Academy of Medicine
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Assessment and Management of Infertility at Primary Healthcare Level

AMS-MOH Clinical Practice Guidelines 1/2013

College of Family
Physicians, Singapore

MINISTRY OF HEALTH
SINGAPORE

Dec 2013

Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
1+ +	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2+ +	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1+ + and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1+ + or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2+ +
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

CLINICAL PRACTICE GUIDELINES

Assessment and Management of Infertility at Primary Healthcare Level

AMS-MOH Clinical Practice Guidelines 1/2013

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Contents

Foreword

Singapore has one of the lowest total fertility rates in the world, at 1.2 per female in 2011.[*] The effective management of infertility is important as infertility affects approximately one out of seven couples,[†] and is a contributing factor to Singapore's low total fertility rate.

When patients present at the primary care level with fertility issues, the primary care physician is in a unique position to provide patient education, begin initial investigations, make appropriate referrals, and offer ongoing counselling and support to couples. Early intervention, starting at the primary healthcare level, is especially important as advanced maternal age (35 years and higher) is associated with significantly decreased natural conception rate as well as the success rates of any artificial reproductive techniques.

The development of these evidence-based guidelines is therefore intended to assist primary care physicians as well as other healthcare professionals in the effective management of infertility at the primary healthcare level. I hope that these guidelines will be able to help couples seeking help for the treatment of infertility.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

[*] Department of Statistics Singapore. Key annual indicators. 2012 [cited 2012 July 10]; Available from: http://www.singstat.gov.sg/stats/keyind.html

[†] Adamson GD, Baker VL. Subfertility: causes, treatment and outcome. Best Pract Res Clin Obstet Gynaecol. 2003 Apr;17(2):169-85.

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

Definition and causes of infertility

GPP People who have not conceived after 1 year of regular unprotected sexual intercourse should be offered further clinical investigation including semen analysis and/or assessment of ovulation (pg 20).

GPP

Basic measures to optimise fertility potential

D Preconceptual counselling in those with advanced age should include a discussion of the increased risks of aneuploidy, spontaneous abortion and obstetric complications (such as delivery by Caesarean section and gestational diabetes) associated with increasing maternal age (pg 21).

Grade D, Level 3

D In women with advanced maternal age (>35 years), consultation with a reproductive specialist should be considered after 6 months of unsuccessful efforts to conceive (pg 22).

Grade D, Level 4

D Sexual intercourse every 2 to 3 days is recommended to optimise the chance of pregnancy; this is less stressful than timing intercourse to coincide with ovulation, which is not recommended unless in circumstances preventing regular intercourse (pg 22).

Grade D, Level 4

B Women trying to get pregnant should be advised against excessive alcohol consumption of more than 2 drinks a day and episodes of binge drinking can cause fetal harm (pg 23).

Grade B, Level 2++

C Men should be warned that excessive alcohol intake is detrimental to semen quality (pg 23).

Grade C, Level 2+

B Women should be informed that smoking is likely to reduce their fertility (pg 23).

Grade B, Level 1+

D Men who smoke should be informed that smoking is associated with reduced sperm parameters (pg 24).

Grade D, Level 4

B Women trying to achieve a pregnancy should be informed that a BMI of 19 to 29 is optimal (pg 24).

Grade B, Level 1+

B Couples seeking treatment for infertility should be routinely screened for usage of long term prescription medication, as some have been known to affect fertility (pg 25).

Grade B, Level 2++

C Couples seeking treatment for infertility should also be routinely screened for occupational hazards and given appropriate advice (pg 25).

Grade C, Level 2+

A Women intending to become pregnant should be informed that dietary supplementation with folic acid before conception and up to 12 weeks' gestation reduces the risk of having a baby with neural tube defects. The recommended dose is 0.4 mg per day. For women who have previously had an infant with a neural tube defect or who are receiving anti-epileptic medication, a higher dose of 5 mg per day is recommended (pg 25).

Grade A, Level 1++

GPP Women who are concerned about their fertility should be offered rubella susceptibility screening so that those who are susceptible to rubella can be offered rubella vaccination and be advised not to become pregnant for at least 1 month following vaccination (pg 26).

GPP

GPP To avoid delay in fertility treatment a specific enquiry about the timing and result of the most recent cervical smear test should be made to women who are concerned about their fertility. Cervical screening should be offered in accordance with the national cervical screening programme guidance (pg 26).

GPP

Assessment and basic investigations of infertility (including referral)

D Couples with fertility concerns should be interviewed separately as well as together, to bring out important history that a partner may want confidential from the other (pg 27).

Grade D, Level 4

D At the initial consult, each couple should be assessed for factors that may optimise or contraindicate the planned pregnancy, possible underlying causes of infertility, and the impact of infertility on the individual and relationship (pg 27).

Grade D, Level 4

D A detailed history-taking and clinical examination should be carried out for couples with fertility concerns. (Refer to Annex A for details.) (pg 27).

Grade D, Level 4

D Patients meeting these criteria should be referred to specialists:

- Women aged <30 years who are unable to conceive after regular unprotected intercourse for 2 years without any known reproductive pathology.
- Women aged >30 years who are unable to conceive after regular unprotected intercourse for 1 year without any known reproductive pathology.
- Patients with a known history of reproductive pathology, e.g. amenorrhea, pelvic inflammatory diseases, endometriosis.
- Patients with a known history or reason for infertility.
- The presence of male problems e.g. history of urogenital surgery varicocele, significant systemic illness.

(pg 27)

Grade D, Level 4

B Semen analysis should be conducted as part of initial investigation and should be compared to the following World Health Organization (WHO) Global reference values (fertile men) 2009:

- Volume: 1.5 ml or more
- pH: >7.2
- Sperm concentration: 15 million spermatozoa per ml or more
- Total sperm number: 39 million spermatozoa per ejaculate or more
- Motility (PR +NP%): 40% or more motile*
- Vitality (%): 58
- White blood cells (10^6 per ml): < 1.0
- Morphology (%): 4 or more

*PR = progressive motility (WHO 1999, grades a+b); NP = non-progressive motility (WHO 1999, grade c).
(pg 28)

Grade B, Level 2+

B If the first sperm analysis result is abnormal, the patient should be offered a repeat test from the same laboratory at least 3 months after the initial analysis (pg 28).

Grade B, Level 2++

GPP Severe abnormality (azoospermia or severe oligozoospermia) of the initial sperm sample however, warrants an immediate referral to a tertiary centre (see section on male infertility) (pg 28).

GPP

D Sperm function tests, screening for antisperm antibodies and postcoital tests on cervical mucus should not be offered as there is no evidence of effective treatment to improve fertility (pg 28).

Grade D, Level 4

D Women with fertility concerns should have their menstrual history taken (pg 29).

Grade D, Level 4

D Use of basal body temperature charts and home ovulation kits alone to predict ovulation should not be recommended to patients with fertility problems as these are not always reliable in predicting ovulation and leads to unnecessary anxiety and stress for the patient (pg 29).

Grade D, Level 4

B Women with infertility should be offered a blood test to measure mid luteal serum progesterone levels (about 7 days before the expected menstrual cycle). If cycles are irregular or prolonged, this test may need to be repeated again weekly thereafter until the next menstrual period (pg 29).

Grade B, Level 2++

B Follicle stimulating hormone and luteinizing hormone investigations should be done on day 2 to 3 of the menstrual cycle. Patients with high levels of gonadotrophins should be informed that they are likely to have reduced fertility (pg 29).

Grade B, Level 2+

B Women with infertility should be offered screening for Chlamydia trachomatis before undergoing instrumentation (pg 29).

Grade B, Level 2++

B If screening for Chlamydia trachomatis has not been carried out, prophylactic antibiotics should be given before uterine instrumentation (pg 29).

Grade B, Level 2++

GPP The result of semen analysis and assessment of ovulation should be completed before the clinician embarks on tubal assessment (pg 30).

GPP

B Hysterosalpingography (HSG) should be used as the first line investigation in tubal assessment (pg 30).

Grade B, Level 2++

A Chlamydia antibody titre (CAT) should be considered as an alternative to hysterosalpingography (HSG) if the resources are available (pg 30).

Grade A, Level 1+

B Laparoscopy and dye hydrotubation should be offered for women with comorbidities, such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis (pg 31).

Grade B, Level 2+

C Fertiloscopy and transvaginal hydrolaparoscopy should not be offered routinely as an alternative to laparoscopy hydrotubation as their diagnostic accuracy still require further evaluation (pg 31).

Grade C, Level 3

C When available, transvaginal ultrasound may be used as a screening test for the assessment of uterine cavity in subfertile women (pg 32).

Grade C, Level 2+

B Operative hysteroscopy should not be offered as an initial investigation (pg 32).

Grade B, Level 2++

Ovulatory dysfunction

C For patients with functional hypothalamic pituitary failure who desire fertility, ovulation induction therapies may be indicated. However, the achievement of a healthy weight and modification of lifestyle should be tried first (pg 34).

Grade C, Level 2+

C Where amenorrhoea (which occurs in functional hypothalamic pituitary failure women) has occurred for longer than a year in duration, assessment of the bone mineral densities should be considered (pg 34).

Grade C, Level 2+

GPP When drug-induced anovulation is suspected, medications should be altered or discontinued if possible. If the medication which causes anovulation cannot be altered or discontinued, referral to a reproductive medicine specialist for further management is indicated (pg 35).

GPP

GPP Patients with anorexia nervosa should be referred to a mental-health care provider for further management (pg 35).

GPP

GPP Patients with organic lesions of the hypothalamus and pituitary gland should be referred to a reproductive specialist (pg 35).

GPP

C Women should be told that premature ovarian failure is not a definitive diagnosis of infertility as approximately 5-10% of these women may conceive spontaneously and unexpectedly after the diagnosis (pg 36).

Grade C, Level 2+

C Women with spontaneous premature ovarian failure should be referred to an endocrinologist to investigate asymptomatic autoimmune adrenal insufficiency (pg 36).

Grade C, Level 3

C Fertility options in women with premature ovarian failure include the use of an oocyte (egg) donor or embryo donor in an Assisted Reproductive Program (ARP) (pg 36).

Grade C, Level 2+

A Dopamine receptor agonists are the first line treatment for patients with idiopathic hyperprolactinaemia secondary to pituitary adenoma (pg 36).

Grade A, Level 1+

C Surgical trans-sphenoidal resection of microadenomas should not be the primary therapeutic approach for patients with hyperprolactinaemia secondary to pituitary adenoma (pg 37).

Grade C, Level 2+

Managing infertility in polycystic ovary syndrome (PCOS)

D Diagnosis of polycystic ovary syndrome should only be made when other aetiologies have been excluded (thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinaemia, androgen secreting tumours and Cushing's syndrome) (pg 38).

Grade D, Level 4

D The following investigations should be done to exclude other aetiologies before a diagnosis of polycystic ovary syndrome should be made:

- Baseline laboratory screen:
  - 0 Thyroid function test (thyroid dysfunction can present as amenorrhoea)
  - 0 Serum prolactin (hyperprolactinaemia can present as amenorrhoea)
  - 0 17 hydroxyprogesterone (only in the presence of clinical or biochemical evidence of hyperandrogenism) (Congenital adrenal hyperplasia can present as amenorrhoea and hyperandrogenism)
  - 0 Free Androgen Index (FAI = total testosterone divided by sex hormone binding globulin x 100 to give a calculated free testosterone level) or free/bioavailable testosterone. (hyperandrogenism as one of the criteria needed to diagnose Polycystic ovary syndrome)

- Diagnostic Imaging:
  Pelvic ultrasound scan to determine features in accordance with the Rotterdam criteria as well as to exclude androgen secreting tumours of the adrenals or ovaries.
  (pg 39-40) **Grade D, Level 4**

D The following are optional tests in the diagnosis of polycystic ovary syndrome:

- Gonadotrophin may be required to determine cause of amenorrhoea (primary ovarian failure)
- Fasting insulin is not necessary routinely but may be considered in those undergoing ovulation induction
- ACTH stimulation test needs to be considered if morning 17 hydroxyprogesterone >5nmol/L in order to exclude non-classical congenital adrenal hyperplasia.

(pg 40) **Grade D, Level 4**

GPP Before any intervention is initiated for women with polycystic ovary syndrome, preconceptional counselling should be provided emphasizing the importance of life style, especially weight reduction and exercise in overweight women, smoking and alcohol consumption (pg 41).

GPP

A The recommended first-line treatment for ovulation induction remains the anti-estrogen clomiphene citrate (pg 41).

Grade A, Level 1+

A Patients with polycystic ovary syndrome should be informed that there is an increased risk of multiple pregnancy with ovulation induction using clomiphene citrate (pg 41).

Grade A, Level 1+

GPP Ultrasound monitoring of follicular development at least during the first cycle of treatment with clomiphene is advisable to ensure that women receive a dose that minimises the risk of multiple pregnancy. (pg 41)

GPP

D Recommended second-line intervention for infertility in women with polycystic ovary syndrome is either exogenous gonadotrophins or laparoscopic ovarian surgery (pg 42).

Grade D, Level 4

GPP The use of exogenous gonadotrophins is associated with increased chances for multiple pregnancy and, therefore, intense monitoring of ovarian response is required (pg 42).

GPP

B Laparoscopic ovarian surgery alone is usually effective in <50% of women and additional ovulation induction medication is required under those circumstances (pg 42).

Grade B, Level 2++

B Low dose therapy with gonadotrophin is recommended as it offers significant lower risk of ovarian hyperstimulation in women with polycystic ovary syndrome (pg 42).

Grade B, Level 2++

C The recommended third-line treatment for infertility in women with polycystic ovary syndrome is in vitro fertilization (pg 42).

Grade C, Level 2+

GPP As aromatase inhibitors are currently not licenced for use as ovulation induction, we do not recommend the clinical use of aromatase inhibitors for routine ovulation induction (pg 43).

GPP

D The routine use of metformin in ovulation induction is not recommended as monotherapy or in combination with clomiphene citrate (pg 43).

Grade D, Level 3

B There is currently insufficient evidence to suggest improvement in live birth rates on treatment with metformin before or during assisted reproductive technique cycles and its routine use is not recommended (pg 43).

Grade B, Level 2+

A The combined use of metformin and clompihene citrate is recommended for women with clomiphene resistance especially if they are obese (BMI > 27.5 kg/m^2) (pg 44).

Grade A, Level 1+

GPP There is insufficient evidence to recommend the widespread use of metformin in pregnant women with polycystic ovary syndrome (pg 45).

GPP

GPP Young women diagnosed with polycystic ovary syndrome should be informed of the possible long-term risks to health that are associated with their condition (pg 45).

GPP

B Patients presenting with polycystic ovary syndrome, particularly if they are obese or have a strong family history of type 2 diabetes or are over the age of 40 should be offered a glucose tolerance test (pg 45).

Grade B, Level 1+

B Women diagnosed with polycystic ovary syndrome should be asked (or their partners asked) about snoring and daytime fatigue/ somnolence and informed of the possible risk of sleep apnoea, and offered investigation and treatment when necessary (pg 46).

Grade B, Level 2++

B Clinicians should continue to identify cardiovascular risk factors (including blood pressure, cholesterol, triglycerides and high density lipoprotein cholesterol) in women with polycystic ovary syndrome and treat these accordingly (pg 46).

Grade B, Level 2++

A Women diagnosed with polycystic ovary syndrome should be advised regarding weight loss through diet and exercise (pg 47).

Grade A, Level 1+

B Combining metformin and lifestyle modification, including calorie restriction and exercise to facilitate weight loss and attenuate central adiposity is recommended for obese patients with polycystic ovary syndrome. Higher doses of metformin, up to 2.5g/day, may be recommended to achieve an optimal response (pg 47).

Grade B, Level 1+

D Ovarian electrocautery should only be reserved for slim women with anovulatory polycystic ovary syndrome (pg 48).

Grade D, Level 3

B Women who have been diagnosed as having polycystic ovary syndrome before pregnancy, especially those requiring ovulation induction for conception, should be screened for gestational diabetes before 20 weeks of gestation, with referral to a specialist obstetric diabetic service if abnormalities are detected (pg 49).

Grade B, Level 1+

Male infertility

GPP Both male and female partners should be investigated concurrently for couples who present for infertility assessment (pg 50).

GPP

B Semen analysis should be done as the primary investigation for male infertility (see section 4) (pg 50).

Grade B, Level 2+

GPP Hormonal investigations for male infertility should be limited to FSH, LH and Testosterone levels (pg 50).

GPP

D Karyotyping and Y microdeletion test should be considered for men with non-obstructive azoospermia (pg 51).

Grade D, Level 3

GPP Referral to a tertiary center should be made for:

- Patients with azoospermia
- Patients with severe semen abnormality
- Patients with clinical evidence of varicocele
- Patients with erectile dysfunction
- Patients with anejaculation
- Patients with retrograde ejaculation
- Patients with suspected androgen deficiency

- Couples who will benefit from assisted reproductive technologies.

(pg 51)

GPP

GPP General advice such as cessation of smoking, steroid use and withdrawal of offensive medication could be given at primary setting (pg 51).

GPP

GPP Couples trying to conceive should generally avoid exposure to harmful chemicals (e.g. by wearing protective clothing when appropriate to reduce risk of exposure to harmful chemicals) (pg 51).

GPP

A Antioxidant supplementation for subfertile males may be used to improve live birth and pregnancy rates for subfertile couples (pg 52).

Grade A, Level 1+

GPP Referral to fertility specialist should be facilitated if the female is over 35 years old (pg 52).

GPP

B Varicocele treatment may be considered when the female evaluation is normal and the man has a palpable varicocele with suboptimal semen quality (pg 52).

Grade B, Level 2++

GPP In azoospermia, spermatozoa may be retrieved from the testis/epididymis using a variety of techniques such as testicular sperm aspiration (TESA), testicular sperm extraction (TESE), microsurgical epididymal sperm aspiration (MESA) and percutaneous epididymal sperm aspiration (PESA). Sperm cryopreservation should be offered at the time of sperm retrieval (pg 53).

GPP

GPP When retrograde ejaculation is suspected, post-ejaculatory urinalysis (looking for presence of sperm and fructose) may be requested (pg 53).

GPP

C It is important to exclude retrograde ejaculation and anejaculation from other causes of azoospermia as drug therapy may be used to allow spontaneous conception (pg 53).

Grade C, Level 3

D When available, penile electrovibration and transrectal electroejaculation should be considered before embarking on surgical sperm retrieval and intracytoplasmic sperm injection (pg 54).

Grade D, Level 4

GPP Delayed ejaculation and anorgasmia may have biogenic or psychogenic aetiology. After exclusion of medical illnesses, referral could be made to a sexual therapist who could help in education, counselling and instruction in revised sexual technique to maximise sexual arousal (pg 54).

GPP

B Management of premature ejaculation depends on the underlying aetiology, patient's needs and preference. For lifelong premature ejaculation, selective serotonin reuptake inhibitors (SSRIs) are preferred while for secondary premature ejaculation, behavioural techniques are the preferred option (pg 54).

Grade B, Level 2++

B Patient with premature ejaculation should be informed that daily SSRI is more effective than on-demand SSRI treatment. On demand use of topical anaesthtics and tramadol may prolong intravaginal ejaculatory latency (pg 54).

Grade B, Level 2++

B Phosphodiesterase type 5 (PDE 5) inhibitors should not be prescribed to men with premature ejaculation when there is no associated erectile dysfunction (pg 54).

Grade B, Level 2++

GPP All patients presenting with erectile dysfunction should have their history taken and assessment done to identify cardiovascular risk factors such as hypertension, hyperdyslipidaemia and diabetes as these are commonly associated with cardiovascular disease (pg 55).

GPP

GPP Although referral to a fertility clinician can help with fertility issues by doing in-vitro fertisilisation/intra cytoplasmic sperm injection, multidisciplinary referral should be considered in the following situations:

- complex endocrine disorder (to endocrinologist)
- history of pelvic or perineal trauma, penile deformities or penile implants (to urologist)
- psychosocial issues or relationship problems (to counsellor, psychologist, psychiatrist).

(pg 55)

GPP

D First line treatment for erectile dysfunction should include patient counseling and education, risk factor modification (smoking cessation, reduce alcohol, improved diet and exercise, weight loss) and addressing psychosocial issues (relationship difficulties, anxiety) (pg 55).

Grade D, Level 4

A Oral agents (PDE5 inhibitors) such as tadalafil (Cialis), Sildenafil (Viagra), Vardenafil (Levitra) have similar efficacy, tolerability and safety for the treatment of erectile dysfunction. Choice of drug should be individualised based on patient needs (pg 55).

Grade A, Level 1+

D Phosphodiesterase type 5 (PDE 5) inhibitors should not be taken with nitrate-containing medications for erectile dysfunction as the concurrent use of nitrate medications and PDE 5 inhibitors is contraindicated. Patients need to be educated that they require sexual stimulation for these medications to work (pg 56).

Grade D, Level 4

C Vacuum devices and rings are suitable for men with erectile dysfunction who have contraindications for pharmacologic therapies. It should only be prescribed by clinicians who are familiar with its use (pg 56).

Grade C, Level 2+

C Men with erectile dysfunction who are resistant to phosphodiesterase type 5 (PDE 5) inhibitors should be referred to a urologist as combination therapy (PDE 5 inhibitor plus vacuum erectile device, intraurethral medication, intracavernosal injection, androgen supplement, α-blocker) or invasive treatment such as penile implant may be considered (pg 56).

Grade C, Level 2+

D Hormone assays should be performed to test for androgen deficiency. As there is diurnal rhythm in hormone secretion, blood samples for testosterone should be taken in the morning (pg 56).

Grade D, Level 4

GPP The result of hormone assays should be interpreted with caution as there is no appropriate standardised reference range for all laboratories. Therefore, clinical assessment (recent changes in sexual function, patterns of body hair and secondary sexual characteristics) is important to diagnose androgen deficiency (pg 56).

GPP

B When fertility is desired, testosterone should not be used to treat androgen deficiency. When the causes are secondary to hypothalamus or pituitary disorders, Human Chorionic Gonadatropin (HCG) injection may be used instead (pg 57).

Grade B, Level 2++

Tubal-Infertility (Preventive strategies & treatment)

C Women with high risk profiles (early sexual debut, multiple partners, non-compliance with safe sexual advice, etc.) should be screened for Chlamydia trachomatis in their urogenital tracts and be treated promptly to prevent future repercussions including tubal infertility (pg 58).

Grade C, Level 2+

C Partners of Chlamydia positive women should be tested and treated as well, to prevent re-infection of the treated women. Positive cases should be referred to the Department of STI Control for contact tracing and treatment (pg 58).

Grade C, Level 2+

A Oral doxycycline (100mg twice daily for 7 to 14 days) and azithromycin (1gm stat dose) are recommended antibiotics against Chlamydia trachomatis (pg 58).

Grade A, Level 1++

B High risk women who are scheduled for invasive instrumentation of the reproductive tract should be empirically treated for Chlamydia, to prevent ascending infection of the upper reproductive tract, or re-activation of past infection (pg 59).

Grade B, Level 2++

GPP Assessment of tubal patency should be considered in all infertile women (pg 59).

GPP

B Women with low risk for tubal disease (based on the history and physical examination), should be screened with a HSG for tubal patency as part of assessment for infertility (pg 59).

Grade B, Level 2++

Endometriosis

C A detailed vaginal examination with bimanual palpation, and / or rectal examination is essential to detect nodular lesion on the uterosacral ligaments, rectovaginal septum, or other surfaces accessible digitally. The detection rate of physical examination is better during menstruation (pg 60).

Grade C, Level 2+

C Magnetic resonance imaging may be considered as an adjunctive investigation tool to laparoscopy in the diagnosis of deeply infiltrating endometriosis (pg 61).

Grade C, Level 2+

B Serum CA125 should not be used in the routine investigation of endometriosis due to inadequate specificity and sensitivity (pg 61).

Grade B, Level 2++

D Diagnosis of endometriosis should be made at laparoscopy unless disease is visible in the vagina or elsewhere (pg 61).

Grade D, Level 4

C Diagnostic laparoscopy for endometriosis should not be undertaken within 3 months of ovarian suppressive treatment, as there is a high risk of missing the lesions and leading to a false negative result (pg 62).

Grade C, Level 2+

1 Introduction

1.1 Objectives and scope of guideline

These guidelines are intended to assist primary care physicians and other healthcare professionals in the management of infertility. This includes increasing awareness and educating about the scale of fertility problems, recognising the various causes of infertility, natural fecundity, and success rates of in-vitro fertilisation (IVF) treatment in relation to female age.

These guidelines also seek to establish clear referral criteria to guide primary care physicians.

1.2 Target group

The primary target group of these guidelines are primary care physicians. Nevertheless, these guidelines would also benefit all healthcare professionals involved in the management of infertility.

1.3 Guideline development

These guidelines have been produced by a committee appointed by the Ministry of Health and the Academy of Medicine, Singapore, with representation from gynaecologists, fertility specialists, urologists and family physicians. They were developed using the best available current evidence and expert opinion.

1.4 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review 3 years after publication, or if new evidence appears that requires substantive changes to the recommendations.

2 Definition and causes of infertility

2.1 Definition

Infertility affects approximately one in seven couples. Established causes of infertility include:[1]

- Ovulation factor infertility (20%)
- Tubal factor infertility - preventing fertilization (35%)
- Uterine factor infertility – impairing embryo implantation or causing miscarriage
- Endometriosis and peritoneal factor infertility – the presence of viable endometrial tissue outside the uterine cavity that prevents pregnancy in a variety of ways
- Male factor infertility (30-40%) – that result in an abnormal semen analysis
- Unexplained (5-10%) - not identifying a cause for infertility does not necessarily mean that the couple is normal or has no problem

Subfertility is defined as the failure to conceive after regular unprotected sexual intercourse for 1 year in the absence of known reproductive pathology.[2]

In all cases of infertility, the prognosis of a pregnancy is greatly influenced by:[3]

1. Age of woman
2. Duration of infertility
3. Occurrence of a previous pregnancy

GPP People who have not conceived after 1 year of regular unprotected sexual intercourse should be offered further clinical investigation including semen analysis and/or assessment of ovulation.

GPP

3 Basic measures to optimise fertility potential

The role of the general practitioner is to initiate the investigation of both partners and ensure timely onward referral to a specialist clinic. It is also important to provide couples with general evidence-based information to help optimise their natural fertility at a primary healthcare level.

One of the measures of fecundity (ability to reproduce) is fecundability (the monthly probability of pregnancy); which is only about 15%. Theoretically, in women under the age of 36 years, the cumulative probability of pregnancy is 60% at 6 months of trying, about 85% at the end of first year and 95% by the end of the second year.[4] Fertility in women peaks at ages 20 to 24 years, decreases little till 30 to 32 and then declines progressively, more rapidly after 40 years.[5] Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women over age 35 years.[6]

There are increased risks of aneuploidy, spontaneous abortion and obstetric complications (such as delivery by Caesarean section and gestational diabetes) associated with increasing maternal age.[7] Conception rates are more than halved by 35 or over.[8]

The effect of age on male infertility is less certain though it has been observed that even men older than 35 have half the chance of achieving a pregnancy compared with men younger than 25.[9] There is a concomitant increase in chromosomal anomalies in offsprings of males after 55 years.[10-11]

D Preconceptual counselling in those with advanced age should include a discussion of the increased risks of aneuploidy, spontaneous abortion and obstetric complications (such as delivery by Caesarean section and gestational diabetes) associated with increasing maternal age.

Grade D, Level 3

D In women with advanced maternal age (>35 years), consultation with a reproductive specialist should be considered after 6 months of unsuccessful efforts to conceive.

Grade D, Level 4

3.1 Frequency of intercourse

Sexual intercourse every 2 to 3 days is advised over timed intercourse as spermatozoa survive in the female reproductive tract for up to seven days after insemination and this reduces emotional stress.[12-13] Abstinence intervals greater than 5 days may adversely affect sperm counts, abstinence intervals as short as 2 days are associated with normal sperm densities.[14] However, devices designed to determine or predict the time of ovulation may be useful for couples who have infrequent intercourse.[6]

D Sexual intercourse every 2 to 3 days is recommended to optimise the chance of pregnancy; this is less stressful than timing intercourse to coincide with ovulation, which is not recommended unless in circumstances preventing regular intercourse.

Grade D, Level 4

3.2 Alcohol consumption

A prospective survey of 7393 women in Stockholm observed that the risk of infertility was significantly increased (relative risk [RR] 1.59; 95% CI, 1.09–2.31) among women who consumed two alcoholic drinks/day, but the risk of infertility was decreased (RR 0.64; 95% CI, 0.46–0.90) for those who consumed less than one drink per day.[15] In general, moderate alcohol (one to two drinks per day) has no demonstrable adverse effect on fertility.[6] Although the effect of alcohol on female infertility is uncertain, excess alcohol intake and episodes of binge drinking can be associated with fetal harm in pregnancy.[16-17] In men, excessive alcohol intake is detrimental to semen quality.[18-21]

B Women trying to get pregnant should be advised against excessive alcohol consumption of more than 2 drinks a day and episodes of binge drinking can cause fetal harm.

Grade B, Level 2++

C Men should be warned that excessive alcohol intake is detrimental to semen quality.

Grade C, Level 2+

3.3 Caffeine consumption

Most studies produced conflicting results. Overall, moderate caffeine consumption (one to two cups of coffee per day or its equivalent) before or during pregnancy has no apparent adverse effects on fertility or pregnancy outcomes.[6] High levels of caffeine consumption (>5 cups of coffee/day or its equivalent; 500 mg) have been associated with decreased fertility.[22] In one trial involving 1207 women who were randomly assigned to drink decaffeinated versus caffeinated coffee (at least 3 cups/day) during pregnancy, there were no observed differences between the two groups in gestational age at delivery or in infant weight, length, head circumference, or abdominal circumference.[23]

There are still no concrete data linking caffeine consumption to fertility in women.

3.4 Smoking

A large meta-analysis comparing 10,928 smoking women with 19,128 nonsmoking women found that smoking women were significantly more likely to be infertile (odds ratio [OR] 1.60; 95% confidence interval [CI], 1.34–1.91).[24] Smoking is associated with increased risks of spontaneous abortion and ectopic pregnancy. The effect of smoking on male infertility is less certain, though there is an association with reduced semen parameters.[25]

B Women should be informed that smoking is likely to reduce their fertility.

Grade B, Level 1+

D Men who smoke should be informed that smoking is associated with reduced sperm parameters.

Grade D, Level 4

3.5 Body weight

Women with ***Body mass index*** (BMI) > 29 are likely to take longer to conceive, and losing weight in anovulatory patients is likely to increase the chance of conceiving.[26-27] Women who have a body mass index of less than 19 and who have irregular menstruation or are not menstruating should be advised that increasing body weight is likely to improve their chance of conception.[28-29]

B Women trying to achieve a pregnancy should be informed that a BMI of 19 to 29 is optimal.

Grade B, Level 1+

3.6 Recreational drugs and prescription medication

The effects of most recreational drugs are difficult to determine because their use is illegal. Nevertheless, such drug use generally should be discouraged for both men and women because they have well-documented harmful effects on the developing fetus.[30] A number of prescription drugs can interfere with male and female fertility, and therefore a specific enquiry about these should be made to people who are concerned about their fertility and appropriate advice should be offered.[31]

- Cimetidine and sulphasalazine and long term-daily use of some antibiotics and androgen injections can affect semen quality and cause oligozoospermia.
- Use of beta-blockers and psychotropic drugs may lead to impotence.
- Immunosuppressive and anti-inflammatory drugs for rheumatic diseases may affect conception.
- Chemotherapy treatment with cytotoxic drugs can induce ovarian failure at different rates for various types of malignancies and treatment regimens.

Occupational exposures to hazards can affect fertility. A specific enquiry should be made to couples concerned about their fertility and appropriate advice should be offered. Some well documented hazards include:[32-34]

1. Women exposed to toxins and solvents such as those used in the dry cleaning and printing industries.
2. Men exposed to heavy metals.
3. Pesticide exposure in agricultural workers.
4. Exposure to lead and industrial microwaves.

B Couples seeking treatment for infertility should be routinely screened for usage of long term prescription medication, as some have been known to affect fertility.

Grade B, Level 2++

C Couples seeking treatment for infertility should also be routinely screened for occupational hazards and given appropriate advice.

Grade C, Level 2+

3.7 Offer preconception advice

A Cochrane meta-analysis demonstrated a 3-fold decreased risk of a first neural tube defect if women took folic acid.[35] The Medical Research Council Vitamin Study found that with high dose folate, mothers who had a child with neural tube defects reduced the risk of having another child with neural tube defects by 72%.[36]

Other vitamin supplements are of doubtful benefit for either sex. Some advocate zinc, selenium, and vitamin E supplements for men with abnormal semen parameters of unknown cause, although the evidence for efficacy is weak.[2]

A Women intending to become pregnant should be informed that dietary supplementation with folic acid before conception and up to 12 weeks' gestation reduces the risk of having a baby with neural tube defects. The recommended dose is 0.4 mg per day. For women who have previously had an infant with a neural tube defect or who are receiving anti-epileptic medication, a higher dose of 5 mg per day is recommended.[30]

Grade A, Level 1++

GPP Women who are concerned about their fertility should be offered rubella susceptibility screening so that those who are susceptible to rubella can be offered rubella vaccination and be advised not to become pregnant for at least 1 month following vaccination.

GPP

GPP To avoid delay in fertility treatment a specific enquiry about the timing and result of the most recent cervical smear test should be made to women who are concerned about their fertility. Cervical screening should be offered in accordance with the national cervical screening programme guidance.

GPP

4 Assessment & basic investigations of infertility (including referral)

D Couples with fertility concerns should be interviewed separately as well as together, to bring out important history that a partner may want confidential from the other.[31, 37]

Grade D, Level 4

D At the initial consult, each couple should be assessed for factors that may optimise or contraindicate the planned pregnancy, possible underlying causes of infertility, and the impact of infertility on the individual and relationship.[31, 37]

Grade D, Level 4

D A detailed history-taking and clinical examination should be carried out for couples with fertility concerns. (Refer to Annex A for details).[31, 37]

Grade D, Level 4

Referral criteria[31, 37]

D Patients meeting these criteria should be referred to specialists:

- Women aged <30 years who are unable to conceive after regular unprotected intercourse for 2 years without any known reproductive pathology.
- Women aged >30 years who are unable to conceive after regular unprotected intercourse for 1 year without any known reproductive pathology.
- Patients with a known history of reproductive pathology, e.g. amenorrhea, pelvic inflammatory diseases, endometriosis.
- Patients with a known history or reason for infertility.
- The presence of male problems e.g. history of urogenital surgery varicocele, significant systemic illness.

Grade D, level 4

4.1 Basic investigations of infertility

B Semen analysis should be conducted as part of initial investigation and should be compared to the following World Health Organization (WHO) Global reference values (fertile men) 2009:[38-39]

- Volume: 1.5 ml or more
- pH: >7.2
- Sperm concentration: 15 million spermatozoa per ml or more
- Total sperm number: 39 million spermatozoa per ejaculate or more
- Motility (PR +NP%): 40% or more motile*
- Vitality (%): 58
- White blood cells (10^6 per ml) : < 1.0
- Morphology (%): 4 or more

*PR = progressive motility (WHO 1999, grades a+b); NP = non-progressive motility (WHO 1999, grade c).

Grade B, Level 2+

B If the first sperm analysis result is abnormal, the patient should be offered a repeat test from the same laboratory at least 3 months after the initial analysis.[31, 40]

Grade B, Level 2++

GPP Severe abnormality (azoospermia or severe oligozoospermia) of the initial sperm sample however, warrants an immediate referral to a tertiary centre (see section on male infertility).

GPP

D Sperm function tests, screening for antisperm antibodies and postcoital tests on cervical mucus should not be offered as there is no evidence of effective treatment to improve fertility. [31, 37, 40]

Grade D, Level 4

4.2 Assessing ovulation

D Women with fertility concerns should have their menstrual history taken. [38-39]

Grade D, Level 4

Women who are concerned about their fertility should be asked about the frequency and regularity of their menstrual cycles. Women with regular monthly menstrual cycles should be informed that they are likely to be ovulating.

D Use of basal body temperature charts and home ovulation kits alone to predict ovulation should not be recommended to patients with fertility problems as these are not always reliable in predicting ovulation and leads to unnecessary anxiety and stress for the patient. [38-39]

Grade D, Level 4

B Women with infertility should be offered a blood test to measure mid luteal serum progesterone levels (about 7 days before the expected menstrual cycle). If cycles are irregular or prolonged, this test may need to be repeated again weekly thereafter until the next menstrual period. [41-43]

Grade B, Level 2++

B Follicle stimulating hormone and luteinizing hormone investigations should be done on day 2 to 3 of the menstrual cycle. Patients with high levels of gonadotrophins should be informed that they are likely to have reduced fertility. [41-43]

Grade B, Level 2+

4.3 Screening for Chlamydia trachomatis

B Women with infertility should be offered screening for Chlamydia trachomatis before undergoing instrumentation.[31,44-45]

Grade B, Level 2++

B If screening for Chlamydia trachomatis has not been carried out, prophylactic antibiotics should be given before uterine instrumentation.[31, 44-45]

Grade B, Level 2++

Chlamydia trachomatis is associated in women with adverse reproductive consequences such as pelvic inflammatory disease and ectopic pregnancy. Endocervical swab for Chlamydia trachomatis using nucleic acid amplification test (NAAT) is the most accurate test for current infection with Chlamydia.[31, 44-45] Serology is non-invasive and may be used as a screening test to detect evidence of past Chlamydia infection. This can identify women at high risk of having tubal damage as a cause of their infertility.[31, 44-45]

4.4 Assessing tubal damage

Tubal factor infertility accounts for about 35% of all cases of infertility. It is one of the main contributing factors for infertility in women. There are several different tests that can be utilised to assess tubal diseases. However, none is ideal as each has its own limitations.

GPP The result of semen analysis and assessment of ovulation should be completed before the clinician embarks on tubal assessment.

GPP

B Hysterosalpingography (HSG) should be used as the first line investigation in tubal assessment.[46]

Grade B, Level 2++

Hysterosalpingography can demonstrate location of tubal occlusion, tubal architectural and may suggest fimbriae adhesion when contrast is loculated in the pelvic cavity. Although it is a reliable indicator to demonstrate tubal patency, only 38% of women with positive HSG will have the result confirmed by laparoscopy.[46]

A Chlamydia antibody titre (CAT)47 should be considered as an alternative to hysterosalpingography (HSG) if the resources are available.

Grade A, Level 1+

Chlamydia infection is a common sexually transmitted disease which results in tubal disease. Approximately 60-80% of women with Chlamydia infection have no symptoms. Untreated infection may

lead to pelvic inflammatory disease which can cause scarring of the fallopian tube and therefore tubal infertility. CAT has been shown to be as accurate as HSG in terms of diagnosing tubal occlusion.[47] The main advantage of CAT compared to HSG is they are without radiation exposure. Therefore, when available at primary setting, this should be considered before offering HSG to patient.

CAT is cheap, less invasive and can be performed at any time during the cycle.

B Laparoscopy and dye hydrotubation should be offered for women with comorbidities, such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis.[48-50]

Grade B, Level 2+

While laparoscopy and dye hydrotubation is the gold standard for tubal assessment, it is not suitable to be used as a screening test. It is more appropriate for women who are thought to have comorbidities such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis. Laparoscopy allows proper assessment of tubal and pelvic pathology and possibility of corrective surgery at the same setting.[48-50] Hysterosocopy may also be carried out at the same time to provide information on the uterine cavity if there was no previous assessment done.

C Fertiloscopy and transvaginal hydrolaparoscopy should not be offered routinely as an alternative to laparoscopy hydrotubation as their diagnostic accuracy still require further evaluation.[51-53]

Grade C, Level 3

Transvaginal hydrolaparoscopy (THL) involves transvaginal endoscopy, dye test, optional hysteroscopy and salpingoscopy performed under local anaesthesia. It could be carried out as an outpatient procedure. It may be used to evaluate posterior uterus, pelvic sidewall, adnexal and to identify tubal pathology. Microendoscopy can be utilised during THL to visualise the entire fallopian tube lumen. Being a relatively new procedure its diagnostic accuracy requires further evaluation.[51-53]

4.5 Assessing uterine abnormalities

Uterine abnormalities are relatively uncommon but intrauterine lesions are much more common in infertile women (up to 50%). These lesions may compromise implantation and pregnancy rates in spontaneous and treatment cycles. Therefore, uterine cavity assessment has been suggested as a routine investigation in subfertile women.[54]

Recommendation

C When available, transvaginal ultrasound may be used as a screening test for the assessment of uterine cavity in subfertile women.

Grade C, Level 2+

Transvaginal ultrasound is well tolerated by patients and has a high positive predictive value (85-95%).[54]

B Operative hysteroscopy should not be offered as an initial investigation.[55-57]

Grade B, Level 2++

Hysteroscopy provides both diagnostic and therapeutic capabilities. However, it should not be offered as an initial investigation due to its invasiveness and availability of other modalities with comparable sensitivity.

Hysterosalpingography and saline infusion sonohysterogaphy are other alternatives which are highly sensitive and specific in identifying intrauterine abnormalities. Saline infusion sonohysterogaphy, by instilling sterile saline into uterine cavity, has a high sensitivity in detecting polyps, submucousal fibroid and synechiae. However, it requires operator skills in cannulating the endocervical canal. The procedure is well-tolerated and can be done as an outpatient procedure.[55-56] Both HSG and saline infusion sonohysterography are comparable to office hysteroscopy in diagnostic accuracy.[55-57]

5 Ovulatory dysfunction

The treatment of ovulatory dysfunction can be classified according to a scheme adopted by the World Health Organization (WHO), which is widely used (Table 1).

Table 1 World Health Organization (WHO) classification of ovulation dysfunction.[58-59]

Group	Ovarian Dysfunction	Pituitary Gonadotropins		PRL	Ovarian Steroids
		FSH	LH		Estradiol
I	Hypothalamic-Pituitary Failure	Low	Low	Normal	Low
II	Ovulatory Dysfunction	Normal	Normal	Normal	Normal
III	Ovarian Failure	High	NA	Normal	Low
IV	Hyper-prolactinaemia	NA	NA	High >20ng/mL on two different occasions	NA

NA = Not applicable

FSH = Follicle-stimulating hormone

LH = Luteinizing hormone

PRL = Prolactin

Management of specific ovulatory dysfunction conditions

The management of ovulatory dysfunction depends on its underlying aetiology. Management of WHO Group I, III and IV ovulatory dysfunction is described here, while management of WHO Group II ovulatory dysfunction will be covered in **Chapter 6.**

A. Management of hypothalamic pituitary failure (WHO group I)

This condition can be broadly divided into four different sub-groups.

1. **Functional hypothalamic pituitary failure -** This group of patients suffers from exercise-associated, nutritional or pyschogenic stresses, leading to a failure of hypothalamic function.

C For patients with functional hypothalamic pituitary failure who desire fertility, ovulation induction therapies may be indicated. However, the achievement of a healthy weight and modification of lifestyle should be tried first.

Grade C, Level 2+

Behavioural modification and achievement of adequate caloric intake is not only simple but highly effective. Moreover, inadequate caloric intake is likely to be inadequate for normal fetal development, resulting in higher rates of miscarriages.[60]

C Where amenorrhoea (which occurs in functional hypothalamic pituitary failure women) has occurred for longer than a year in duration, assessment of the bone mineral densities should be considered.[61-62]

Grade C, Level 2+

The diagnosis of osteopaenia may spur patients to increase caloric intake or to reduce exercise levels. This is especially important as weight gain has been shown to have a greater effect on bone mineral densities than hormone replacement therapy in the form of the combined oral contraceptive pill.[61-62]

2. Drug induced anovulation

GPP When drug-induced anovulation is suspected, medications should be altered or discontinued if possible. If the medication which causes anovulation cannot be altered or discontinued, referral to a reproductive medicine specialist for further management is indicated.

GPP

Certain drugs such as opiate agonists and anti-psychotics with anti-dopaminergic activity may cause the cessation of pulsatile Gonadotropin-releasing hormone (GnRH) release.

3. Anorexia Nervosa

GPP Patients with anorexia nervosa should be referred to a mental-health care provider for further management.

GPP

Anorexia nervosa is more common among younger women and results in derangement of the hypothalamic-pituitary axis with hypersecretion of cortisol and inhibition of gonadotropin releasing hormone. Interdisciplinary management is hinged upon supportive, non-specific interventions,[63] with about half of patients achieving adequate weight gain and resumption of their menstrual cycle.[64]

4. Organic lesions of the hypothalamus and pituitary gland

GPP Patients with organic lesions of the hypothalamus and pituitary gland should be referred to a reproductive specialist.

GPP

This group of patients include those with hypothalamic lesions such as craniopharyngiomas, pinealomas, infiltrative diseases (sarcoidosis, histiocytosis) of infections (HIV, tuberculousis), congenital conditions (Kallman syndrome), functional and non-functional pituitary tumours (see below), iatrogenic damage (surgery and irradiation), Sheehan syndrome and head trauma. Exogenous gonadtrophins will be necessary to induce ovulation.

B. Management of ovarian failure - WHO group III

C Women should be told that premature ovarian failure is not a definitive diagnosis of infertility as approximately 5-10% of these women may conceive spontaneously and unexpectedly after the diagnosis.[65-66]

Grade C, Level 2+

About 1% of women suffer from premature ovarian failure (< 40 years of age) for which the cause is unknown in the majority, although Turner syndrome and pre-mutations carriers of Fragile X Syndrome are over-represented in this group.[67-68]

C Women with spontaneous premature ovarian failure should be referred to an endocrinologist to investigate asymptomatic autoimmune adrenal insufficiency.[69]

Grade C, Level 3

Screening for asymptomatic autoimmune adrenal insufficiency, which affects three percent of these women should be done.[69]

C Fertility options in women with premature ovarian failure include the use of an oocyte (egg) donor or embryo donor in an Assisted Reproductive Program (ARP).

Grade C, Level 2+

Success rates for donor oocyte programs within IVF cycles approaches those without premature ovarian failure.[70-71]

C. Management of WHO Group IV - Hyperprolactinaemia

A Dopamine receptor agonists are the first line treatment for patients with idiopathic hyperprolactinaemia secondary to pituitary adenoma.[72-73]

Grade A, Level 1+

Treatment with cabergoline 0.5mg to 1.0mg twice weekly results in the achievement of normoprolactinaemia in 83% of women compared with 59% for bromocriptine 2.5 to 5.0mg twice daily.[72-73]

C Surgical trans-sphenoidal resection of microadenomas should not be the primary therapeutic approach for patients with hyperprolactinaemia secondary to pituitary adenoma.[74-75]

Grade C, Level 2+

Surgical treatment of micro and macro-adenomas are associated with high recurrence rates of up to 39 to 50% within the first 5 years after treatment.[74-75]

6 Managing infertility in polycystic ovary syndrome (PCOS)

6.1 Introduction

Polycystic ovary syndrome (PCOS) is a common disorder characterised by chronic anovulatory infertility and hyperandrogenism with the clinical manifestation of oligomenorrhoea, hirsutism and acne.[76] Most clinical data suggest it has a prevalence of 6-7%,[77-80] but this may differ according to ethnic background, for example, women of South Asian origin present at a younger age, have more severe symptoms and a higher prevalence. [81-82]

Many women with polycystic ovary syndrome are obese and exhibit an adverse cardiovascular risk profile, characteristic of the cardiometabolic syndrome as suggested by a higher reported incidence of hypertension, dyslipidaemia, visceral obesity, insulin resistance and hyperinsulinaemia.[83] They also have a higher prevalence of type 2 diabetes[84-85] and sleep apnoea.[86-87] Therefore it is important that there is a good understanding of the long term implications of the diagnosis in order to offer a holistic approach to the treatment of the disorder.

6.2 Diagnosis of polycystic ovary syndrome

D Diagnosis of polycystic ovary syndrome should only be made when other aetiologies have been excluded (thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinaemia, androgen secreting tumours and Cushing's syndrome).

Grade D, Level 4

The Rotterdam consensus sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ARSM)[88] are current best practice for diagnosis of polycystic ovary syndrome.

Diagnostic criteria of polycystic ovary syndrome (2 of the following):

1. Polycystic ovaries by doing a pelvic ultrasound scan to determine features in accordance with the Rotterdam criteria (either 12 or more follicles measuring 2-9 mm in diameter, or an ovarian volume of > 10 cm^3)
2. Oligo- or anovulation
3. Clinical and/or biochemical signs of hyperandrogenism.

These new diagnostic criteria have affected the value of a number of systematic reviews as the majority of the reviews are based on the NIH 1990 criteria that may not be entirely representative of those patients diagnosed by the new Rotterdam criteria in use today.

A raised LH/FSH ratio is no longer within the diagnostic criteria for Polycystic ovary syndrome due to its inconsistency.[89]

The following aetiologies must be excluded before a diagnosis of polycystic ovary syndrome can be made:

- thyroid dysfunction by thyroid function test
- congenital adrenal hyperplasia
- hyperprolactinaemia by serum prolactin level
- androgen-secreting tumors by determining the Free Androgen Index
- Cushing's syndrome.

D The following investigations should be done to exclude other aetiologies before a diagnosis of polycystic ovary syndrome should be made:[88]

- <u>Baseline laboratory screen:</u>
  - 0 Thyroid function test (thyroid dysfunction can present as amenorrhoea)
  - 0 Serum prolactin (hyperprolactinaemia can present as amenorrhoea)

- 17 hydroxyprogesterone (only in the presence of clinical or biochemical evidence of hyperandrogenism) (Congenital adrenal hyperplasia can present as amenorrhoea and hyperandrogenism)
- Free Androgen Index (FAI = total testosterone divided by sex hormone binding globulin x 100 to give a calculated free testosterone level) or free/bioavailable testosterone. (hyperandrogenism as one of the criteria needed to diagnose polycystic ovary syndrome)

- Diagnostic Imaging:

  Pelvic ultrasound scan to determine features in accordance with the Rotterdam criteria as well as to exclude androgen secreting tumours of the adrenals or ovaries.

Grade D, Level 4

D The following are optional tests in the diagnosis of Polycystic ovary syndrome:[88]

- Gonadotrophin may be required to determine cause of amenorrhoea (primary ovarian failure)
- Fasting insulin is not necessary routinely but may be considered in those undergoing ovulation induction
- ACTH stimulation test needs to be considered if morning 17 hydroxyprogesterone >5nmol/L in order to exclude non-classical congenital adrenal hyperplasia.

Grade D, Level 4

Management of polycystic ovary syndrome

Effective treatment of patients with polycystic ovary syndrome requires that the specific goal(s) of therapy be first established. Individual goals may include weight management, fertility, treatment for hirsutism and/or acne, achieving a regular menstrual cycle and the prevention of the long term consequences associate with polycystic ovary syndrome – or all of the above.

In women not attempting to get pregnant, treatment with oral contraceptive pills, progestins and insulin sensitising agents are appropriate.

Managing infertility in polycystic ovary syndrome

GPP Before any intervention is initiated for women with polycystic ovary syndrome, preconceptional counselling should be provided emphasizing the importance of life style, especially weight reduction and exercise in overweight women, smoking and alcohol consumption.

GPP

A The recommended first-line treatment for ovulation induction remains the anti-estrogen clomiphene citrate.[90-92]

Grade A, Level 1+

A Patients with polycystic ovary syndrome should be informed that there is an increased risk of multiple pregnancy with ovulation induction using clomiphene citrate.[92]

Grade A, Level 1+

Clomophene citrate has traditionally been first-line treatment agent for anovulatory women, including polycystic ovary syndrome and several multicentre randomized controlled trials have upheld the use of clomiphene as first line therapy.[92-93] It is the preferred first line option over other ovulation induction methods due to the relatively low cost of medication, the oral route of administration that is patient friendly and the abundance of clinical data on its safety profile.[90-93] Six month live birth rates ranges from 20-40%.[92-94] Most pregnancies will occur within the first six ovulatory cycles and women should be offered treatment for up to 12 months because it is likely to induce ovulation. However, a recent randomised trial data analysis suggested that there may be a role in using metformin as first line therapy for ovulation induction among women with lower BMI within a subgroup of BMI >32 kg/m^2 population.[95]

GPP Ultrasound monitoring of follicular development at least during the first cycle of treatment with clomiphene is advisable to ensure that women receive a dose that minimises the risk of multiple pregnancy.

GPP

D Recommended second-line intervention for infertility in women with polycystic ovary syndrome is either exogenous gonadotrophins or laparoscopic ovarian surgery.[90]

Grade D, Level 4

These agents are recommended as second line due to the higher cost in comparison to clomiphene and the invasive nature of laparoscopic ovarian surgery with no evidence of superiority over clomiphene treatment.

GPP The use of exogenous gonadotrophins is associated with increased chances for multiple pregnancy and, therefore, intense monitoring of ovarian response is required.

GPP

B Laparoscopic ovarian surgery alone is usually effective in <50% of women and additional ovulation induction medication is required under those circumstances.[96]

Grade B, Level 2++

B Low dose therapy with gonadotrophin is recommended as it offers significant lower risk of ovarian hyperstimulation in women with polycystic ovary syndrome.[97]

Grade B, Level 2++

The high costs and the risk of multiple pregnancy and ovarian hyperstimulation syndrome are drawbacks of the treatment.

Surgical risks need to be considered in these patients.

C The recommended third-line treatment for infertility in women with polycystic ovary syndrome is in vitro fertilization.[90]

Grade C, Level 2+

Anovulation is not a specific indication for IVF and instead, these patients should be treated with ovulation induction. However, if the patient failed ovulation induction or has additional associated factors that impair their fertility, IVF may be considered earlier. IVF is a reasonable option as it is effective in patients with polycystic ovary syndrome.

Indeed, more patient-tailored approaches should be developed for ovulation induction based on initial screening characteristics of women with polycystic ovary syndrome. Such approaches may result in deviation from the above mentioned first-, second- or third-line ovulation strategies in well-defined subsets of patients.

Aromatase inhibitors such as letrozole and anastrazole have been proposed as agents for ovulation induction and results appeared comparable to clomiphene from a small trial.[98] As ovulation induction is currently not a licensed indication for the use of aromatase inhibitors, we do not recommend the use of aromatase inhibitors for routine ovulation induction.

GPP As aromatase inhibitors are currently not licenced for use as ovulation induction, we do not recommend the clinical use of aromatase inhibitors for routine ovulation induction.

GPP

Metformin therapy in management of infertility

D The routine use of metformin in ovulation induction is not recommended as monotherapy or in combination with clomiphene citrate.

Grade D, Level 3

The routine use of metformin in ovulation induction as monotherapy or its combined use with clomiphene citrate does not significantly improve the live birth rate over that of clomiphene citrate alone.[92-93]

B There is currently insufficient evidence to suggest improvement in live birth rates on treatment with metformin before or during assisted reproductive technique cycles and its routine use is not recommended.

Grade B, Level 2+

Metformin is also useful for women with longer timelines for achieving pregnancy (i.e. those who are younger in age and able to defer pregnancy until later in life).[99] In these cases, pre-treatment of obese women with polycystic

ovary syndrome with metformin combined with lifestyle modification may result in weight loss, which reduces the likelihood of clomiphene resistance and the risk for gestational or obstetrical complications.

A The combined use of metformin and clompihene citrate is recommended for women with clomiphene resistance especially if they are obese (BMI > 27.5 kg/m^2).[95, 100-101]

Grade A, Level 1+

A recent randomised controlled trial suggested that metformin co-treatment in patients undergoing IVF improves pregnancy outcome and reduces the risk of ovarian hyperstimulation despite the fact that it fails to improve the response to stimulation and fertilization rate.[102]

The most common dose regimens for metformin are 500mg three times daily or 850mg twice daily. Long acting preparations are associated with fewer gastrointestinal side effects.[103]

Metformin in pregnancy

Metformin therapy throughout pregnancy may reduce the risk of early miscarriage after spontaneous or assisted conception or gestational diabetes in women with polycystic ovary syndrome.[104-107] There was no differences in height, weight, and motor-social development in the infants during the first 18 months of life[108] and metformin during lactation appears to be safe.[109] A meta-analysis of preliminary studies in diabetic women unselected for polycystic ovary syndrome and nondiabetic women with polycystic ovary syndrome was reassuring for the safety of metformin use in the first gestational trimester with no major neonatal malformations.[107]

Although currently available data seem to suggest that metformin is safe in pregnancy, we still lack long term follow-up data of children exposed to metformin during pregnancy. However, there may be specific circumstances when metformin is continued or started in pregnancy and this should be made after obtaining informed consent from the woman including discussion on the limitation of current data.

GPP There is insufficient evidence to recommend the widespread use of metformin in pregnant women with polycystic ovary syndrome.

GPP

Long term consequences in polycystic ovary syndrome

GPP Young women diagnosed with polycystic ovary syndrome should be informed of the possible long-term risks to health that are associated with their condition.

GPP

Polycystic ovary syndrome and risk of type II diabetes

B Patients presenting with polycystic ovary syndrome, particularly if they are obese or have a strong family history of type 2 diabetes or are over the age of 40 should be offered a glucose tolerance test.

Grade B, Level 1+

Insulin resistance in polycystic ovary syndrome has been linked to later development of impaired glucose tolerance and type 2 diabetes.[110] Evidence from small long-term cohort studies, case-control studies and case series, points to a risk of type 2 diabetes in middle age of 10-20%,[85, 111-112] with a high rate of impaired glucose tolerance suggesting that further cases of diabetes will develop later. Increased body mass, particularly truncal obesity, and a strong family history of diabetes (up to 83% in one study[88]) increase the risk of developing type 2 diabetes in the presence of polycystic ovary phenotype.[85]

However, the frequency of type II diabetes is also increased in slim polycystic ovary syndrome patients,[85, 112] suggesting that polycystic ovary syndrome is an independent risk factor for type 2 diabetes in middle age. A sensible approach to ensure early detection of diabetes might be to offer screening to women with polycystic ovary syndrome with measurement of fasting blood glucose, on a regular basis, perhaps annually, and if fasting blood glucose is 5.6mmol/L or greater, then an oral glucose tolerance test should be arranged. Fasting insulin and HOMA-IR (homeostatic model assessment-insulin resistance) are not required in routine practice.

Polycystic ovary syndrome and obstructive sleep apnoea

B Women diagnosed with polycystic ovary syndrome should be asked (or their partners asked) about snoring and daytime fatigue/somnolence and informed of the possible risk of sleep apnoea, and offered investigation and treatment when necessary.

Grade B, Level 2++

Sleep apnoea is an independent cardiovascular risk factor and has been found to be more common in polycystic ovary syndrome. The difference in prevalence of obstructive sleep apnoea in women with polycystic ovary syndrome remained significant even when controlled for BMI.[86-87, 113-115]

Polycystic ovary syndrome and cardiovascular risk

B Clinicians should continue to identify cardiovascular risk factors (including blood pressure, cholesterol, triglycerides and high density lipoprotein cholesterol) in women with polycystic ovary syndrome and treat these accordingly.

Grade B, Level 2++

The presence of cardiovascular risk factors of obesity, insulin resistance and dyslipidaemia may predispose women with polycystic ovary syndrome to coronary heart disease. In the Nurses' Health Study, menstrual cycle irregularity was associated with an increased risk of non-fatal and fatal coronary heart disease, although no data were available for confirmation of a diagnosis of polycystic ovary syndrome.[116] Despite the increase in cardiovascular risk factors, morbidity and mortality from coronary heart disease among women with polycystic ovary syndrome has not been shown to be as high as predicted.[117]

Strategies for reduction of metabolic risk

1. Exercise and weight control

A Women diagnosed with polycystic ovary syndrome should be advised regarding weight loss through diet and exercise.[118-121]

Grade A, Level 1+

Lifestyle changes through diet and exercise remain the first line for treatment of obesity in polycystic ovary syndrome. As obesity worsens, insulin resistance increases and that may exacerbate this dysfunction; loss of significant weight has been reported to result in spontaneous resumption of ovulation,[122] improvement in fertility,[123] increased sex hormone binding globulin and reduced basal level of insulin[124-125] accompanied by a normalization in glucose metabolism[126] therefore reducing the likelihood of developing type 2 diabetes later in life. In the absence of any robust long term follow-up data for lifestyle interventions, it would seem appropriate to advise regular exercise aiming for a mean of 30 minutes sweat-inducing exercise five days a week, and to have a healthy, balanced diet of regular, hypocalorific meals through the day.

2. Drug therapy

B Combining metformin and lifestyle modification, including calorie restriction and exercise to facilitate weight loss and attenuate central adiposity is recommended for obese patients with polycystic ovary syndrome. Higher doses of metformin, up to 2.5g/day, may be recommended to achieve an optimal response.[127-128]

Grade B, Level 1+

The demonstration of the potential long-term health consequences of polycystic ovary syndrome have lead to an interest in the use of insulin sensitising agents such as metformin and thiazolidinediones (rosiglitazone and pioglitazone) to reduce insulin resistance and thereby reduce risk of developing diabetes and other metabolic sequelae.[129-138] Both metformin and thiazolidinedione[129-138] have been shown to have

beneficial short-term effects on both reproductive function and insulin resistance in non diabetic women with polycystic ovary syndrome. There is evidence that metformin may modestly reduce androgen levels in women with polycystic ovary syndrome compared to placebo, and modest reductions in body weight,[139] although not all studies are able to show weight reduction.[140-141] Even if metformin contributes to weight loss, the potential mechanism mediating this effect is unclear. There are some suggestions that this may be through mediation of central hormone appetite regulators.[142] Metformin appear to be less effective in those who are significantly obese (body mass index > 35 kg/m^2).[135, 140]

A meta-analysis suggested that metformin therapy significantly decreases systolic blood pressure and low density lipoprotein (LDL) cholesterol levels.[143] However, metformin should be considered an adjunct to lifestyle changes in improving cardiovascular risk and extreme obesity with minimal amount of weight loss may account for the persistent metabolic and cardiovascular abnormalities even in those women treated with the combination of metformin and lifestyle intervention.[144]

3. Surgery

D Ovarian electrocautery should only be reserved for slim women with anovulatory polycystic ovary syndrome.

Grade D, Level 3

Laparoscopic ovarian electrocautery has been shown to induce ovulation and normalisation of serum androgens and sex hormone binding globulin particularly in slim polycystic ovary syndrome.[145-146] However, no prospective studies have been powered to look at cardiovascular risk profiles and ovarian electrocautery should be reserved for selected slim women with anovulatory polycystic ovary syndrome.

Hirsutism in polycystic ovary syndrome

Hirsutism should ideally be quantified using the Ferriman-Gallwey score,[147] with a score of over 8 indicating hirsutism, although this is often not really practicable.

Licensed treatments include:

- Oral contraceptive pills
- Dianette (oestrogen + cyproterone acetate)
- Cosmetic measures (e.g. laser, electrolysis, bleaching, waxing and shaving)
- Eflornithine (Vaniqa) for facial hirsutism

Usually a combination of methods is required to achieve an acceptable cosmetic result.

Non-licensed treatments e.g. metformin, spironolactone and anti-androgens (flutamide and finasteride) are also used in specialist centres when deemed appropriate.

Adequate contraceptive measures are essential.

Polycystic ovary syndrome and pregnancy

B Women who have been diagnosed as having polycystic ovary syndrome before pregnancy, especially those requiring ovulation induction for conception, should be screened for gestational diabetes before 20 weeks of gestation, with referral to a specialist obstetric diabetic service if abnormalities are detected.

Grade B, Level 1+

There is a higher risk of gestational diabetes in women with polycystic ovary syndrome.[148-149] The risk is believed to be greatest in obese women with polycystic ovary syndrome who required ovulation induction in order to conceive. This is due to these women being obese, which by nature makes it more difficult for them to conceive and puts them at higher risk of metabolic syndrome and thus diabetes.[150]

7 Male infertility

GPP Both male and female partners should be investigated concurrently for couples who present for infertility assessment.

GPP

A male factor was found to be the sole contributory factor in up to 33% of infertile couples. In up to 50% of infertile couples, the male partner was found to be partly responsible for the problem. Therefore, infertility needs to be assessed and managed as a couple.[38-39]

Reduced male fertility can be the result of congenital and acquired urogenital abnormalities, infections of the male accessory glands, increased scrotal temperature (varicocele), endocrine disturbances, genetic abnormalities and immunological factors. In 40–60% of cases the only abnormality is the semen analysis and there is no relevant history or abnormality on physical examination and endocrine laboratory testing (idiopathic male infertility). Semen analysis reveals a decreased number of spermatozoa (oligozoospermia), decreased motility (asthenozoospermia) and many abnormal forms on morphological examination (teratozoospermia). Usually, these abnormalities come together and are described as the OAT-syndrome (oligo-astheno-teratozoospermia).[38-39]

7.1 Oligo-astheno-teratozoospermia (OAT)

B Semen analysis should be done as the primary investigation for male infertility (see section 4).[38-39]

Grade B, level 2+

Primary care physicians can begin with semen analysis which is simple and inexpensive. However, it is important to know that semen analysis is not a direct test of fertility but provides guidance to fertility.

GPP Hormonal investigations for male infertility should be limited to FSH, LH and Testosterone levels.

GPP

In men diagnosed with azoospermia or extreme OAT, it is important to distinguish between obstructive and non obstructive causes. A normal FSH and bilaterally normal testicular volume is predictive of obstruction.

D Karyotyping and Y microdeletion test should be considered for men with non-obstructive azoospermia.[151-153]

Grade D, Level 3

Klinefelter syndrome is the most usual cause of male hypogonadism[154] and occurs in up to 10% of NOA men.[151] Recent research also found that approximately 15% of spermatogenesis failure is related to Y chromosomal deletion.[152] The knowledge of the presence of genetic disorder can help resolve stress, blame or feelings of guilt while the type of genetic disorder could prognosticate the success of sperm retrieval with testicular biopsy.[153]

GPP Referral to a tertiary center should be made for:

- Patients with azoospermia
- Patients with severe semen abnormality
- Patients with clinical evidence of varicocele
- Patients with erectile dysfunction
- Patients with anejaculation
- Patients with retrograde ejaculation
- Patients with suspected androgen deficiency
- Couples who will benefit from assisted reproductive technologies

GPP

GPP General advice such as cessation of smoking, steroid use and withdrawal of offensive medication could be given at primary setting.

GPP

GPP Couples trying to conceive should generally avoid exposure to harmful chemicals (e.g. by wearing protective clothing when appropriate to reduce risk of exposure to harmful chemicals).

GPP

A Antioxidant supplementation for subfertile males may be used to improve live birth and pregnancy rates for subfertile couples.[155]

Grade A, Level 1+

However, there is no head to head comparison available to conclude which antioxidant is superior.[155]

GPP Referral to fertility specialist should be facilitated if the female is over 35 years old.

GPP

As female fertility declines with time, female age should be taken into consideration and time should not be wasted in treating male infertility alone.

B Varicocele treatment may be considered when the female evaluation is normal and the man has a palpable varicocele with suboptimal semen quality.[156-159]

Grade B, Level 2++

Varicocele is a physical abnormality present in 2–22% of the adult male population. It is more common in men of infertile couple, affecting 25–40% of those with abnormal semen analysis.[156-157] The exact association between reduced male fertility and varicocele is unknown, [158-160] but analysis of the WHO data clearly indicates that varicocele is related to semen abnormalities, decreased testicular volume and decline in Leydig cell function.[156]

Clinical studies on the varicocele treatment yields different results on post operative sperm parameters and pregnancy rate.[161-164] This could be due to heterogeneity in the parameters of the populations studied or confounding variables such as technique of repair and lack of control.

Nonetheless, if surgical expertise is available and in the event where female partner evaluation was normal, varicocele repair is a reasonable consideration in a man with a palpable varicocele and suboptimal semen quality.[165]

GPP In azoospermia, spermatozoa may be retrieved from the testis/epididymis using a variety of techniques such as testicular sperm aspiration (TESA), testicular sperm extraction (TESE), microsurgical epididymal sperm aspiration (MESA) and percutaneous epididymal sperm aspiration (PESA). Sperm cryopreservation should be offered at the time of sperm retrieval.

GPP

7.2 Ejaculatory disorder

GPP When retrograde ejaculation is suspected, post-ejaculatory urinalysis (looking for presence of sperm and fructose) may be requested.

GPP

C It is important to exclude retrograde ejaculation and anejaculation from other causes of azoospermia as drug therapy may be used to allow spontaneous conception.[166]

Grade C, Level 3

Anejaculation may be treated with alpha-agonistic drugs such as imipramine, pseudoephedrine or a parasympathomimetic drug and neostigmine. A systematic review recommended parasympathomimetic drugs over alpha-agonists due to higher success rate with the former (19% with alpha-agonists versus 51% with parasympathomimetics).[166] However, these are associated with considerable adverse effects such as headache, nausea and vomiting and therefore not generally recommended as the treatment of first choice.

In the event where anejaculation is a result of erectile dysfunction secondary to psychogenic disorders, treatment of erectile dysfunction with anxiolytic drugs and/or sildenafil may be helpful.[167]

Retrograde ejaculation may be treated by alpha-agonistic or anticholinergic and antihistamine drugs such as imipramine, milodrin, chlorpheniramine or brompheniramine. There were no significant differences between the different medical treatments.[166]

In ejaculatory disorder, penile electrovibration and transrectal electroejaculation stimulation may recover sufficient sperm to allow the use of intrauterine insemination.

D When available, penile electrovibration and transrectal electroejaculation should be considered before embarking on surgical sperm retrieval and intracytoplasmic sperm injection.[168]

Grade D, Level 4

GPP Delayed ejaculation and anorgasmia may have biogenic or psychogenic aetiology. After exclusion of medical illnesses, referral could be made to a sexual therapist who could help in education, counselling and instruction in revised sexual technique to maximise sexual arousal.

GPP

B Management of premature ejaculation depends on the underlying aetiology, patient's needs and preference. For lifelong premature ejaculation, selective serotonin reuptake inhibitors (SSRIs) are preferred while for secondary premature ejaculation, behavioural techniques are the preferred option.[169]

Grade B, Level 2++

B Patient with premature ejaculation should be informed that daily SSRI is more effective than on-demand SSRI treatment. On demand use of topical anaesthtics and tramadol may prolong intravaginal ejaculatory latency.[169]

Grade B, Level 2++

Phosphodiesterase type 5 (PDE 5) inhibitors are often prescribed for erectile dysfunction (see section 7.3). As erectile dysfunction and ejaculatory disorder are separate disorders with different underlying causes, PDE 5 inhibitors should not be prescribed to men with premature ejaculation when there is no associated erectile dysfunction.

B Phosphodiesterase type 5 (PDE 5) inhibitors should not be prescribed to men with premature ejaculation when there is no associated erectile dysfunction.[169]

Grade B, Level 2++

7.3 Erectile dysfunction

Erectile dysfunction is a common condition affecting one in five men over the age of 40 years. Erectile dysfunction is also commonly associated with chronic disease such as coronary artery disease, hypertension and diabetes.

GPP All patients presenting with erectile dysfunction should have their history taken and assessment done to identify cardiovascular risk factors such as hypertension, hyperdyslipidaemia and diabetes as these are commonly associated with cardiovascular disease.

GPP

GPP Although referral to a fertility clinician can help with fertility issues by doing in-vitro fertisilisation/intra cytoplasmic sperm injection, multidisciplinary referral should be considered in the following situations:

- complex endocrine disorder (to endocrinologist)
- history of pelvic or perineal trauma, penile deformities or penile implants (to urologist)
- psychosocial issues or relationship problems (to counsellor, psychologist, psychiatrist)

GPP

D First line treatment for erectile dysfunction should include patient counseling and education, risk factor modification (smoking cessation, reduce alcohol, improved diet and exercise, weight loss) and addressing psychosocial issues (relationship difficulties, anxiety).[170]

Grade D, Level 4

A Oral agents (PDE5 inhibitors) such as tadalafil (Cialis), Sildenafil (Viagra), Vardenafil (Levitra) have similar efficacy, tolerability and safety for the treatment of erectile dysfunction. Choice of drug should be individualised based on patient needs.[171]

Grade A, Level 1+

D Phosphodiesterase type 5 (PDE 5) inhibitors should not be taken with nitrate-containing medications for erectile dysfunction as the concurrent use of nitrate medications and PDE 5 inhibitors is contraindicated. Patients need to be educated that they require sexual stimulation for these medications to work.[171]

Grade D, Level 4

C Vacuum devices and rings are suitable for men with erectile dysfunction who have contraindications for pharmacologic therapies. It should only be prescribed by clinicians who are familiar with its use.[172]

Grade C, Level 2+

C Men with erectile dysfunction who are resistant to phosphodiesterase type 5 (PDE 5) inhibitors should be referred to a urologist as combination therapy (PDE 5 inhibitor plus vacuum erectile device, intraurethral medication, intracavernosal injection, androgen supplement, α-blocker) or invasive treatment such as penile implant may be considered.[172]

Grade C, Level 2+

7.4 Androgen deficiency

Androgen deficiency is common and affects one in 200 men under 60 years old.[173] It is a clinical diagnosis confirmed by hormone assays.

D Hormone assays should be performed to test for androgen deficiency. As there is diurnal rhythm in hormone secretion, blood samples for testosterone should be taken in the morning.[173]

Grade D, Level 4

GPP The result of hormone assays should be interpreted with caution as there is no appropriate standardised reference range for all laboratories. Therefore, clinical assessment (recent changes in sexual function, patterns of body hair and secondary sexual characteristics) is important to diagnose androgen deficiency.

GPP

B When fertility is desired, testosterone should not be used to treat androgen deficiency. When the causes are secondary to hypothalamus or pituitary disorders, Human Chorionic Gonadatropin (HCG) injection may be used instead.[174-176]

Grade B, Level 2++

8 Tubal-infertility (preventive strategies & treatment)

A significant proportion of infertile women cannot conceive due to damaged fallopian tubes. The common causes of tubal infertility are pelvic infections, endometriosis and scarring secondary to other insults, including surgery. Although the pathogenesis is varied, the approach to assessment of tubal patency and the treatment for tubal infertility remains similar.

Chlamydia trachomatis is a common pathogen, affecting up to 16% of asymptomatic local women below 25 years of age who present with unwanted pregnancies. The prevalence increases in the infertile population. Chlamydial infection of the fallopian tubes results in scarring and in some cases occlusion of the lumen, leading to infertility. Unlike gonorrhoea, women affected by Chlamydia are often asymptomatic.

8.1 Screening for Chlamydia trachomatis

C Women with high risk profiles (early sexual debut, multiple partners, non-compliance with safe sexual advice, etc.) should be screened for Chlamydia trachomatis in their urogenital tracts and be treated promptly to prevent future repercussions including tubal infertility.[177-182]

Grade C, Level 2+

8.2 Management of Chlamydia trachomatis infection

C Partners of Chlamydia positive women should be tested and treated as well, to prevent re-infection of the treated women. Positive cases should be referred to the Department of STI Control for contact tracing and treatment.[179, 183-184]

Grade C, Level 2+

A Oral doxycycline (100mg twice daily for 7 to 14 days) and azithromycin (1gm stat dose) are recommended antibiotics against Chlamydia trachomatis.[185-188]

Grade A, Level 1++

B High risk women who are scheduled for invasive instrumentation of the reproductive tract should be empirically treated for Chlamydia, to prevent ascending infection of the upper reproductive tract, or re-activation of past infection.[44,189-190]

Grade B, Level 2++

Endometriosis affecting the pelvic structures can damage the fallopian tubes. Adhesions around the fallopian tubes due to previous infection, inflammation or surgery can lead to occlusion of the tubes. About 14% of infertile women have tubal disease as a contributory cause.[152] Available tests for tubal patency include hysterosalpingography (HSG), and the current gold-standard is laparoscopic chromotubation. Referral to a fertility expert is recommended, so that the most appropriate assessment modality may be used for the individual woman. Women with tubal infertility should be referred to fertility surgeons who can provide counselling on their treatment options, as well as, access to the services required (assisted reproductive technologies or microsurgery).

8.3 Screening for tubal disease

GPP Assessment of tubal patency should be considered in all infertile women.

GPP

B Women with low risk for tubal disease (based on the history and physical examination), should be screened with a HSG for tubal patency as part of assessment for infertility.

Grade B, Level 2++

9 Endometriosis

Endometriosis is defined as the presence of endometrial-like tissue outside of the endometrial cavity. It is one of the commonest causes for female infertility with up to half of infertile women having endometriosis.[191] Fecundity in normal women is 0.15 to 0.20 (probability of pregnancy) per month, but decreases to 0.02 to 0.10 in women with untreated endometriosis.[192] This condition is present in all populations and not limited to any ethnic or social groups. It affects women in the reproductive age-group, although some may still experience symptoms after menopause, mainly due to the scarring from previously active disease.

Women affected by endometriosis may present with a wide plethora of symptoms, which commonly includes dysmenorrhea, chronic pelvic pain, dyschezia and dysparuenia. Some may not experience any symptoms, while others suffer from infertility. When the history is suggestive, physical examination should be directed at identifying disease in the pelvis.

Women with endometriosis and infertility should be referred to a centre with expertise in laparoscopic treatment of the disease, as well as provide artificial reproductive techniques to circumvent infertility attributed to endometriosis in selected cases.

9.1 Examination and imaging for suspected endometriosis

C A detailed vaginal examination with bimanual palpation, and / or rectal examination is essential to detect nodular lesion on the uterosacral ligaments, rectovaginal septum, or other surfaces accessible digitally. The detection rate of physical examination is better during menstruation.[193]

Grade C, Level 2+

Transvaginal ultrasound scan is a useful diagnostic tool for ovarian endometrioma with positive likelihood ratios between 7.6 to 29.8 and negative likelihood ratio ranging from 0.12 to 0.4.[194] It is less reliable in detecting surface disease or lesions infiltrating the peritoneum or

rectovaginal septum. Magnetic resonance imaging (MRI) may be able to detect deeply infiltrating lesions or rectovaginal septum disease, but evidence is still lacking. As deep lesions with minimal surface signs may be missed on laparoscopy, pre-operative MRI may be a useful complement.[195-196]

9.2 Magnetic Resonance Imaging (MRI)

C Magnetic resonance imaging may be considered as an adjunctive investigation tool to laparoscopy in the diagnosis of deeply infiltrating endometriosis.[195-196]

Grade C, Level 2+

9.3 Blood test

B Serum CA125 should not be used in the routine investigation of endometriosis due to inadequate specificity and sensitivity.[193, 197-198]

Grade B, Level 2++

Serum CA125 has limited value in the diagnosis of mild endometriosis, but is a more useful aid in diagnosing moderate-severe disease as the level of serum CA125 may be raised in endometriosis, as well as other diseases involving the pelvic organs and peritoneum, including cancer.

9.4 Laparoscopy

D Diagnosis of endometriosis should be made at laparoscopy unless disease is visible in the vagina or elsewhere.[199]

Grade D, Level 4

The gold standard for diagnosis of endometriosis is laparoscopy. It should be undertaken by experienced gynaecologists who can recognize the widely variable appearance of active endometriosis, as well as the residual scarring. Routine histological proof of endometriosis found at laparoscopy is not necessary and a negative histology does not preclude the diagnosis.

9.5 Ovarian suppressive treatment

C Diagnostic laparoscopy for endometriosis should not be undertaken within 3 months of ovarian suppressive treatment, as there is a high risk of missing the lesions and leading to a false negative result.[200]

Grade C, Level 2+

10 Cost-effectiveness issues

Moayeri et al (2009) conducted a cost-effectiveness analysis of laparascopy in women with unexplained infertility, using a computer-generated decision analysis tree and data extracted from the published literature and an infertility clinic in the USA. The authors found that laparoscopy with expectant management was more cost-effective (with an incremental cost-effectiveness ratio of US$128,400 per live birth) than no treatment, standard infertility treatment algorithm and laparoscopy with infertility therapy. The authors concluded that laparoscopy was cost-effective in the initial management of young women with infertility, particularly when infertility treatment dropout rates exceeded 9% per cycle.[201]

However cost-effectiveness analyses from other countries are not easily generalisable to Singapore's context and should be interpreted with caution as the costs in these countries tend to be very different from those in Singapore, and costs between public and private institutions in Singapore also tend to vary greatly.

A study conducted in Singapore[202] examined whether surgical reversal of women with previous tubal sterilization was viable for women who had undergone tubal sterilization and subsequently sought to give birth. The study concluded that surgical reversal after sterilization for patients younger than 40 years old was favourable and suggested that when conditions were suitable, laparoscopic reversal of tubal sterilization should be performed instead of in-vitro fertilization as the estimated average cost per delivery for laparoscopic reversal was lower when there were no multiple pregnancies.

11 Clinical quality improvement

The following are some suggested clinical quality improvement parameters, based on recommendations in these guidelines:

1. Proportion of patients seeking treatment for infertility at a primary healthcare setting, who received lifestyle advice/counselling (e.g. on optimal Body Mass Index, smoking and drinking habits) to help optimise their natural fertility.

2. Proportion of couples seeking treatment for infertility, for which a detailed history-taking and clinical examination is carried out. (Refer to Annex A for details.)

Annex A History taking and clinical examination

History taking

1. Female Partner

- Detailed history of the duration of infertility, previous pregnancies, age, occupation including contact with radiation/chemicals
- Other symptoms like galactorrhea, hirsutism, acne, hot flushes
- Menstrual history including irregular, painful or heavy periods
- Contraceptive history and its associated problems encountered
- Sexual history including problems with intercourse, frequency and timing
- Current and past medical history including diabetes, hypertension, pelvic infection, ovarian cyst, eating disorders, abnormal pap smears, cervical conization, surgery, rubella status
- Current and past medical therapy including consumption of folate, steroids, traditional medications
- Lifestyle factors, including details on smoking, alcohol consumption and exercise
- Family history, including cancers, medical disease and consanguinity
- Social history, including family support.

2. Male Partner

- Detailed history of the duration of infertility, age, occupation including contact with radiation/chemicals
- Sexual history including problems of erectile dysfunction, ejaculatory problems, loss of libido, previous marriage or children from a previous relationship
- Contraceptive history including permanent methods like vasectomy
- Current and past medical history of mumps, sexually transmitted diseases, hydrocele, varicocele, undescended testis and hernia repair. Diabetes, hypertension
- Lifestyle factors, including details on smoking, alcohol consumption and exercise
- Family history of similar problems among the male members and consanguinity
- Social history, including family support.

Clinical examination

1. Female Partner

- Weight and height including body mass index calculation (BMI)
- General examination for hirsutism, acanthosis nigricans, acne, thyroid gland disorders
- Breast examination for lumps, galactorrhea
- Abdominal examination for masses, surgical scars
- Pelvic examination for enlarged clitoris, cervical excitation, size of uterus, adnexal mass or tenderness, abnormal vaginal discharge, thickened uterosacral ligament

2. Male Partner

- Weight and height including body mass index calculation (BMI)
- General examination for secondary sexual characteristics
- Breast examination for gynaecomastia
- Abdominal examination for abdominal masses, undescended testis, inguinal hernia
- Genital examination noting size and shape of penis, position of external meatus, testicular volume, palpation of epididymis and vas deferens and rectal examination for prostate enlargement

Annex B Known causes of male infertility

1. Spermatogenesis failure
    a. Chromosomal/ genetic causes
    b. Undescended testis
    c. Infections
    d. Torsion
    e. Heat
    f. Varicocele
    g. Medication / toxin
    h. Radiation / chemotherapy
    i. Unknown cause

2. Blockage of sperm transport
    a. vasectomy
    b. Infection / STI
    c. Prostate related problems
    d. Absence of vas deferens

3. Sperm antibodies

4. Sexual problems
    a. Retrograde and premature ejaculation
    b. Failure of ejaculation
    c. Infrequent intercourse
    d. Spinal cord injury
    e. Prostate surgery
    f. Erectile dysfunction

5. Hormonal problems
    a. Pituitary tumours
    b. Hypogonadotrophic hypogonadism
    c. Steroid abuse

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Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System. Alternatively, you can claim one CME point under Category 3B (Distance Learning - Verifiable Self Assessment) if you answer at least 60% of the following MCQs correctly. You can submit your answers through the SMJ website at this link: http://sma.org.sg/publications/index.aspx?ID=26 *(the link will only be available once the February 2014 issue of the SMJ becomes available)*. The answers will be published in the SMJ April 2014 issue and at the MOH webpage for these guidelines after the period for submitting the answers is over.

Instruction: Indicate whether each statement is true or false.

		True	False
1.	The following advice could be given to couples to optimise their natural fertility:		
	A) Advise couples to time sexual intercourse to coincide with ovulation.	☐	☐
	B) A Body Mass Index (BMI) of 19 to 29 is optimal for women trying to achieve pregnancy.	☐	☐
	C) Smoking is not associated with reduced fertility.	☐	☐
	D) Excessive alcohol intake is detrimental to semen quality.	☐	☐
2.	The following should be conducted as part of investigations of infertility:		
	A) Semen analysis for men.	☐	☐
	B) Sperm function tests for men.	☐	☐
	C) Taking of menstrual history for women.	☐	☐
	D) Transvaginal hydrolaparoscopy for assessment of tubal damage.	☐	☐

		True	False
3.	In the management of infertility in women with polycystic ovary syndrome,		
	A) Preconceptional counselling should be provided to emphasise the importance of lifestyle, especially weight reduction and exercise in overweight women, smoking and alcohol consumption.	☐	☐
	B) The recommended first-line treatment for ovulation induction is the anti-estrogen clomiphene citrate.	☐	☐
	C) Metformin should be routinely used in combination with clomiphene citrate for ovulation induction.	☐	☐
	D) Patients presenting with polycystic ovary syndrome, particularly if they are obese, have a strong family history of Type 2 diabetes or are over the age of 40, should be offered a glucose tolerance test.	☐	☐
4.	In the management of male infertility,		
	A) Semen analysis should be done as the primary investigation.	☐	☐
	B) Advice on cessation of smoking, steroid use and withdrawl of offensive medication should be given at the primary care setting.	☐	☐
	C) Phosphodiesterase type 5 (PDE 5) inhibitors should be prescribed to men with premature ejaculation, regardless of whether there is associated erectile dysfunction.	☐	☐
	D) Phosphodiesterase type 5 (PDE 5) inhibitors such as tadalafil, sildenafil and vardenafil have similar efficacy and the choice of drug should be individualised based on patient needs.	☐	☐

		True	False
5.	In the management of tubal infertility,		
	A) Women with high risk profiles (e.g., early sexual debut, multiple partners, non-compliance with safe sexual advice) should be screened for Chlamydia trachomatis in their urogenital tracts.	☐	☐
	B) Chlamydia trachomatis should be treated promptly to prevent future repercussions, including tubal infertility.	☐	☐
	C) The assessment of tubal patency should be considered in all infertile women.	☐	☐
	D) A blood test for serum CA125 should be used as routine investigation of endometriosis.	☐	☐

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