregnancy should be avoided for at least 6 months to allow HCG monitoring
- After partial mole is treated, contraception should continue until 2 monthly consecutive hCG levels are normal

Contraception in older age groups

20% of pregnancies in women aged > 40 are unplanned and 28% of these pregnancies end in termination

Method of contraception	Time of discontinuation
Non-hormonal methods	• Women aged >50 can stop contraception 1 year after cessation of menstruation • Women aged <50 can stop contraception 2 years after cessation of menstruation
Oral progesterone only contraception	• Contraception should be discontinued 1 year after reporting 2 FSH levels >30 IU/l taken at least 6 weeks apart • It is not recommended to use FSH for the purpose of discontinuation of contraception in women <50 years
Combined hormonal contraception	Combined hormonal contraception should be discontinued 2 weeks before serum FSH is checked
Progestin injectables	Combined hormonal contraception should be discontinued 12 months before serum FSH is checked

Alternatively, contraception can be continued until the age of 55

Contraception in teenagers

Prescription of contraception to girls younger than 16 years should follow Fraser Guidelines:

- The girl can understand doctor's advice

- The girl does not have to tell her parents and the doctor should not tell her parents against her will. No parental consent is required

Reproductive endocrinology

Infertility Overview

Background

- **Definition:**

  Failure of a couple to conceive within one year of regular unprotected sexual intercourse without the use of contraception

- **Incidence:**
  - 80% of couples will conceive within 1 year and 90% within 2 years if a woman age less than 40, does not use any contraception, and has regular sexual intercourse
  - Regular Sexual intercourse every 2-3 days increases pregnancy chance
  - Fertility of females and to a lesser extent male fertility decline with age

- **Risk factors:**
  - **Alcohol:**
    - For women seeking conception, alcohol intoxication should be avoided, and should not exceed 1-2 units of alcohol once or twice weekly
    - For men, 3-4 units/day of alcohol unlikely affects sperm quality. Excess alcohol intake should be avoided
  - **Smoking:**
    - In women, passive and active smoking affects fertility
    - In men, it may decrease sperm quality. However, clinical impact of smoking is not clear
  - **Occupation, over the counter (OTC), and recreational Drugs:**

    These factors may have a negative effect on fertility
  - **Underwear in males:**

    It increases scrotal temperature, which may reduce semen quality

- **Body mass index (BMI):**
  - In women:
    - Women with BMI > 30 take a longer time to conceive. If there is ovulatory dysfunction, weight reduction is recommended to increase probability of conception. Engagement in a group program is more effective
    - Women with BMI < 19 and irregular menstruation or no menstruation should be advised on weight gain
  - In men: BMI > 30 in males reduces fertility and weight reduction is recommended

Assessment

- **History:**

Personal history	▪ Couple's age and duration of relation ▪ Occupation e.g. some men occupations may affect semen quality and scrotal temperature ▪ Special habits for the couple e.g. smoking, alcohol, recreational drugs
menstrual history	▪ Menstrual pattern (regularity of menses is indicative of ovulatory cycles) ▪ Date of last menstrual period ▪ Presence of dysmenorrhea and premenstrual syndrome ▪ Symptoms of hyperandrogenism e.g. acne, hirsutism
obstetric history	▪ Number of pregnancies and abortions ▪ Type of delivery, indications of caesarean section if applicable, and any obstetric complications ▪ Type and management of previous abortions ▪ Number of living children, use of any contraception methods, and duration of use
Sexual history	▪ Sexual history including frequency of intercourse ▪ History of sexual abuse
Family history	▪ Couple consanguinity ▪ History of infertility in the family
Medical history	▪ History of diseases and medications ▪ Time and results of the last cervical cancer screening

- **Investigations:**

Initiation of investigations

- Investigations are considered after one year of no conception despite unprotected intercourse OR After 6 months of failed intrauterine insemination
- Earlier evaluation is needed if women are 36 years or older OR if there is known infertility cause or risk factors of infertility

- **Male investigations:**
  - Semen analysis is the first step in assessment of a couple with infertility
  - If the semen analysis is abnormal, it should be repeated after 3 months. However, it should be repeated as soon as possible if there are severe abnormalities e.g. azoospermia, severe oligospermia. Testing anti-sperm antibodies is not recommended

- **Female investigations:**

❶ Ovarian factor assessment:

① Assessment of ovarian reserve:

- Ovarian reserve indicates ovarian response to ovarian stimulation
- Age is the initial and most important predictor of ovarian reserve and success of natural or in-vitro fertilization (IVF) conception. Other predictors of ovarian reserve include:

	Antral follicle count (AFC)	Anti-Müllerian hormone (AMH)	Follicle stimulating hormone (FSH)
Low response	AFC ≤ 4	AMH ≤ 5.4 pmol/l	FSH > 8.9 IU/l
High response	AFC > 16	AMH ≥ 25 pmol/l	FSH < 4 IU/l

- There is no role for ovarian volume, ovarian blood flow, inhibin B, Estradiol E2 in assessment of ovarian reserve

② **Assessment of ovulation and ovulatory dysfunction:**

Diagnosis of ovulation	Diagnosis of causes of anovulation
□ Mid-luteal serum progesterone (day 21 of the 28-day cycle) should be considered in all women even if the cycle is regular If the cycle is irregular, the test needs to be delayed (e.g. day 28 if cycle length is 35 days) and should be repeated weekly till next menses. □ Serum FSH and LH: should be considered in women with irregular cycles □ Basal body temperature (BBT): is not reliable, and should not be used	□ Serum prolactin: should be considered in women with ovulatory dysfunction, agalactorrhea, or possible pituitary tumor □ Thyroid Function Test: should not be considered routinely except if there are symptoms of thyroid disease □ Luteal phase defect (LPD): should not be investigated with endometrial biopsy (no evidence that the treatment of LPD improves pregnancy rate)

❷ **Tubal factor assessment:**

Assessment of risk of comorbidities should be assessed first:
(pelvic inflammatory diseases (PID), previous ectopic pregnancy, and endometriosis)

Present → Direct assessment with laparoscopy and chromotubation (dye test) to test tubal patency and assess tubal pathology

Absent → Hysterosalpingography or Hysterosalpingo-contrast ultrasonography

❸ Uterine factor assessment:

- Uterine cavity can be assessed along with tubal patency using hysterosalpingography or Hysterosalpingo-contrast ultrasonography
- Hysteroscopy is not offered for screening unless clinically indicated

❹ Uterine factor assessment:

Post-coital testing of cervical mucus is not recommended

❺ Pre-treatment investigations:

- Rubella antibodies should be tested. Non-immune women should be offered rubella vaccine and pregnancy should be delayed for 1 month after vaccination
- If intrauterine insemination (IUI) is planned, screening for chlamydia trachomatis should be considered:
  - If it tests positive, the couple should be treated
  - If screening was not done, consider prophylactic antibiotics prior to the procedure
- Before IVF, women should be tested for HIV, hepatitis B, and C

Management

- **Couple counselling:**

Couple counselling in the first visit

- Counsel both partners in the same setting
- Counsel couples to wait for one year if their age is younger than 36
- Counseling throughout the process of management should be offered by a person not involved in fertility medical care
- Counsel couples that infertility is stressful, and it may affect relation, libido, frequency of intercourse and offer fertility support group
- Counsel the couple regarding side effects and risks associated with infertility management
- Counsel on lifestyle modification e.g. weight reduction and smoking cessation

- **Couple preparation and initial management:**
  - **Folic acid:**
    - Folic acid should be considered before conception and for 12 weeks
    - Standard dose is 0.4 mg/day. A higher dose (5mg/day) should be considered in the following indications:
      ① Previous history of neural tube defect
      ② Diabetes
      ③ Women treated with antiepileptics
      ④ Haemoglobinopathies
  - **Lifestyle modifications:**
    Smoking cessation, weight reduction, cessation of alcohol and recreational drugs should be considered prior to conception
  - **Management of chronic viral infection:**
    Women with hepatitis B, C, or HIV should be referred to centres with appropriate experience
    - **HIV:**
      - If a man is infected with HIV, a discussion should be held between the couple, fertility specialist and HIV specialist regarding risk of transmission with unprotected sexual intercourse, risks to the mother and foetus, and risks with lactation
      - Risk of sexual transmission is negligible if:
        ① The patient is compliant with Highly Active Antiretroviral Therapy (HAART)
        ② Viral load < 50 for more than 6 months
        ③ HIV is not associated with other infections
        ④ Unprotected intercourse is limited to ovulation time only

If these criteria are present	Sperm washing is not preferred (it does not decrease risk of transmission and it may decrease likelihood of pregnancy. However, it may be done if requested by the couple Pre-exposure prophylaxis to women is not indicated
If these criteria are absent	Sperm washing should be offered (it reduces but does not eliminate risk of transmission)

    - **Hepatitis B:**
      Partners of hepatitis B patients should be offered the vaccine. Sperm washing is not indicated for hepatitis B men

- **Hepatitis C:**
  Hepatitis C infection should be discussed with the couple, IVF specialist, and hepatitis specialist. Treatment options to eradicate hepatitis C should be considered before conception

- **Management of male factor infertility:**
  - **Medical management:**

Hypo gonadotrophic hypogonadism	Gonadotrophins may be offered to improve fertility of males Medications (e.g. androgens, bromocriptine) has not role to treat semen abnormalities
Genital infection	Antibiotics are offered to treat infection. However, it should not be offered for" leukocytes in semen" without identified infection

  - **surgical treatment:**
    - **Obstructive azoospermia:** surgical correction of epididymal blockage can be offered by an experienced surgeon. Otherwise, sperm surgical retrieval is offered
    - **Varicocele:** surgery for varicocele is not recommended (does not improve pregnancy rate)

- **Management of female factor infertility:**
  - **Ovarian factor infertility:**
    - **WHO group I (hypothalamic-pituitary failure):**
      - If BMI is below 19, advise women to gain weight and to practice moderate exercise instead of high exercise level
      - Induction of ovulation is achieved using pulsatile gonadotrophins releasing hormone (GnRH) or gonadotrophins with luteinizing hormone (LH) activity

    - **WHO group II (hypothalamic-pituitary-ovarian dysfunction, polycystic ovary syndrome):**
      - If BMI is above 30, women should be advised on weight reduction. Weight reduction may restore ovulation, improve response to ovulation Induction, and improve obstetric outcomes

– Ovulation induction:

	Treatment	Monitoring
First line	Clomiphene Citrate (CC) or metformin or combination of both for a maximum of 6 months	Ultrasound monitoring should be considered at least during the first cycle to determine the dose and minimize the risk of multiple pregnancies
Second line	Gonadotrophins or ovarian drilling is offered to women with CC resistance If gonadotrophins are used, concomitant use of GnRH agonist should be avoided as it provides no improvement in pregnancy rate and it increases the risk of ovarian hyperstimulation syndrome (OHSS)	If gonadotrophins are used, ovarian ultrasound monitoring is mandatory in all cycles to avoid multiple pregnancy and OHSS

Adjuvant treatment e.g. growth factor or pulsatile GnRH are not recommended

- **Tubal factor infertility:**
  - IVF is the standard management in women with tubal factor infertility. However, surgical treatment may be considered in mild tubal disease and is superior to no surgery
  - Laparoscopic salpingectomy is recommended prior to IVF in women with hydrosalpinges. It increases likelihood of livebirth

- **Uterine factor infertility:**

  Women with amenorrhea secondary to intrauterine adhesions, may be offered hysteroscopic adhesiolysis. It may restore menses and improve likelihood of pregnancy

- **Unexplained infertility:**
  - Couples with infertility are advised to try to get pregnant spontaneously for 1 more year (a total of 2 years)
  - If no conception happened after 2 years of regular unprotected intercourse, IVF should be offered (no role for IUI or ovulation induction)

Intra-uterine insemination (IUI)

Indications	Outcomes
• Couple who are unable to have intercourse • Same sex couples • Need for sperm washing e.g. HIV infected men IUI has not role in unexplained infertility, mild male factor, or mild endometriosis	• 50% of couples will conceive within 6 cycles if the couple is younger than 40 • 75% of couples will conceive after 12 cycles • Fresh sperms are superior to frozen-thawed sperms. IUI is superior to intracervical insemination in both cases

IUI is offered for 6 cycles. However, couples may be counselled, and its use may be extended to 6 more cycles

In-vitro fertilization (IVF)

- **Criteria of referral to IVF:**

① Women younger than 40 who:

- Has not conceived after 2 years of unprotected intercourse or
- Underwent 12 cycles (or at least 6 cycles) of IUI

For these women, 3 cycles of IVF with or without ICSI are offered. However, if the patient reaches the age of 40, no more cycles should be offered

② Women aged between 40-42 years who:

- Has not conceived after 2 years of unprotected intercourse or
- Underwent 12 cycles (or at least 6 cycles) of IUI

For these women, one cycle of IVF should be offered with or without ICSI if:

- The patient has never had previous IVF
- Ovarian reserve is not low

These women should be counselled on risk of pregnancy in this age group

③ Women who are not possible to conceive with expectant management should be referred immediately to an IVF specialist

If women had a previous cycle of IVF and they are younger than 40, it counts as one of the 3 cycles that should be offered. The next 2 cycles should be by provided by NHS. Cancelled cycles due to low ovarian reserve should be considered

- **Predictors of IVF success:**

  ① Female age: success rate is higher among younger women

  ② Number of previous cycles: rate of success decreases with increased number of trials

  ③ Previous pregnancy: it increases likelihood of success

  ④ Women BMI: BMI should be ideally between 19 and 30

  ⑤ Alcohol consumption: alcohol consumption > 1 unit/day decreases IVF success rate

  ⑥ Maternal and paternal smoking: decrease likelihood of success of IVF

  ⑦ Caffeine consumption: it decreases likelihood of success of IVF

- **IVF protocol:**
  - **Pre-treatment:**
    - IVF pre-treatment with combined oral contraceptives (COCs) or progestin preparations does not affect the chance of live birth
    - Pre-treatment is only considered to facilitate scheduling of IVF treatment in women not treated with long down-regulation protocol
  - **Controlled ovarian stimulation:**
    - Natural IVF cycles are not recommended. Both CC stimulated and gonadotrophin stimulated IVF cycles are superior to natural cycles
    - Either urinary or recombinant gonadotrophins preparations can be used
    - The starting dose of FSH depends on certain factors:

      ① Age

      ② BMI

      ③ PCOS

      ④ Ovarian reserve

      The maximum dose of gonadotrophins is 450 IU/day
    - Response should be monitored with ultrasound with or without oestradiol level
  - **Down regulation:**

    Down-regulation with GnRH antagonist or agonist (long protocol) regimen is considered to avoid premature LH surge. GnRH agonist protocol is only offered if risk of OHSS is low

- **Ovulation triggering:**

  HCG (urinary or recombinant) is used to trigger ovulation

- **Retrieval of oocytes:**
  - Transvaginal retrieval of oocytes is done under conscious sedation
  - If at least 3 follicles are seen before oocyte retrieval, follicle flushing is not indicated (does not increase the number of retrieved oocytes and it increases duration of retrieval and procedure pain)
  - Assisted hatching is not recommended as it does not increase pregnancy rate
- **Embryo transfer:**
  - Ultrasound-guided embryo transfer improves pregnancy rate
  - If endometrial thickness is less than 5 mm, embryo transfer is not recommended as it is unlikely to result in pregnancy
  - Frozen-thawed embryos are comparable to fresh embryos
  - Number of transferred embryos is related to age:

Age	First cycle	Second cycle	Third cycle
< 37 years	1 embryo	1 embryo (or 2 embryos if embryos are not top-quality)	2 embryos
37 – 39 years	1 embryo (or 2 embryos if embryos are not top-quality)	1 embryo (or 2 embryos if embryos are not top-quality)	2 embryos
40-42 years	2 embryos		

If a donated oocyte is used, age depends on donor's age

  - Bed rest after embryo transfer does not improve IVF outcome
- **Luteal phase support:**
  - Progesterone should be offered for luteal phase support
  - HCG should not be offered due to the risk of OHSS
  - Duration of luteal phase support is 8 weeks

Intracytoplasmic sperm insemination (ICSI)

- **Indications of ICSI:**

  ① Azoospermia either obstructive or non-obstructive

  ② Severe semen abnormalities

  ③ Failure of previous IVF treatment due to failed or very poor fertilization

  ICSI is known to improve fertilization over IVF. Otherwise, it is not superior to conventional IVF in pregnancy rate

- **Pre-procedure investigations:**
  - ICSI should be preceded by appropriate investigations to detect genetic deficits
  - If severe deficits in semen quality or non-obstructive azoospermia is present, male karyotyping should be offered
  - Y chromosome microdeletions are not tested routinely before ICSI

Gamete donation

Indications of donor insemination	Indications of oocyte donation
• Poor semen parameters: donor insemination may be offered to men with obstructive azoospermia, non-obstructive azoospermia, and severe deficits if ICSI is declined • High risk of transmitting a genetic disorder to offspring • High risk of transmission of infection to women or offspring • Severe Rh iso-immunization Before donor insemination, assess ovarian and tubal factors in women with risk factors before donor insemination If donor insemination fails after 3 cycles, tubes should be assessed even in absence of risk factors	• Premature ovarian failure • Gonadal dysgenesis • Bilateral oophorectomy • Ovarian failure • Certain cases of IVF failure • High risk of transmission of genetic diseases

Cryopreservation

- Cryopreservation (including embryos, sperms, or oocytes) is considered for fertility preservation. No lower age limit is considered in cancer patients
  - **Sperms:** freezing of sperms in liquid nitrogen vapor is the preferred way
  - **Oocyte and embryo cryopreservation:**
    This is offered to women who can tolerate ovarian stimulation and oocyte retrieval without affecting her general condition provided that this step will not postpone cancer treatment. Vitrification is preferred for preservation if possible
- Gametes are stored for an initial period of 10 years. Men at risk are offered continued storage
- There is no association between cryopreservation and maternal invasive cancer, childhood cancers, or other children adverse effects on the short and medium-term. There may be a small increase in borderline ovarian tumours

Male Factor Infertility

Background

- Male factor infertility represents 30% of cases of infertility
- Normal male reproductive function us managed by pituitary gonadotrophins:
  - FSH: it binds to Sertoli cells in the testes and stimulate production of spermatogonia and maturation of spermatocytes
  - LH: binds to Leydig cells and stimulates secretion of testosterone which is responsible for spermatid maturation and male secondary sexual characters

Causes

Approximately 50% of cases of male factor infertility are unexplained. The following factors contribute to or cause male factor infertility:

- **General causes:**
  - **Male age:** Sperm quality starts to decline significantly after the age of 50
  - **Endocrine disorders:** e.g. hyperprolactinemia, thyroid disorders
  - **Environmental factors:**
    - Heat and radiation
    - Lead and mercury
    - Sedentary life
    - Obesity
    - Heavy alcohol intake and smoking
    - Administration of anabolic-androgenic steroids (it can cause azoospermia, which may be reversed within 4-12 months, and may be treated with use HCG or HMG)
    - Recreational drugs (decrease libido and erectile dysfunction)

- **Pre-testicular causes (hypogonadotropic hypogonadism):**
  - Rare (< 1%)
  - Examples of causes include Kallmann syndrome, Prader-Willi syndrome, Laurance-Moon-Biedl syndrome, craniopharyngioma, and pituitary surgery.

- **Testicular causes (hypergonadotropic hypogonadism):**
  - Testicular failure is associated with azoospermia and low testosterone with subsequent rise in FSH and LH. Elevation of FSH only is seen in patients with isolated Sertoli failure
  - Examples of causes include bilateral cryptorchidism, radiotherapy, and chemotherapy

Varicocele

- Clinical significance is doubtful
- 25% of women with varicocele have abnormal semen parameters
- 11% of women with varicocele have normal semen parameters

- **Post-testicular causes (obstructive azoospermia):**
  - 40% of cases
  - Diagnosis is made by the triad of:
    ① Normal testicular size
    ② Normal FSH
    ③ Normal spermatogenesis on biopsy despite azoospermia
  - Examples of causes are surgical trauma, vasectomy, infection, and bilateral congenital absence of vas deferens

Clinical assessment

History

- History of pubertal development
- Sexual history
- History of genital and hernial surgery
- history of genitourinary infection
- History of prior diagnosis of infertility and treatment history

Examination

- General examination including height, weight, body mass index and blood pressure
- Assessment of secondary sexual characters e.g. hair growth and distribution
- Assessment of gynecomastia
- Assessment of testicular size and consistency (normal volume is 20 ml and normal consistency is firm
- Assessment penile and prostatic abnormalities
- Assessment of varicocele (using Valsalva maneuver)

Investigations

- **Semen analysis:**
  - **Prerequisites of semen analysis:**

    It should be done after 3 days of abstinence

    It should be tested within 1 hour of sample collection

  - **Normal parameters:**

Sperm volume	> 1.5 ml *
Sperm concentration	> 15 million/ml
Total sperm count	> 39 million
Sperm motility	> 32% progressive motility (A + B sperms)
Sperm morphology	> 4%

* A low volume < 1.5 may indicate retrograde ejaculation, post-testicular obstruction, androgen deficiency or incomplete sample collection

- **Hormonal profile:**
  - Serum FSH and LH
  - Testosterone level
  - Serum prolactin

- **Genetic testing:**
  - **Indications:**

    Non-obstructive azoospermia or severe oligospermia
  - **Tests:**
    - Karyotyping: most common genetic cause is Klinefelter syndrome (XXY)
    - Y chromosome microdeletion (Yq): it accounts for 10-15% of cases of azoospermia and 5-10% cases of severe oligospermia:
      - Azoospermia Factor a (AZFa), Azoospermia factor b (AZFb) microdeletion are associated with poor prognosis. Surgical retrieval should not be offered

- Azoospermia factor-c (AFZc) is associated with good prognosis and surgical retrieval is recommended

- **Ultrasound:**
  - **Scrotal ultrasound:**
    It is only indicated if testicular mass or varicocele is suspected during clinical assessment

  - **Renal ultrasound:**
    Renal ultrasound is indicated if vas deferens is absent to rule out renal anomalies (association is present in 30% of cases)

- **Testicular biopsy:**
  - **Indications:**
    Azoospermia, severe oligospermia
  - **Approach:**
    Percutaneous or open needle biopsy
  - **Results:**
    - Normal findings: normal cells, complete spermatogenesis
    - hypo-spermatogenesis: all cells are present in normal ratio but a small number
    - Maturation arrest: failure of spermatogenesis at a certain stage
    - Sertoli cell-only syndrome (Del Castiollo syndrome): no germ cells

Management

- **Medical treatment:**
  - Treatment of the cause: e.g. hyperprolactinemia, thyroid dysfunction, congenital adrenal hyperplasia (CAH)
  - Hormonal therapy: gonadotrophin injections in patients with hypogonadism

  Antioxidants may improve fertility. However, medical treatment should not be offered in idiopathic cases

- **Sperm retrieval, donor sperm or cryopreservation:**
  - These options are offered to patients with primary testicular failure
  - Sperm retrieval e.g. Microscopic testicular sperm extraction (microTESE) is associated with:
    - 100% success rate with obstructive cases (with better fertilization and clinical pregnancy rate)
    - 50% success rate with non-obstructive cases

- **Surgical management:**

Reversal of vasectomy	Varicocelectomy
• Outcomes of reversal are variable since restoration of anatomy may not restore fertility. Examples include development of anti-sperm antibodies and secondary epididymal obstruction • Technique and skills, and time since surgery affects outcomes of reversal	• Although it may improve sperm parameters if it is large enough to be clinically palpable and in the presence of low testosterone, impact of surgery on pregnancy rate is not clear • It is currently not recommended by NICE guidelines

- **Assisted reproduction:**

Procedure	Indication	Outcome
Intrauterine insemination	It may be offered in cases of mild male factor infertility (mild oligozoospermia) It may be tried for up to 6 cycles	Pregnancy rate is 8-16% per cycle
In-vitro fertilization with intracytoplasmic sperm injection (ICSI)	Severe male factor infertility	Pregnancy rate is 33% per embryo transfer (ET)

Polycystic Ovary Syndrome

Definition

Diagnosis of polycystic ovary syndrome (PCOS) is made by Rotterdam criteria. To meet diagnostic criteria, two of the three following criteria should be present:

- Hyperandrogenism or hyperandrogenaemia (clinical or biochemical)
- Ovulatory dysfunction
- Polycystic ovaries on ultrasound

Hyperandrogenism or hyperandrogenaemia	• Clinical hyperandrogenism: ▪ Features of clinical hyperandrogenism include acne, alopecia, and hirsutism ▪ Modified Ferriman Gallway is used to to assess hirsutism (a score ≥ 4-6 is consistent with hirsutism). Hirsutism is determined by terminal hair which should be differentiated from vellus hair (terminal hair is pigmented, thicker than 5mm) ▪ Ludwig visual scale is used to assess alopecia ▪ There is no scoring system for acne • Biochemical hyperandrogenism: ▪ Biochemical testing is indicated if clinical signs are unclear or absent. This feature is diagnosed by: ① Calculated free testosterone (Direct free testosterone is not used) ② Free androgen index **(the best test)** It equals (total testosterone/sex hormone binding globulin) X 100 ③ Calculated bioavailable testosterone

	▪ Women should be tested while on hormonal contraception. They should be stopped 3 months before testing ▪ Serum androstenedione and DHEAS may be tested if testosterone is not elevated in the presence of clinical hyperandrogenism (limited role in diagnosis of PCOS itself) ▪ If there is significant rise in androgen levels, androgen secreting tumours should be ruled out
Ovulatory dysfunction	• Irregular menstrual cycles are indicative of ovulatory dysfunction. Menstrual irregularities are related to age: ▪ Within 1 year of menarche: menstrual irregularities are normal ▪ Within 1-3 years of menarche: cycles are abnormal if shorter than 21 or longer than 45 days ▪ Beyond 3 years post-menarche (or perimenopausal): cycles are abnormal if shorter than 21 or longer than 35 days OR if cycle frequency is fewer than 8/year ▪ Primary amenorrhea is considered if there are no menses by 3 years after thelarche OR by age of 15 • Ovulatory dysfunction may occur with regular cycles. In these cases, anovulation is diagnosed by mid-luteal serum progesterone
Polycystic ovaries on ultrasound	• Ultrasound diagnosis should not be used within 8 years of menarche • Sonographic features include: ▪ Follicle number > 12 or ovarian volume >= 10 cm^3 with no corpus luteum, cysts or dominant follicles ▪ Each follicle is 2-9 mm in diameter (dominant follicle is 10 mm or more diameter) • Transvaginal ultrasound is the standard. If transabdominal ultrasound is used, only ovarian volume feature is used

Racial variations

caucasians have mild phenotype, but higher body mass index (BMI), Asians have lower BMI and less hirsutism, while Africans have higher BMI and metabolic features. Hirsutism is more prominent in Middle Eastern and Hispanics

Assessment

- In women in their reproductive years, PCOS is assessed if they complain of menstrual irregularities or infertility
- Adolescents with features suggestive of PCOS should be assessed 8 years after menarche. This includes those who experience significant weight gain in adolescence, PCOS features before using COCs, or if persistent symptoms of PCOS are present
- In postmenopausal women, PCOS is considered if there is long-term history of PCOS or PCOS symptoms, or continuous evidence of hyperandrogenism
  However, new onset or severe symptoms should be carefully assessed to rule out androgen secreting tumours or ovarian hyperthecosis
- Congenital adrenal hyperplasia (CAH) and androgen secreting tumours should be ruled out if:
  ① Hyperandrogenism symptoms are acute (less than 1 year between onset and consultation)
  ② Total testosterone is significantly elevated (> 5 nmol/l)
- CAH should be ruled out if there is family history of CAH or in Ashkenazi Jews. In these women, serum 17 hydroxyprogesterone is measured. If results are inconclusive, ACTH stimulation test cn be performed

Complications

- **Cardiovascular disease:**

  Cardiovascular risk should be assessed in women with PCOS. Women are at high risk of in the presence of other risk factors e.g. obesity, smoking, hypertension, impaired glucose tolerance, hyperlipidaemia, sedentary lifestyle. Conventional cardiovascular calculators are not validated in women with PCOS

  - **Weight monitoring:**
    Weight should be monitored every 6-12 months, this includes monitoring of body mass index (BMI) and waist circumstance (specially in Asian women and high-risk group)
  - **Lipid profile screen:**
    - Women with PCOS and high BMI (overweight or obese) should have lipid profile screen regardless of age. Lipid lowering medications are not offered as a routine

- Statins improve lipid profile if findings are abnormal. They also improve hyperandrogenaemia. However, they should not be used solely for this indication

- **Blood pressure monitoring:**
  - Blood pressure should be assessed at diagnosis, during treatment with combined hormonal contraceptives, and should be followed-up at least annually
  - Hypertension should be treated if:
    - Blood pressure is persistently higher than 140/90 despite lifestyle measures
    - Blood pressure is higher than 30/80 in the presence of diabetes (or other significant risk factors of cardiovascular disease)

- **Diabetes mellitus:**

Women with PCOS are at higher risk of type 2 diabetes, gestational diabetes, and glucose intolerance regardless of age and BMI. Obesity exacerbates the risk. Insulin resistance is present in 70-75% of patients with PCOS

- **Screening for type 2 diabetes:**
  - Screening is indicated every 1-3 years depending on the presence of other risk factors
  - Screening can be done using oral 75 gram 2-hour glucose tolerance test (GTT), fasting glucose or HgbA1C
  - Oral GTT is specifically used in women who have other risk factors of diabetes:
    ① Family history of diabetes
    ② Overweight or obesity (BMI > 25 or 23 in Asians)
    ③ History of glucose intolerance or impaired fasting glucose
    ④ Personal history of gestational diabetes or hypertension
    ⑤ Age > 40 years
  - Women with impaired fasting glucose (6.1-6.9 mmol/L) or impaired glucose tolerance (7.8-11.1 mmol/L) should be followed-up with annual GTT
- **Screening in pregnancy:**
  - Women who are planning to get pregnant or in early pregnancy should undergo 75 g oral GTT before conception or earlier than 20 weeks of gestation to rule out pregestational diabetes

- Women should be rescreened for gestational diabetes between 24 and 28 weeks of gestation (risk of gestational diabetes is doubled in women with PCOS)

- **Obstructive sleep apnoea (OSA):**
  - Women with PCOS are assessed for OSA only if clinically indicated (i.e. symptomatic) and treated to alleviate symptoms. There is inadequate evidence that management of OSA improves CVD risk
  - Screening is performed using Berlin tool. If findings are positive, women should be referred to a specialist for management

- **Endometrial cancer:**

PCOS increases risk of endometrial cancer by 3 folds. Endometrial cancer associated with PCOS often presents before menopause

  - Routine screening not recommended
  - Assessment using transvaginal ultrasound if there is prolonged amenorrhoea, abnormal uterine bleeding, or excess weight gain:
    - Endometrial thickness < 7 mm makes diagnosis of hyperplasia unlikely (sensitivity 100%, specificity 56%). In general, risk of hyperplasia increases by 1.5 folds with each 1mm
    - If there is increased endometria thickness, biopsy and/or hysteroscopy should be considered
  - Prevention may be achieved by administering combined oral contraceptives or progestins to PCOS patients whose cycles extend beyond 90 days (higher risk of endometrial hyperplasia). Progestins are recommended to induce bleeding at least every 3-4 months if patients remain amenorrheic
  - PCOS is not associated with higher risk of breast or ovarian cancer and no screening is required

- **Impaired quality of life:**
  - **Anxiety and depression:**
    - These disorders are common in PCOS patients specially adolescents
    - Depression/anxiety screening should be considered in each clinical visit

- If depression or anxiety is a concern on direct questions, PHQ or GAD7 screening tool should be used and referral should be considered if screening tests are positive

- **Psychosexual disorders:**
  - PCOS women may be at risk of psychosexual disorders
  - Female sexual function index may be used if suspected e.g. negative body image
- **Eating disorders:**

  If there is a concern, SCOFF screening tool may be used

Management

- **Lifestyle modifications:**

5-10% of weight reduction within 6 months may result in significant clinical improvement. This can be achieved through diet, exercise, and management of other related issues e.g. anxiety, depression, negative body image. In addition, lifestyle modifications are associated with improved long-term outcomes

- **Diet:**
  - Dietary regimens are similar to those used with general population
  - Target caloric intake is 1.200-1500 kcal/day (30% energy deficit)
- **Exercise:**

Goal	Requirement
Preventing weight gain	• 150 min/week of moderate exercise OR • 75 min/week of vigorous exercise For Adolescents, it should be 60 minutes/day
Modest weight loss	• 250 min/week moderate exercise OR • 150 min/week of vigorous exercise

Activity can be increased by 5% weekly

- **Behavioural strategies:**

They may improve outcomes by managing associated issues

- **Bariatric surgery:**
  It may be considered in women with BMI > 40 or > 35 in the presence of other risk factors after failure of other measures. Risk of mortality is 0.1-1% with these surgeries

- **Medical treatment:**

Combined oral contraceptives (COCs)	• COCs is given to adult women with PCOS to improve irregular bleeding, hyperandrogenism symptoms and to provide endometrial protection • COCs may be considered in adolescents with diagnosed or high risk of PCOS for the same indications • All COC types are comparable and can be used in treatment of PCOS symptoms including hirsutism (no specific type is recommended) • Combined use of 35 mcg of ethinyl oestradiol and cyproterone should be avoided because of venous thromboembolism risk with this combination
Metformin	• Metformin may be used in combination with COCs for metabolic benefits in women with BMI > 25 • Treatment is most beneficial among high metabolic risk group (e.g. glucose intolerance) • Metformin reduces androgen levels by approximately 10% • Gastrointestinal side effects are dose dependent and they are a common cause of drug discontinuation. Therefore, medication should start by 500mg, and increase every 1-2 weeks. Extended release forms are better tolerated
Anti-androgen drugs	• They may be added to COCs if hirsutism is not responsive after 6 months of COCs and cosmetic therapy • It may be used to treat alopecia • Their use should be combined to a contraception to avoid male under-virilization
Anti-obesity medications	They may be used as per general population in women with high BMI

- **Treatment of infertility:**
  - **Complete assessment:**
    Before commencing ovulation induction for PCOS, semen analysis of the partner and tubal assessment should be done
  - **Lifestyle modifications:**
    Similar to other symptoms, ovulation function and menstrual pattern improves with weight reduction and lifestyle modification
  - **Ovulation induction:**
    Pregnancy should be excluded prior to ovulation induction

Letrozole	• Letrozole is the first line of ovulation induction in women with PCOS and is superior to clomiphene citrate. • Letrozole is associated with lower risk of multiple pregnancy compared to clomiphene citrate
Clomiphene citrate (CC)	• CC may be used for ovulation induction • It may be combined to metformin in women with CC-resistance
Metformin	Metformin may be used to induction regimen to improve ovulation, pregnancy rate and live birth rate specially in women with BMI > 30
Gonado-trophins	• Gonadotrophins are the second line of ovulation induction (unless otherwise opted by the couple as a first line after explaining risks) • It is used in women with CC resistance and is superior to combined CC and metformin in these women • Gonadotrophins may be combined with metformin in the presence of CC resistance • Trigger of ovulation should be done only if 2 mature follicles are available and should be avoided if > 2 are present
Laparoscopic drilling	• Laparoscopic drilling: may be offered as a second line treatment to CC-resistant patients as an alternative to gonadotrophins • It may be offered as a first line if laparoscopy is performed for another indication • Laparoscopic drilling is particularly beneficial in women with normal BMI. In this group, 60% will have persistent ovulation and normalization of androgen for up to 20 years after treatment • Ovarian drilling is associated with risk of periaxial adhesions, small risk of diminishing ovarian reserve, and loss of ovarian function

- **Invitro fertilisation (IVF):**

  IVF is offered as a third line treatment

  - **Controlled ovarian hyperstimulation:**
    - Urinary or recombinant FSH without LH should be used
    - GnRH antagonist protocol is superior to long GnRH agonist protocol and is associated with shorter induction, fewer doses, and lower risk of ovarian hyperstimulation (OHSS)
    - Metformin (1000-2250 mg daily) may be used before and/or during FSH stimulation to improve pregnancy rate and reduce risk of OHSS. Treatment stops if pregnancy test is positive or with menses
  - **Trigger of ovulation:**
    - The lowest HCG dose should be used to trigger ovulation
    - Alternatively, GnRH agonist should be used specially in women at high risk of OHSS if they received GnRH antagonist protocol for stimulation and fresh embryo transfer is not planned
  - **Embryo transfer:** Single embryo transfer is used to minimize risk of multiple pregnancy

Anti-obesity medication and bariatric surgery are experimental in management of PCOS-related infertility

Once pregnancy occurs, women should be monitored closely during pregnancy because of increased risk of maternal and foetal complications

Ovarian Hyperstimulation Syndrome

Incidence

- After conventional in-vitro fertilization (IVF), 1/3 develop mild ovarian hyperstimulation syndrome (OHSS), 3-8% develop moderate to severe OHSS
- Incidence of hospitalization due to OHSS 0.3%

Protocols

- Women undergoing IVF should be counselled on risk of OHSS
- Verbal and written information should be provided including a 24-hour contact information for medical assistance
- All Infertility units should have local protocols for management of OHSS
- OHSS should be reported according to HEFA (Human Fertilisation and Embryology Authority) regulations. It should be reported within 12 hours verbally, and within 24 hours in a written form. OHSS should be reported to the initial infertility centre

Risk factors

- History of OHSS
- Polycystic ovary syndrome
- High antral follicle count
- High anti-Mullerian hormone

Protective factors

- GnRH antagonist regimen (compared to agonist regimens)
- Trigger with GnRH agonist (compared to hCG trigger)

Diagnosis

- OHSS is a clinical diagnosis
- Women should be seen and assessed if diagnosis is doubtful or if OHSS severity is likely more than mild

- Initial assessment should include haematocrit value, serum electrolytes, osmolality, and pelvic ultrasound. Elevated haematocrit, low sodium and osmolality are indicative of OHSS

Assessment of OHSS	
History	• Relation of symptoms to trigger time • Medications used for triggering • Number of follicles on the last scan and number of collected ova • Number of embryo transfer • History of polycystic ovary syndrome (PCOS)
Symptoms	• Abdominal bloating, distension, and pain • Nausea and vomiting • Shortness of breath • Diminished urine output • Leg and vulvar swelling • Venous thrombosis
Examination	• Assessment of vital signs • Assessment of dehydration • Assessment of oedema and body weight • Assessment of ascites, peritonism, and palpable mass • Measurement of abdominal girth • Assessment of pleural effusion and pulmonary oedema
Work-up	• Complete blood count (CBC) and haematocrit value • C-reactive protein (may be used monitor severity) • Serum urea and electrolytes • Serum osmolality • Liver function test • Coagulation profile • Serum hCG • Abdominal ultrasound

- In the presence of severe abdominal pain and pyrexia, other causes should be ruled out e.g.
  - Pelvic infection or abscess
  - Appendicitis
  - Ovarian torsion or cyst rupture
  - Bowel perforation

Classification

	Clinical features	Sonographic features	Laboratory features
Mild	Bloating and mild abdominal pain	Ovarian size < 8 cm	
Moderate	Moderate pain Nausea and vomiting	Ovarian size 8-12 cm	
Severe	Clinical ascites/hydrothorax Oliguria (< 30ml/hour, < 300ml/day)	ovarian size > 12 cm	haematocrit > 0.45 Serum sodium < 135 mmol/L Serum potassium > 5 mmol/L Serum osmolality < 282 mosm/kg hypoproteinaemia < 35 g/l
Critical	Tense ascites/severe hydrothorax Oliguria/anuria Thromboembolism Acute respiratory distress syndrome (ARDS)		Serum haematocrit > 0.55 White blood cell count > 25000/µl

Early onset OHSS occurs within 7 days of ovulation trigger and is caused by exogenous hormones

Late onset OHSS: occurs after 10 days, and is caused by endogenous hCG of pregnancy

Management

- **Outpatient management:**
  - **Indications:**
    Mild to moderate (some selected severe cases)
  - **Management:**
    - Women should be educated on monitoring fluid intake and output

- Women are encouraged to drink in response to thirst
- Paracetamol or codeine are safe for pain. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided (risk of renal function compromise)

In severe cases treated as outpatient, low molecular weight heparin should be considered. Paracentesis can be done as an outpatient procedure abdominally or vaginally under ultrasound guidance

- **Follow-up:**
  - Patients should be followed up every 2-3 days
  - Immediate assessment is indicated if:
    - Symptoms and signs of worsening OHSS develop e.g. worsening abdominal distension or pain, weight gain, shortness of birth
    - Urine output is less than 1000 ml/day or if fluid balance is positive by 1000 ml

    In these cases, labs should be repeated (haematocrit is the most important investigation)

- **Inpatient management:**
  - **Indications of hospitalization:**

    ① Failure of pain control
    ② Failure of hydration due to persistent nausea and vomiting
    ③ Unable to follow-up as outpatient
    ④ Worsening symptoms
    ⑤ Critical OHSS

  - **Management:**
    - **Setting:**

      Women with critical OHSS should be admitted to the intensive care unit
    - **Clinical assessment:**

      Daily assessment of body weight, abdominal girth, fluid chart and labs should be performed. More frequent assessment is required in critical and complicated cases
    - **Symptomatic treatment:**
      - Treatment includes antiemetics and analgesia
      - NSAIDs and any medications contraindicated in pregnancy should be avoided
    - **Hydration:**
      - Oral hydration is preferred, and I should be guided by thirst

- Persistent haemoconcentration despite volume replacement with IV colloids is an indication of invasive fluid input and anaesthetic management

- **Diuretics:**
  - Diuretics should not be used to treat oliguria in women with OHSS
  - Diuretics are only indicated if oliguria is present despite adequate fluid replacement and drainage of ascites
- **Paracentesis:**

Indications of paracentesis	Fluid replacement after paracentesis
• Ascites causing severe abdominal pain and distension, or respiratory compromise • Oliguria despite volume replacement (2 litres are usually aspirated)	If large fluid volume is removed by paracentesis, IV colloids are given (e.g. human albumin solution 25% 50-100g) over 4 hours. It can be repeated every 4-12 hours

- **Low molecular weight heparin (LMWH):**
  - LMWH should be considered in women with severe OHSS, critical OHSS or any admitted OHSS
  - Women with moderate OHSS may be managed with anti-embolic stocking or LMWH if indicated (depending on risk factors)

In women who develop unusual neurologic symptoms after several weeks of apparent improvement of OHSS, venous thrombosis should be suspected

- **Surgery:**

Surgery is only indicated if ovarian torsion, ovarian rupture, or ectopic pregnancy is diagnosed

Women with OHSS are at high risk of preterm labour and preeclampsia

Premature Ovarian Insufficiency

Definition

Premature ovarian insufficiency (POI) refers to the loss of ovarian function, which is manifested by amenorrhoea, oligomenorrhoea, decrease in oestradiol, and increase in gonadotropins, before the age of 40

Epidemiology

Incidence of POI is **1%**

Diagnosis

- **Establishment of diagnosis: (diagnostic criteria):**
  Diagnosis of POI is made by the following criteria:
  ① Oligomenorrhea/amenorrhea for at least 4 months AND
  ② Serum FSH > 25 IU/l on two occasions 4 weeks apart

- **Assessment of underlying causes and associations:**
  - **Chromosomal analysis:**
    It should be evaluated in all women with non-iatrogenic POI
    - **Turner syndrome:**

Positive cases	Negative cases
• Refer to endocrinologist, cardiologist, and geneticist • If Y chromosome is detected, gonadectomy is indicated (risk of malignancy)	Second analysis of epithelial cells is indicated if there is high clinical suspicion

- **Fragile-X syndrome:**
  - Refer to geneticists
  - Before testing for fragile X pre-mutation, patients should be counselled on sequences of a positive test result
  - If testing is positive, relatives should be offered genetic counselling and testing

  No autosomal genetic testing is indicated, except when specific mutations are suspected

- **Testing for autoantibodies:**

  They are checked, where POI cause is unknown or when immune disorders are suspected

  - **21OH-ab (or adrenocortical antibodies)**

    If antibodies are positive, patients should be referred to an endocrinologist to check cortical function
  - **(TPO-Abs):**

    If antibodies are positive, serum TSH should be checked annually

If these antibodies are negative, DO NOT repeat the test unless new relevant symptoms develop

Relatives of women with non-iatrogenic POI

- No testing is indicated unless genetic mutation is detected in the patient
- No preventive measures are indicated
- Potential risk of early menopause should be considered and discussed
- When planning for a family, fertility preservation may be a promising option. However, evidence is still lacking

Complications

- **Life expectancy:**
  - Life expectancy may be reduced significantly due to cardiovascular disease if not treated
  - Women should be advised on regular exercise, cessation of smoking, and maintaining healthy weight

- **Fertility:**

  Fertility is significantly reduced. However, there is a small chance of conception. Therefore, if pregnancy is not desired, contraception is advised

- **Obstetric outcomes:**
  - Spontaneous pregnancy after idiopathic POI or chemotherapy is NOT associated with higher obstetric or neonatal risks
  - Risk assessment and management should be individualized based on underlying cause e.g. cardiac risk in women treated with anthracycline

- **Bone loss:**
  - POI is associated with decreased Bone Mineral Density (BMD)
  - Bone protection may be achieved by:
    - Lifestyle measures: regular exercise, avoidance of smoking, maintaining normal weight, balanced diet with adequate calcium and vitamin D intake
    - Oestrogen replacement (combined oral contraceptives may be used instead of hormone replacement therapy but are generally less effective)
    - Bisphosphonate (only prescribed by osteoporosis specialist). They should not be taken if a woman is trying to conceive
  - Check BMD at time of diagnosis of POI in all women especially those with additional risk factors of osteoporosis:

If BMD is normal	Consider oestrogen replacement, no need to repeat DEXA scan
If there is osteoporosis	Start treatment and repeat DEXA scan every 5 years

- **Cardiovascular risks:**
  - When POI is diagnosed, CV risk is required with annual monitoring of blood pressure, weight, smoking status, lipid profile, fasting glucose, and HbA1c
  - Patients with cardiovascular risk should be advised on exercise, healthy weight, and cessation of smoking
  - Women with Turner syndrome should be evaluated by an experienced cardiologist. Oestrogen may be cardioprotective, and it should continue till the average age of menopause

- **Psychological and sexual dysfunction:**
  - Lifestyle and psychological support should be available
  - Routine screening on sexual function and sexual wellbeing is indicated
  - Hormonal replacement therapy improves these symptoms. If systemic oestrogen is not enough, local oestrogen is required to control dyspareunia. Lubricants can be used in women not using hormonal therapy
  - Patients should be adequately counselled on using testosterone for sexual dysfunction. Safety of this treatment is unknown. If androgen therapy is initiated, treatment should be evaluated after 3-6 months and should be limited to 24 months

- **Cognitive impairment:**
  - There is risk of cognitive deterioration after hysterectomy and/or oophorectomy in women younger than 50
  - Hormonal therapy should be considered till the natural age of menopause

Hormonal replacement therapy (HRT)

- **Treatment regimen:**
  - **Oestrogen:** 17β-oestradiol is superior to oethinyl-oestradiol or conjugated equine oestrogens
  - **Progestins:** Progestins should be used for endometrial protection. Oral cyclical combined treatment should be used if the uterus is present

- **Indications for HRT:**
  - Menopausal symptoms
  - Primary prevention of cardiovascular disease and bone protection

- **Contraindications:**
  - Breast cancer survivors
  - Using combined oral contraceptives instead of HRT for puberty induction is contraindicated

> - Migraine is not a contraindication to HRT. Change dose or use transdermal route if it becomes worse. I
> - Hypertension is not a contraindication to HRT. However, transdermal patch is preferred in hypertensive patients
> - Fibroid is not a contraindication to HRT
> - BRCA carrier status is not a contraindication to HRT
> - HRT does not increase risk of breast cancer if given prior to natural age of menopause
> - Women with prior venous thromboembolism requires referral to haematologist before starting HRT. Transdermal route is preferred

- **Follow-up:**

  HRT requires annual monitoring for assessment of symptoms, new risk factors and compliance

- **HRT in special situations:**
  - **Turner syndrome:**
    - HRT should be considered throughout reproductive lifespan till the natural age of the menopause
    - Puberty induction is achieved by 17 β-oestradiol starting with a low dose at age 12 with gradual increase of dose over 2-3 years. Cyclical progestogens are started after at least 2 years of oestrogen treatment or when breakthrough bleeding occurs

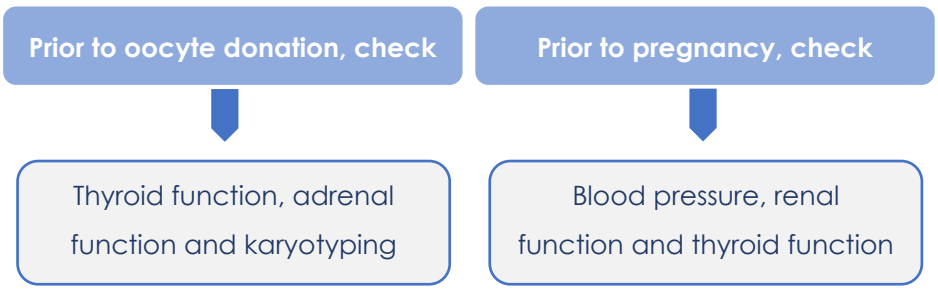
> Transdermal route achieves physiologic hormonal levels and it may be superior to oral route

- **Endometriosis:**
  - Combined oestrogen/progestin is indicated after oophorectomy for endometriosis
  - Treatment prevents/improves potential vasomotor symptoms and reduces disease recurrence
- **Obesity:**

  Transdermal route is preferred in obese and overweight

Management of infertility

- There is no intervention to raise chance of spontaneous pregnancy. Fertility preservation is not an option in women with diagnosed POI
- Oocyte donation should be offered to women interested in pregnancy
  - Counsel the patient that oocyte donation from sisters is associated with higher risk of cycle cancellation
  - Women who have medical risk of pregnancy may not be an appropriate candidate for oocyte donation



If there is history of high dose cyclophosphamide, mediastinal irradiation or anthracycline treatment, consider echocardiography before pregnancy and referral to a cardiologist

Tubal Factor Infertility

Assessment of tubal patency

Tubal factor infertility accounts for 11-30% of cases of infertility

- **Medical history:**
  If the following history is present, laparoscopy will be offered:
  ① History of pelvic inflammatory disease (PID) or sexually transmitted infections (STIs)
  ② History of complicated appendicitis
  ③ History of pelvic surgery

- **Laboratory assessment:**
  - Chlamydia antibody testing (C. trachomatis is the most common cause of acquired tubal pathology)
  - Micro-immunofluorescence is superior to ELISA and immunofluorescence assay.

- **Imaging assessment:**

	Procedure	Advantages	Disadvantages
Hystero-salpingography (HSG)	• The test is done between day 7-12 of the cycle. • It identifies site and laterality of tubal block. • Bilateral tubal block is associated with	• Good screening test for tubal block (53% sensitivity and 87% specificity) • Oil soluble contrast medium may have therapeutic effect (restores tubal	• Technical failure may occur due to failed catheterization or poor seal around cervix • False positive findings may

	72% decrease in fecundity rate	patency). However, it is not usually used because of risk of oil embolism, granulomas and reduced image quality	occur due to tubal spasm and debris • Risk of pelvic infection (1-3%) • Exposure to radiation
Hystero-salpingo-contrast-sonography (HyCoSy)	• Patient is placed in a semi-lithotomy position. Water soluble contrast medium is injected through the cervix using 5F or 7F catheter • Visualization of the uterus is best obtained by normal saline. Tubes are best visualized by hysterosalpingo-foam sonography	• Higher sensitivity, specificity compared to HSG • Higher tolerability than HSG	• Possibility of uncertain findings is higher (9%) compared to HSG (0.5%) • Intra-observer reliability is less specially on left side • Technical difficulties with obese women, acute retroversion, or high ovaries
Selective salpingography and tubal catheterization	The procedure is performed by passing a catheter under fluoroscopic control and direct injection of radio-opaque dye into tubal ostium	• It is a second line test to improve diagnostic accuracy of proximal tubal obstruction. • It decreases false positive results associated with HSG (due to tubal spasm or debris) • It can be used to measure tubal perfusion pressure (a prognostic factor)	With tubal catheterization: • Risk of tubal perforation is 2% • Risk of ectopic is 3%

- **Endoscopic assessment:**

Conventional laparoscopy	• It is the standard test for diagnosis of endometriosis and adhesions. Furthermore, it plays a therapeutic role in women with mild endometriosis and peri-adnexal adhesions • Laparoscopy may require general anaesthesia. The procedure is associated with risk of visceral and/or vascular injury (0.13%)
Transvaginal hydro-laparoscopy	• A fluid is instilled via a Veress needle that passes through the posterior fornix and a small diameter angled rigid scope is inserted. A dye is injected into the uterus and the scope is used to assess whether the dye comes out from the tube • Minor procedures may be performed through this approach e.g. drilling, adhesiolysis • The procedure can be performed in an outpatient setting with local anesthesia • Risk of bowel injury (0.61% rectosigmoid) is higher than conventional laparoscopy. The procedure should be avoided with obliterated Douglas pouch, fibroids, or endometriosis
Salpingoscopy	• The procedure is done during laparoscopy • An endoscopy is used to visualize lateral endosalpinx and tubal ampulla
Falloposcopy	• The procedure is done during hysteroscopy • It is used to visualize all endosalpinx
Fertiloscopy	• It is an outpatient procedure that combines hysteroscopy, Transvaginal hydro-laparoscopy and salpingoscopy • Findings are highly concordant with laparoscopic findings

Tubal surgery

- Standard management of tubal factor infertility is in-vitro fertilization
- Tubal surgery for infertility includes the following:
  - **Destructive tubal surgery:**
    - Salpingectomy and tubal occlusion are indicated in women with hydrosalpinx cases prior to IVF.
    - Best candidates are those with severe disease (bilateral hydrosalpinx, hydrosalpinx visualized by ultrasound)
    - Salpingectomy may double chance of pregnancy. However, patient will be dependent on IVF in future pregnancy

Diagnosis of hydrosalpinx

- 2D ultrasound is the standard method (sensitivity is 85%, specificity is 99%)
- Assessment if uterine cavity within 2 cycles prior to IVF may be performed using HyCoSy to assess tubal patency in the same setting
- Invasive methods to diagnose hydrosalpinx not detectable by ultrasound are not recommended unless there is recurrent implantation failure of high-quality blastocyst transfer

Primary salpingectomy vs interim salpingectomy (after failed IVF)

Outcomes are similar after a maximum of 3 IVF cycles

- **Reconstructive tubal surgery:** tubal pathology may be proximal, distal or combined

Site	Procedure	Success rate	Risk of ectopic
Proximal tubal disease (15%)	• Resection anastomosis	44%	7%
	• Hysteroscopic/fluoroscopic tubal catheterization (for less common causes e.g. tubal debris, intraluminal adhesions)	60–90% (30% pregnancy rate)	
Distal tubal disease (85%)	• Salpingo-ovariolysis	50%	5%
	• Fimbrioplasty	50%	7%
	• Salpingostomy	30%	9%
Reversal of tubal sterilization	• Re-anastomosis using microsurgical techniques (via laparotomy or laparoscopy) • Predictors are of success are age < 35 years and residual length > 4 cm	50%	5%

* Most common cause is salpingitis isthmica nodosa (SIN)

Unexplained Infertility

Contributing factors

Unexplained infertility is considered when no clear cause is detected after routine infertility investigations. Some underlying causes or contributing factors of infertility are suggested in this group of patients. However, these factors are not typically investigated, and management should be the same:

Factor	Risk factor	Effect
Age	Advanced maternal age	It adversely impacts number and quality of oocytes and is associated with increased risk of aneuploidy. These factors may result in failure of implantation and subsequent infertility
Body mass index	BMI > 30 or BMI < 19 (for both partners)	• In women: Abnormal weight adversely affects follicular development. Therefore, it affects embryo quality and implantation rate. • In men: it may cause erectile dysfunction, damage to sperm DNA
Smoking	Cigarette smoking (for both partners)	• In women, it affects ovarian reserve, tubal function, and uterine environment. • In men, it may affect sperm quality (affects sperm DNA, mitochondria, and fertilisation capacity)

Alcohol intake	Excessive alcohol intake especially in women	• In women, it may cause luteal phase defects, failure of implantation, and poor development of the embryo • In men, although it may affect sperm quality, clinical impact is unclear
Tubal dysfunction	Defective tubal function despite patency as a sequence of mild pelvic infection	Failure of oocyte and zygote transport
Fertilisation defects	Defects in the gametes that results in failure of proper fertilisation e.g. sperm DNA fragmentation	These defects may result in failure of fertilisation or high risk of miscarriage
Pelvic pathology	Endometriosis, adenomyosis, uterine fibroids	The role of these diseases is not clear. Although 30% of women with unexplained infertility may have mild endometriosis, it should still be treated similarly as outcomes are comparable. Ablation of endometriosis minimally alters live birth rate

Investigations

If there is no cause identified after basic investigations were performed, the following advanced investigations are recommended before diagnosis of unexplained infertility is made:

- **Assessment of ovulation:** if a woman has regular cycles, possibility of anovulation is low
- **Assessment of tubal patency**: these tests do not provide information on anatomical but not functional patency
- **Ovarian reserve tests**
- **Laparoscopy:**
  Laparoscopy is considered if 3-6 cycles of ovarian stimulation and timed intercourse fail
- **Assessment of uterine cavity**:
  Hysteroscopy (or saline Infusion Sonography, 3-dimensional ultrasound) is used to assess to assess polyps, septum, and adhesions. Treatment of these lesions may increase pregnancy rate

treatment

Expectant management	Tubal flushing or perturbation	In-vitro fertilisation (IVF)	Intracytoplasmic sperm injection (ICSI)
75% of couples with unexplained infertility may conceive spontaneously	Tubal flushing with oil or water-soluble media may increase pregnancy chance by 3 times This effect may be attributed to both mechanical and immunological action	IVF success rate is 30% per cycle in women younger than 37 years*	ICSI is indicated If IVF pregnancy fails due to failure of fertilisation (5-25% of cases). Every 5 ICSI procedures prevent 1 fertilisation failure **

* Intrauterine insemination (IUI) with or without ovarian stimulation is NOT recommended if regular intercourse is possible. Success rate is 9% per cycle and has similar multiple pregnancy rate to IVF

** Split IVF-ICSI may be considered to detect fertilisation defects and reduce risk of IVF failure

Recurrent Pregnancy Loss

Background

Definitions

Recurrent miscarriage describes 3 or more consecutive pregnancy losses. This obstetric problem affects 1% of all women.

Risk factors

Epidemiologic factors

- **Advanced maternal and paternal age:** women ≥ 35 years of age and men ≥40 years of age are at higher risk
- **Previous miscarriage:** the risk is 40% after 3 consecutive miscarriages (particularly in elderly women)

Environmental factors

- **Dose dependent smoking and caffeine:** insufficient evidence.
- **Heavy alcohol consumption:** it may increase the risk of sporadic miscarriage even if consumed in moderation (5 units or more/week)
- **Obesity:** increases the risk of sporadic and recurrent miscarriage

Anti-phospholipid syndrome

- It is the most important treatable cause of recurrent miscarriage
- Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage versus < 2% in low risk women

Genetic factors

Parental chromosomal rearrangements	In 2-5% of cases of recurrent miscarriage (mostly balanced reciprocal or Robertsonian translocation).
Embryonic chromosomal abnormalities	The risk of miscarriage in related to advancing maternal age. if present, the risk is 30-57% in next miscarriages

Anatomical factors

Uterine malformation

- More common in second rather than first trimester miscarriage
- Arcuate uteri are associated with second trimester miscarriage, while septate uteri are associated with the first trimester miscarriage

	Cervical weakness	It is typically characterized by recurrent second-trimester miscarriage preceded by spontaneous rupture of membranes or painless cervical dilatation
Endocrine factors	**Diabetes mellitus**	• Uncontrolled diabetes (indicated by high HBA1c) is at risk of first trimester miscarriage • Controlled diabetes is not a risk factor
	Thyroid dysfunction	• Anti-thyroid antibodies are a possible cause of recurrent miscarriage • Treated thyroid dysfunction is not a risk factor
	Polycystic ovary syndrome	• Insulin resistance, hyperinsulinemia and hyperandrogenemia may explain the risk • Elevated free androgen index predicts the risk of subsequent miscarriage in women with recurrent miscarriage
Immune factors	**HLA incompatibility**	There is no evidence to support a causal relationship between these factors and recurrent miscarriage
	Natural killer cells	• Uterine natural killer (uNK) cells differ in function and shape from peripheral natural killer (NK) cells • Altered peripheral NK cells may be related to recurrent miscarriage. However, this is not supported by evidence and should not be investigated routinely
	Cytokines	• The normal shift to T-helper-2 cell response (which produces anti-inflammatory cytokines e.g. IL 4, 6, 10) over T-helper-1 cell response (produces inflammatory cytokines e.g. IL2, IFN γ, TNF α) occurs during pregnancy. • Shift towards TH-1 response is suspected in recurrent miscarriage (needs further research)
Infective factors		• **TORCH and Listeria:** should not be accused or routinely screened • **Bacterial vaginosis:** first trimester infection predisposes to second trimester miscarriage/preterm labour. Oral clindamycin in early in the second trimester reduces the risk
Inherited thrombophilia		They are suggested causes of recurrent miscarriage and late pregnancy complications (possibly due to thrombosis of uteroplacental circulation)

Management

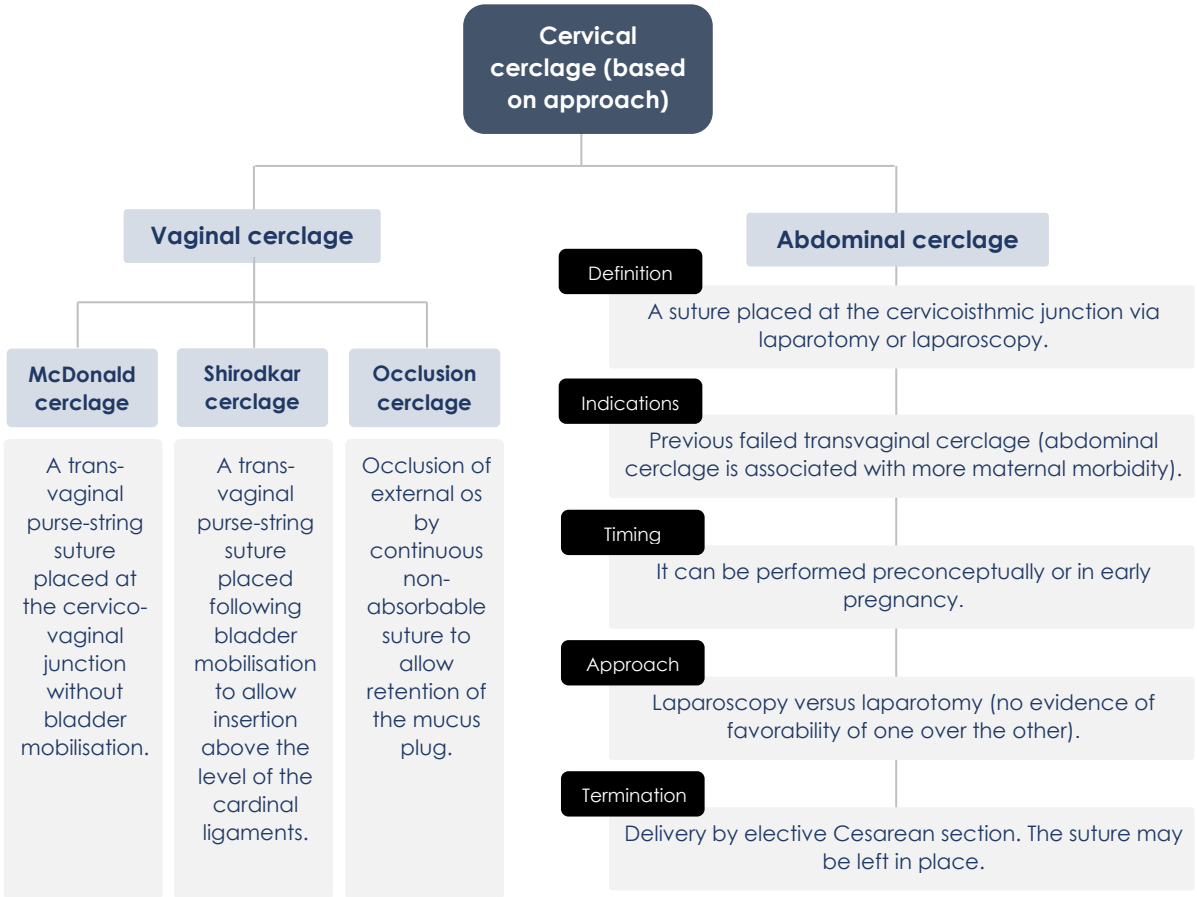
	Indications of testing	Assessment	Treatment
Anti-phospholipid syndrome	• Women with recurrent 1st trimester miscarriage • Women with 1 or more 2nd trimester miscarriage	Diagnosis is made by 2 positive tests at least 12 weeks apart of lupus anticoagulant or anti-cardiolipin antibodies (IgG and/or IgM, medium or high titre over 40 ml/l or > the 99th percentile)	Low-dose aspirin plus heparin (to prevent further miscarriage). This is no rule for steroids or immunoglobulin
Cytogenetic (genetic) analysis	Third and subsequent consecutive miscarriage(s) are indication for genetic analysis. This provides data about the prognosis.	Cytogenetic analysis of the products of conception. This may reveal: • **Fetal aneuploidy:** the risk of miscarriage decreases with increasing number of miscarriages (better prognosis in next the pregnancy). • **Unbalanced structural chromosomal abnormality:** if present, parental peripheral blood karyotyping of both partners is indicated. Referral to a clinical geneticist is indicated	Management of chromosomal rearrangements includes: • Trying another natural pregnancy with or without prenatal diagnosis test • Gamete donation. • Preimplantation genetic screening • Adoption.
Anatomical factors	All women with recurrent 1st trimester miscarriage and all women with 1 or more 2nd trimester miscarriages	• **Initial screening tests:** 2D pelvic ultrasound and/or HSG. • **Tests for definitive diagnosis:** combined hysteroscopy and laparoscopy ± 3D ultrasound scanning. The rule of MRI is controversial.	• **Congenital uterine malformations:** septum resection may be done (not supported by sufficient evidence) • **Cervical weakness:** cerclage (see later)
Thrombophilias	Women with second-trimester miscarriage (evidence on testing is conflicting)	screened for inherited thrombophilias including factor V Leiden, factor II (prothrombin) gene mutation and protein S.	Heparin therapy during pregnancy may improve the live birth rate (insufficient evidence)
Endocrine	All women with recurrent miscarriage (particularly first trimester)	Testing for diabetes, thyroid function test, polycystic ovary syndrome	Control of diabetes and thyroid function Progesterone, hCG, LH suppression, and metformin are not supported by evidence
Immune factors	These should not be routinely investigated or treated (only for research)		
Unexplained	Unexplained recurrent miscarriage has an excellent prognosis for future pregnancy without treatment. Only supportive care in early pregnancy assessment unit is needed. IVF and Preimplantation genetic screening do not improve outcome in unexplained miscarriage		

Fact Box: Anti-phospholipid syndrome

Antiphospholipid antibody syndrome is related to anti-phospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies and anti-B2 glycoprotein-I antibodies).

- **For assessment of Antiphospholipid syndrome:** lupus anticoagulant, anticardiolipin antibodies are assessed by:
  - ***For lupus anticoagulant:*** the dilute Russell's viper venom time test and platelet neutralisation procedure are more sensitive and specific than activated partial thromboplastin time test or the kaolin clotting time test.
  - ***For anticardiolipin antibodies:*** detected using a standardised ELISA.
- **Percussions and problems:**
  - Temporal fluctuation of antibody titres in individual women.
  - Transient positivity with infections.
  - Suboptimal sample collection and preparation and lack of standardization of laboratory tests can influence the results.


Cervical cerclage (based on indication)
History induced cerclage
Definition
Insertion of a cerclage based on woman's obstetric or gynaecological history.
Indications
• 3 or more previous preterm births and/or second-trimester losses.
• Suggestive features (e.g. painless dilatation of the cervix or rupture of the membranes before the onset of contractions) or history of cervical surgery are not evident to indicate cerclage.
• The use of prepregnancy diagnostic techniques for cervical weakness in suspected women (e.g. Cervical resistance index, hysterography or insertion of cervical dilators) is not evident as an indication of history induced cerclage.
Timing
A history-indicated suture is performed as prophylaxis in asymptomatic women at 12–14 weeks of gestation.
Ultrasound induced
Definition
Insertion of a cerclage based on cervical length shortening as diagnosed by transvaginal ultrasound
Indications
• Women with a history of 1 or more spontaneous mid-trimester losses or preterm births should be followed with transvaginal Sonography of cervical length. Cerclage is indicated if the cervix is 25 mm or less and before 24 weeks
• There is no indication if there is cervical funneling without shortening or shortening without history of spontaneous pregnancy loss or preterm labour.
• Women candidate for a history-indicated cerclage who have undergone the procedure can be followed up by sonographic surveillance for cervical shortening.
Timing
Whenever the cervix is shortened while the cervix is followed up between 14 and 24 weeks
Rescue cerclage
Definition
Insertion of cerclage as a salvage for premature cervical dilatation with exposed fetal membranes in the vagina.
Indications
A senior obstetrician-based decision is made for women with premature cervical dilatation and exposed fetal membranes in the vagina (diagnosed clinically or by ultrasound in response to specific complains e.g. vaginal bleeding, discharge, heaviness). The decision depends on 2 arms:
• The advantage of delaying labour for ± 5 weeks with 2-fold reduction in delivery < 34 weeks
• The high risk of severe preterm delivery and neonatal mortality and morbidity even with cerclage. There is also high failure rate of cerclage with > 4 cm cervical dilation and membrane prolapse beyond the external os
Timing
No evidence of superiority of immediate versus delayed procedure in either rescue or ultrasound indicated cerclage (however, delayed procedure may increase the risk of infection).

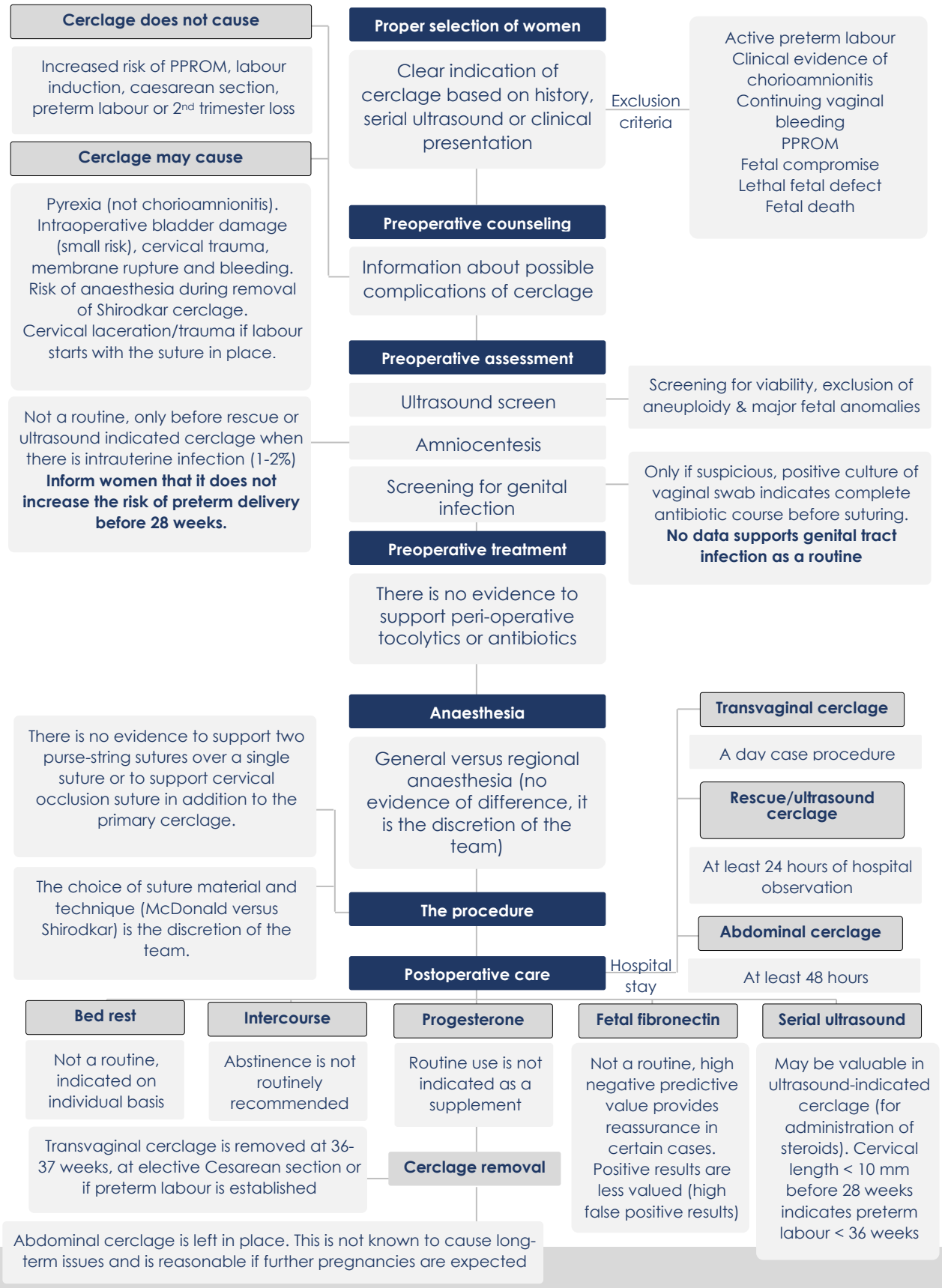


Fact Box: Special situations with abdominal cerclage

Delayed miscarriage or fetal death in women with an abdominal cerclage is a challenging situation that needs a senior obstetrician with adequate skill in this procedure to take a decision. Options include:

- Suction curettage or dilatation and evacuation (up to 18 weeks of gestation) through the stitch.
- Cutting the suture via a posterior colpotomy.
- Hysterotomy or caesarean section if other measures fail.

Management of cerclage



Fact Box: Management of cervical cerclage

- Preoperative white blood count and C-reactive protein before rescue cerclage (to diagnose infection) are not recommended unless clinically indicated.
- The value of amnioreduction before rescue cerclage is controversial.
- Postoperative upper cervical length (closed cervix above cerclage) is detected by transvaginal ultrasound following ultrasound indicated cerclage.

Appendix **Cerclage in certain obstetric situations**

Multiple pregnancy

The insertion of a history- or ultrasound-indicated cerclage in women with multiple pregnancies is not recommended because it may be associated with an increase in preterm delivery and pregnancy loss.

Uterine anomalies

History- or ultrasound-indicated cerclage is not recommended in women with müllerian anomalies.

Cervical trauma

History- or ultrasound-indicated cerclage is not recommended in women with previous cervical surgery (cone biopsy, large loop excision of the transformation zone or destructive procedures (laser ablation or diathermy) or multiple dilatation and evacuation.
The decision to place a cerclage in women who had radical trachelectomy should be individualized.

PPROM

- **In women with PPROM between 24 and 34 weeks of gestation:** if there is no evidence of infection or preterm labour, delayed removal of the cerclage (for 48 hours) may be beneficial for a course of prophylactic steroids to be completed and/or in utero transfer to be arranged.
  However, delayed suture removal until labour or until delivery is indicated not recommended because it is associated with an increased risk of maternal/fetal sepsis
- **In women with PPROM before 23 and after 34 weeks of gestation:** the risk of neonatal and/or maternal sepsis is considerable and the benefit of 48 hours of latency is minimal. Immediate removal of the cerclage is recommended.

Post-cerclage cervical shortening

- An ultrasound-indicated cerclage due to cervical length shortening is not recommended over expectant management because this may be associated with an increase in both pregnancy loss and delivery before 35 weeks of gestation.
- A rescue cerclage following history or ultrasound-indicated cerclage is an individualized decision according to circumstances.

Outflow Tract Disorders

Background

- The urogenital system develops from intermediate mesothelium of the peritoneal cavity and the endoderm of the urogenital sinus
- Incidence of congenital anomalies of the genital tract is 3%
- Abnormalities of uterine fusion with septate uteri constituting 90% of cases

Disorders

❶ Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome (Müllerian agenesis)

- Incidence is approximately 1:5000 female births
- Patients present as teenagers with primary amenorrhoea (absent uterus and vagina)
- There are normal secondary sexual characteristics due to functioning ovaries
- 40% of cases have associated renal abnormalities
- Treatment consists of psychological support and use of vaginal dilators to dilate the vaginal dimple to allow sexual intercourse
- Surgical treatment is also an option

❷ Imperforate Hymen

- The hymen is a thin membrane that occurs at the junction of the sinovaginal bulb with the urogenital sinus. It usually perforates during fetal life
- An imperforate hymen results in haematocolpos (blood collection in the vagina proximal to the hymen) forms after menstruation starts. It presents with primary amenorrhoea and severe cyclic abdominal pain
- Treatment involves a cruciate incision to relieve the obstruction and drain old blood. Hymen tissue can be excised or left

❸ Transverse vaginal septum

- Incidence is approximately 1:40,000
- Typical symptoms are increasing cyclical abdominal pain and primary amenorrhoea secondary to haematocolpos
- Treatment involves the excision of the septum and end to end vaginal anastomosis
- Vaginal mould is inserted for 10 days after surgery and use of vaginal dilators reduce the risk of stenosis
- Pregnancy rates are 100% with lower third obstruction, 40% with middle third and 20% with upper third obstruction

❹ Longitudinal vaginal septum

- These fusion defects may occur in the presence of two hemi-uteri and two hemi-cervices. Each cervix fuses with the urogenital sinus to create two hemi-vaginas
- Symptoms include difficulty in inserting tampons and painful sexual intercourse. It is sometimes diagnosed in pregnancy
- It may present with a mass if one hemi-vagina is obstructed forming a haematocolpos. In this case, there is no amenorrhoea since menses flow via the other hemi-vagina
- Excision of the septum is advised to treat symptoms, improve chance of conception, and reduce complications associated with vaginal delivery

Hirsutism

Background

- Hirsutism is the presence of coarse terminal hairs in a male pattern distribution in women
- Incidence is 5–15%
- Hirsutism is diagnosed by the presence of terminal hair only. Other types of hair (lanugo or vellus) do not indicate hirsutism
- Hair growth is influenced by circulating androgens:
  - Testosterone is converted within hair follicle to its more potent form dihydrotestosterone (by the enzyme, 5 alfa-reductase), which stimulates hair growth
  - Weaker androgens (e.g. androstenedione) are metabolized to testosterone and dihydrotestosterone in the skin
- Deficiency in thyroid or growth hormones alters anagen: telogen ratio.

Phases of hair growth

Anagen (active growing)

Catagen (involuting phase)

Telogen (resting, shedding)

Aetiology

Androgen excess

- Polycystic ovary syndrome (PCOS):
  - It is the most common cause of chronic anovulation
  - It accounts for 70-80% of cases
- Androgen-secreting tumours:
  - Incidence is 1 in 300 and 1 in 1000 of cases of hirsutism
  - Diagnosis is suspected clinically rather than laboratory. Diagnosis is considered if:
    ① Symptoms are rapid in onset and progression
    ② Hirsutism is associated with virilization
    ③ Cushingoid features are present
  - It is suspected if there are rapid symptoms, virilizing or associated with cushingoid.
- Non-classic congenital adrenal hyperplasia:
  - It accounts for 2% of cases
  - It is caused by 21-hydroxylase deficiency
  - It is associated with high level of 17 - hydroxyprogesterone
- Other endocrine cause: e.g. Thyroid dysfunction, acromegaly, Cushing syndrome, hyperprolactinemia.
- HAIRAN syndrome
- Medications: e.g. testosterone, danazol, anabolic steroids.

Non-androgen causes

Medications e.g. phenytoin, minoxidil, diazoxide, streptomycin, psoralen, penicillamine

Idiopathic

No cause is identified in 7% of cases

Clinical classification

Mild hirsutism	Moderate to severe hirsutism
• Ferryman Galloway score 8-15	• Ferryman Galloway score >15
• Treatment can be started based on clinical findings. Investigations are indicated if hirsutism is not responsive to treatment or is getting worse.	• Investigations are recommended to determine the cause: ▪ If testosterone is extremely high (>1.5–2 ng/ml), an underlying androgen-secreting tumour is likely. Pelviabdominal imaging may help to determine diagnosis ▪ 17-hydroxyprogesterone > 200 ng/dl is suggestive of non-classical congenital adrenal hyperplasia.

Treatment

Life-style changes

Weight reduction (5-10% of total weight) may improve hirsutism by 40-55% within 6 months

Physical methods

- Laser photo thermolysis is more appropriate for white women. After 3 sessions, it decreases hair density by approximately 30%
- Electrolysis, waxing, and shaving are not recommended

Hormonal treatment

Hormonal treatment provides the best effect after 9-12 months
Patients should be counselled that treatment needs time to get a response

Combined oral contraceptives	• It acts by reducing production of LH and increasing production of sex hormone-binding globulin, which binds to, and decreases level of free androgens • Drospirenone-containing pills have additional anti-androgen effect
Spironolactone	• It is superior to Finasteride and cyproterone • Its effect is better if combined with combined oral contraceptives
Cyproterone	• It reduces LH level and has peripheral antiandrogenic effect • It improves hirsutism by 15-40% after 6 months • Side effects include weight gain, depression, fatigue, and sexual dysfunction • Because of the low, bur serious risk of liver impairment, liver function tests should be checked before treatment and after 6 months
Finasteride	• It is a 5a-reductase inhibitor • It is superior to cyproterone (comparable efficacy with less side effects) • Combined oral contraceptives should be used with Finasteride to prevent pregnancy. Otherwise, there is risk of feminization of male foetuses
Flutamide	• It is an androgen receptor blocker • It is inferior to spironolactone (comparable efficacy with more side effects e.g. greenish urine, dry skin, liver impairment can be fatal)

Metformin	• In patients with PCOS, it may protect against type2 diabetes and cardiovascular disease • It decreases androgen level by 20%
Eflornithine	• It is an irreversible inhibitor of ornithine decarboxylase • It should be applied topically to the skin and face for 4 months. If no response, a longer trial is not recommended. Improvement is reported in 60% of cases

Antenatal Care Following Assisted Reproduction

Early pregnancy complications

During antenatal care of women who conceived by assisted reproductive technology (ART), obstetricians should be aware and recognize the risks associated with ART and adjust obstetric care to diagnose and manage these risks

Condition	Incidence/risk	Recommendations
Ovarian hyperstimulation syndrome (OHSS)	Mild: incidence ~33% Moderate - severe: incidence 3.1–8%	• Establish evidence-based protocols for assessment and management of OHSS • Admitting centre to inform fertility clinic about admission and diagnosis • Fertility clinic to report all cases of severe/critical OHSS to Human Fertilisation and Embryology Authority (HEFA)
Miscarriage	Incidence ~15–20%	• Manage as per spontaneous conception • Women should have access to specialist counsellors before, during and after ART
Ectopic pregnancy	Incidence ~1.4%	• Manage as per spontaneous conception • Women should have access to specialist counsellors before, during and after ART • In women who are reliant on ART to conceive, a salpingectomy may be preferential to salpingotomy
Subclinical Hypothyroidism (SCH)	-	• Current guidelines recommend treatment with levothyroxine in pregnant women with SCH but there is insufficient evidence that it improves clinical outcomes

Advanced pregnancy complications

Maternal complications		
Condition	Incidence/risk	Recommendations
Pregnancy-induced hypertension/pre-eclampsia	RR 1.49 Absolute increase in risk ~2%	Risk assessment as per local and national guidelines ART is not an indication for aspirin prophylaxis in the absence of other risk factors (which may be more common in women requiring ART to conceive)
Gestational diabetes mellitus	RR 1.48 Absolute increase in risk ~1%	Risk assessment as per local and national guidelines In the UK, ART is not an indication for a glucose tolerance test in the absence of other risk factors
Venous thromboembolism	Highest in first trimester	Risk assessment as per local and national guidelines In the absence of other risk factors, no need for anticoagulation

Foetal complications		
Condition	**Incidence/risk**	**Recommendations**
Structural abnormalities	30–40% increased incidence Absolute risk still low: 6.5–7%	No additional surveillance recommended
Fetal growth restriction	Odds ratio is 1.6	No additional surveillance in absence of other risk factors (which may be more common in women requiring ART to conceive)
Stillbirth	Odds ratio is 2.4	Consider induction of labour at term Elective caesarean section is more common in assisted conceptions (as per patients' request)
Preterm labour	Incidence of preterm labour is 11.2%. Incidence of very preterm labour is 2.6%	No additional surveillance recommended

- Congenital abnormalities may be more common in children conceived following intracytoplasmic sperm injection than standard IVF
- Unrecognised chromosomal abnormalities are more common in those requiring ART than in the general population
- Minor anomalies of the male genitalia as hypospadias may be related to subtle Y chromosomal genetic defects. The incidence of autosomal translocations or inversions is 4.6–13.7% and the incidence of Y chromosome microdeletions is 5–15% in oligozoospermic men
- Incidence of reciprocal balanced translocations is 7 times higher following ART
- There are concerns on foetal imprinting disorders such as Angelman and Beckwith–Weidermann syndromes following ART. However, the risk is extremely rare

Placental complications		
Condition	Incidence/risk	Recommendations
Placenta praevia	Odds ratio is 3.8	No additional surveillance recommended
Placenta accreta	Odds ratio is 2.3	No additional surveillance recommended
Placental abruption	Odds ratio is 1.9	No additional surveillance recommended
Vasa praevia	-	If low lying placenta diagnosed during anomaly scan, transvaginal ultrasound with colour Doppler to exclude vasa praevia should be undertaken

- Placental complications are likely related to ART itself rather than underlying maternal causes of infertility
- ART using a cryopreserved embryo is associated with lower risk of placenta praevia compared to fresh embryos

Reproductive endocrinology

Abstract

Although infertility presents a single symptom in gynaecology, the symptom is worthy of a complete subspecialty in the field. Fertility issues may be a sequalae of a spectrum of hormonal and structural abnormalities. Such abnormalities could be easily corrected with medical treatment or could require complex interventions including surgery and in vitro fertilization. In this chapter, we will discuss major causes of infertility and other related problems and how to diagnose and manage these disorders

Keywords

Infertility, PCOS, contraception, ovulation induction, IVF

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