The subfertile couple

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Abstract

Difficulty conceiving affects one in seven couples. Infertility, and its treatment, is stressful. Initial investigations are generally recommended after 12 months of failure to conceive, but this should be individualized. Advice on lifestyle changes that may have a positive impact on conception and general long-term health of the couple should be offered. Counselling should be offered to support couples in exploring their feelings and to help maximize emotional wellbeing.

Keywords endometriosis; female; infertility; investigations; male; subfertile couple; unexplained

Introduction and Epidemiology

Around one in seven couples may have difficulty conceiving. A woman's maximum monthly chance of becoming pregnant after unprotected intercourse is about 30% per cycle. Traditionally, subfertility is defined as failure to conceive after regular unprotected sexual intercourse for 12 months. Failure to conceive may have significant psychological impact, eliciting a variety of moral, cultural, spiritual and emotional feelings. This is true across all population groups. However, in certain communities, especially ethnic minorities, the consequences of infertility can be overwhelming, sometimes leading to rejection and isolation from the community. This is especially true for the female partner who is often viewed as being responsible for the failure to produce children. Sensitivity, awareness and understanding are important for all staff involved in the management of the infertile couple.

Aetiology

Subfertility is caused by a variety of factors, both female and male contributing almost equally. The most common causes of infertility are ovulatory disorders (25%), tubal pathology (15%), sperm dysfunction (30%) and uterine or peritoneal factors (10%). Twenty per cent of cases are unexplained.

Ovulatory disorders

Disorders of ovulation are classified by WHO into three groups.

i. Group I (hypothalamic pituitary failure)

Hypothalamic/pituitary disorders characterised by low FSH/LH and low oestradiol. This may occur secondary to stress, endurance exercise, brain tumours, head injury, genetic abnormalities. It may also be idiopathic.

ii. Group II (dysfunction of the hypothalamic-pituitary-ovarian axis)

Hypothalamic-pituitary-ovarian dysfunction characterised by normal FSH/LH and normal or slightly elevated oestradiol levels. Polycystic ovarian syndrome and weight related hormonal disorders are the most common causes in this group.

iii. Group III (ovarian failure)

Primary ovarian dysfunction is characterised by high FSH/LH and low oestradiol. The cause is most often premature ovarian failure (chromosomal, genetic or infective, immunological, iatrogenic (surgery, radiation or chemotherapy) or idiopathic.

Tubal pathology

Post infective tubal disease remains an important cause of infertility.

Sperm dysfunction

The quality of the semen is reported to be gradually deteriorating, with multiple underlying contributory factors implicated such as smoking, obesity, environmental contamination, underlying genetic causes and advancing age.

Unexplained infertility

This is where investigations demonstrate normal ovulatory function, tubal patency and normal sperm parameters and constitutes one of the largest groups.

History taking and physical examination

Thorough history of both partners is essential. The extent of any physical examination during the clinic visit is usually guided by the history and is directed at identifying potential causes or comorbidities, as listed in Table 1.

Investigating infertility

NICE guidelines recommends initiating investigation of the infertile couple after 12 months of actively trying to conceive. However, if there is no obvious reproductive pathology then investigations may be delayed for up to 2 years. This is especially so for young couples as they have good chance of spontaneous conception. Equally, if there is an obvious reason for failing to conceive (e.g. amenorrhoea), then referral and investigation should start sooner than the recommended 12 months.

Investigations are aimed at finding underlying causes, but also should screen for infections which may have been causative/contributory or which may nevertheless influence management. These investigations are summarised in Table 2.

Semen analysis, mid-luteal D21 progesterone and infection screening are commonly done by the primary care provider. Other investigations are usually reserved for secondary and tertiary centres depending on availability.

Infection screening

Screening for chlamydia and syphilis should be offered and rubella immunity should be checked. HIV and hepatitis screening

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History and physical examination for the subfertile couple

Female	Male
History	**History**
1 Demographics -age, BMI	1 Demographics-age, BMI
2 Previous pregnancies	2 Past pregnancies in other relationships
3 Menstrual history	3 Medical and surgical history
a Dysmenorrhoea	4 Testicular problems e.g. infection, injury, maldescent or surgery
b Oligomenorrhoea	5 Smoking/alcohol/substance misuse
4 Smoking/alcohol/substance misuse	6 Family history of subfertility or genetic problems
5 Medical and surgical history	7 Medication (including anabolic steroids)
6 Medication	8 Sexual history, erectile dysfunction
7 Sexual history	9 Past history of STI and treatment given
8 Sexually transmitted disease and type of treatment received	**Examination**
9 Cervical smear history	1 BMI
10 Family history of genetic problems	2 Abdominal examination looking for inguinal surgical scars.
Examination	3 Testicular examination-assessment for varicosities, testicular masses, tenderness and testicular volume.
1 BMI	
2 Hirsutism, acne	
3 Pelvic and abdominal examination as indicated in the history	

Table 1

is not done routinely at the primary care level, but are usually required for those couples seeking assisted conception or where there is a specific clinical indication based on history.

Management of the subfertile couple

Management of the infertile couple must be individualized, based on the results of history taking, examination and the results of investigations. However, there are also general measures applicable to all, including lifestyle changes, support and counselling.

Lifestyle changes

There are various modifiable lifestyle changes that may have a positive impact on conception and general long-term health of the couple. These should be addressed as an essential part of subfertility management and counselling. They include weight reduction, nutrition, exercise, stopping smoking, reduction in alcohol consumption as well as reviewing medication, including the potential abuse of anabolic steroids. Couples may be too embarrassed to report unsatisfactory sexual activity, and health care providers often do not capture this aspect clearly in their history. Coital problems are responsible for failure to conceive in up to 6% of couples. Satisfying and regular sexual activity can be adversely affected by erectile dysfunction, dyspareunia and the demands and stresses of modern day living, and these should be considered.

Counselling

The negative impact of subfertility on psychological and emotional wellbeing is well recognized, however formal support and/or counselling has not routinely been provided to couples experiencing subfertility, or undergoing investigation and treatment for it. Health care staff must appreciate this and help to signpost and refer for formal counselling, ideally to professionals who have experience of helping to support couples in this situation. These services are mainly provided in tertiary assisted conception facilities where HFEA regulations make provision of counselling mandatory. Counselling helps couples better understand the implications of their treatments, the choices they make and to better accept the outcomes of treatment, particularly if unsuccessful.

The British Infertility Counselling Association (BICA) is the national association for fertility counsellors and has very helpful information on their website for patients and healthcare providers; https://www.bica.net/browse.

Case discussions

Three cases are presented to help illustrate the early steps in the investigation and management of subfertility.

Case 1

Mr & Mrs S are referred to a hospital infertility clinic by their GP with a history of failure to conceive for 14 months' duration. Mrs S is 28 years old and has never been pregnant. Her partner is 32 years old and he has never had a pregnancy in any past relationships.

Both have no significant medical or surgical history, take no medications and are non-smokers.

Examination of the both partners is normal.

Mrs S has regular cycles and her mid-luteal phase progesterone is 40 nmol/L. Her pelvic ultrasound scan shows normal ovaries and a hystero-salpingogram (HSG) confirms patent fallopian tubes. Mrs S is negative for chlamydia and she is rubella immune.

Mr S has a semen sample analysed with the following results:

- Volume: 2.5 ml
- Sperm count: 4.5 millions/ml
- Normal forms: 4%
- Total Motility: 30%

What are the next steps?

When an abnormal semen analysis result is obtained, the test should be repeated 10–12 weeks later, or sooner if the couple are >35 years of age. Mr S repeats the test which again shows semen parameters suggestive of oligospermia.

Abnormal sperm parameters are a common occurrence during investigations for subfertility and in at least half of all cases there is no underlying cause (idiopathic). However, in the remaining cases, causes of oligospermia can be classified as pretesticular, testicular or post-testicular (Table 4)

An abnormal semen result can come as a great shock and therefore sensitivity and clarity when explaining the results, and their implications, is vital. It is important to emphasise that low sperm count reduces the chance of conception but does not mean sterility. Therefore, there remains the possibility of spontaneous conception in all but the most extreme cases.

Investigations for the subfertile couple

Target	Investigation	Comment
Male factor	Semen analysis	• Use quality assured laboratory • Timing; <3 h between production and analysis • Abstinence of 2–3 days prior to sample production • Use an appropriate container supplied by the fertility service • Be aware of potential cultural issues; some prohibit masturbation • UseWHO (2010) guidance for normal levels (see Table 3)
Tubal factor	HSG	• Advantages ○ outpatient service ○ rapid results ○ intrauterine adhesions (Asherman's syndrome) can be diagnosed • Risks ○ exacerbation of pelvic infection ■ Chlamydia screening is essential ■ prophylactic antibiotic should be used where screening has been missed. ○ Some patients find this procedure painful.
	HyCoSy	• uterine, ovarian and adnexal morphology can be investigated • tubal patency is assessed • out-patient procedure • not universally available
	Laparoscopy and dye test	• Laparoscopy with attendant risks ○ tubal patency assessed and other pelvic pathology can be diagnosed. ○ treatment can potentially be carried out at the same time for certain pathologies
Ovulatory factor Irregular cycles/ anovulation	D21 progesterone (mid luteal)	• simple test to carry out for woman with regular monthly cycles • mid-luteal phase levels >30 nm/l suggest ovulation
	Ultrasound follicular tracking	• timing may be a problem with irregular cycles • there may be cycle to cycle variations in levels therefore may need repeating.
	FSH/LH/oestradiol/ prolactin/testosterone levels d2-5	• requires skill and hospital attendance • not usually available in most primary and secondary care settings. If a woman is having very infrequent menses, these hormone profiles may need to be performed following a progesterone challenge test
Ovarian reserve	Antral Follicle Count (AFC)	• >4 follicles per ovary is considered sufficient (not usually available in primary care) • Not usually recommended in the primary care
	Anti-Mullerian hormone (AMH)	• Follicular phase gonadotrophins
	FSH,LH, oestradiol	(d2-4 (as high baseline levels of FSH/LH and low levels of oestradiol provide indirect evidence of lower ovarian reserve)
Endometrial and uterine Factor	Pelvic ultrasound	• diagnosis of o Fibroids ○ Endometrial polyps ○ Hydrosalpinx ○ Endometrioma ○ Ovarian cysts ○ Uterine anomalies
	Hysteroscopy	• Allows assessment of the endometrium for polyps, submucous fibroids and uterine anomalies

Table 2

This couple should be referred to a tertiary centre for assisted conception.

Case 2

A 28-year-old woman presents with a history of secondary infertility of 18 months' duration. She gives a history of previous spontaneous conception 5 years ago, resulting in a normal pregnancy and delivery. Her BMI is 35 and she has a normal menstrual cycle. She has no significant medical or surgical history. She is a non-smoker and is not currently taking any medications. Her partner is 35 years old. They have been in stable relationship for the past 8 years. He is not currently on any medication.

A number of basic investigations are perfomed, and the results are as follows;

- Rubella Immune

Normal Semen Parameters (WHO 2010)

Normal Semen Parameters (WHO 2010)	Normal ranges
Semen volume (ml)	1.5(1.4–1.7)
Sperm concentration (million/ml)	15 (12–16)
Total sperm count (million/ml in ejaculate)	39(33–46)
Progressive motility (PR) (%)	32(31–34)
Total motility (PR + Non PR)	40(38–42)
Vitality; live spermatozoa (%)	58 (55–63)
Normal sperm morphology (%)	4 (3.0–4.0)

Table 3

- Mid-luteal phase progesterone: 32 nmol/L
- Pelvic ultrasound – normal appearance of both ovaries and of uterine cavity
- HSG shows bilateral tubal patency with prompt flow of dye
- Chlamydia screening negative

Her partner's semen analysis is reported as follows:

- Volume: 3.5 ml
- Count: 24.5 millions/ml
- Normal forms: 3%
- Total motility: 50%

All parameters are normal apart from a slightly lower proportion of normal forms, but within the normal range. However, the good sperm count and sperm motility is reassuring. This sample should be regarded as potentially fertile.

What are the next steps?

Causes of male factor infertility

Type	Cause
Pretesticular (Hypothalamic or pituitary disorder)	• Kalman's syndrome • Pituitary damage by tumour • Hyperprolactinaemia • Male exogenous steroids
Testicular (Spermatogenetic failure)	• Idiopathic • Genetic defects • Kleinfelter's syndrome • Noonan's syndrome • Y- microdeletions • Undescended testis • Testicular disease (orchitis, tumours)
Post testicular (Obstructive or sperm dysfunction)	• Congenital bilateral absence of vas deferens (CBAVD) (commonly secondary to cystic fibrosis) • Infection and subsequent blockage of the vas deferens • Kartagener's syndrome • Vasectomy • Erectile dysfunction

Table 4

No further investigations are required. The Investigations carried out are normal, meaning that this is unexplained secondary subfertility. The woman should be advised to lose weight and to take a higher dose of folic acid (5 mg) in the peri-conceptual period.

Unexplained infertility is, strictly speaking, not an actual diagnosis. It describes the failure of conception in the presence of regular unprotected sexual intercourse, demonstrable tubal patency, regular ovulation and normal semen analysis. Unexplained subfertility is present in approximately 30–40% of subfertile couples. In such cases, the chances of becoming pregnant during the subsequent 24 months of actively trying is high. Fertilisation and implantation requires competent gametes, a functional fallopian tube, a supportive peritoneal milieu and a receptive endometrium. Advanced female age, and to a lesser extent male age are detrimental to gamete quality leading to less efficient fertilization and poor-quality embryos. This also results in an elevated miscarriage risk. Tubal patency is not synonymous with normal tubal function. Mild asymptomatic tubal infection without blockage can damage epithelial activity and compromise gamete transfer and fertilisation. Mild endometriosis and peritoneal adhesions are associated with subfertility however these will only have been excluded if a laparoscopy has been performed during the investigative work up.

Obesity is associated with reduced fertility in both men and women. Male obesity is linked to decreased libido, reduced sperm quality and increased sperm DNA damage, the latter not being assessed in a standard semen analysis. In women, obesity is associated with anovulatory cycles, a longer time to achieve a pregnancy, and an increased subsequent miscarriage risk.

Weight reduction through diet and exercise should be advised, with NICE recommending a target BMI of 30.

Expectant management is appropriate after addressing the lifestyle issues because the couple are still young. A period of up to 2 years would be appropriate as they have a good chance of spontaneous conception and they would not be eligible for free assisted conception treatment through the NHS.

Couples may find this unacceptable. Alternatively, various forms of assisted reproductive technology can be offered. Timed intercourse, intra-uterine insemination in the peri-ovulatory phase, ovarian stimulation, with or without intrauterine insemination (IUI), or even in vitro fertilization (IVF), can be considered.

A Scottish multi-centre trial comparing timed intra-uterine insemination in a spontaneous cycle with expectant management did not report any significant difference in pregnancy rates between the study groups. Recently, Farquhar and colleagues conducted a randomized controlled trial to compare ovarian stimulation with IUI against expectant management for the care of unexplained infertility. The Cumulative Live Birth Rates (intention-to-treat) was significantly higher in the IUI group (31% vs 9%; risk ratio [RR], 3.41; 95% confidence interval [CI], 1.71–6.79).

In Vitro Fertilization (IVF) is an option and the couple should be counselled with regards its success rates, risk of multiple pregnancies, complications (including ovarian hyperstimulation syndrome) and high failure rate.

Case 3

A 32-year-old nulliparous woman with a BMI of 24 has been trying to conceive for the past 18 months. She has regular periods but they are extremely painful. She suffers from chronic pelvic pain and complains of deep dyspareunia. There is no past history of pelvic infection. Pelvic examination demonstrates tenderness in both adnexae. Her partner is 36 years and has a BMI of 32. He is a non-smoker and has had two children in a previous relationship.

Simple investigations are reported as follows;

- Mid luteal phase progesterone: 45 nmol/L
- Pelvic ultrasound: normal
- Chlamydia screening negative

His semen analysis results are:

- Volume: 4.5 ml
- count: 54.5 millions/ml
- Normal forms: 4%
- Total motility: 70%

What other investigations should be considered?

The clinical presentation with dysmenorrhoea, chronic pelvic pain and deep dyspareunia raise the possibility of pelvic pathology. She should be offered a laparoscopy and dye test in preference to hysterosalpingogram (HSG) to assess tubal patency as this procedure will also to diagnose or rule out pelvic pathology such as endometriosis and adhesions.

Bilateral tubal patency was demonstrated. Deep deposits of endometriosis were noted on both uterosacral ligaments and superficial deposits were also noted on the surface of both ovaries. It was possible to ablate all visible deposits of endometriosis at the time of the laparoscopy because consent for this had been taken in advance of the procedure.

Endometriosis is a common condition although the true prevalence in the general population is unknown. Many women with endometriosis are asymptomatic and conceive spontaneously. Commonly, endometriosis presents with pelvic pain, dysmenorrhoea, heavy menstrual bleeding, dyspareunia and subfertility. Endometriosis is 6–8 times more common in women experiencing subfertility and is found in approximately 7% of patients undergoing laparoscopic sterilisation. Most often, a diagnosis of endometriosis is made on clinical grounds. Ultrasound imaging is helpful in identifying endometriomas. Laparoscopy remains the gold standard for diagnosing endometriosis.

Although endometriosis is more common in subfertile women, a causal relationship has not been clearly established. The time to natural conception in women with minor endometriosis is longer compared to those with unexplained subfertility, suggesting that endometriosis may be a contributing factor.

How does endometriosis contribute to subfertility?

Multiple mechanisms have been postulated to explain the role of endometriosis in subfertility. Inflammation leading to adhesion formation, can lead to tubal dysfunction or blockage as well as interfere with ovulatory activity.

Impaired immunological activity and inflammation of the pelvic organs may interfere with peritoneal fluid composition, follicular development, ovulation, fertilisation, early embryo development and implantation. Interference with follicular development may lead to poor oocyte quality. Endometriomas have been shown to be associated with a reduction in the number of primordial follicles thus reducing ovarian reserve. Coital frequency is significantly affected by pelvic pain and dyspareunia and this reduces the chances of conception.

Treatment for endometriosis associated subfertility

Medical treatment of endometriosis does not improve fertility. Surgical ablation or excision of mild and minor endometriosis has been shown to be beneficial. For moderate and severe endometriosis surgery may improve fertility although this has not been subject to randomized studies. Surgery in these cases should be undertaken by appropriately trained and experienced gynaecologists. Laparoscopic surgery is the preferred approach. The benefits on fertility in such cases may be due to restoration of pelvic anatomy, and amelioration of pain symptoms leading to increased coital frequency.

2Management of endometrioma identified in subfertile patients can be challenging. The RCOG has recently published a scientific impact paper to offer guidance. Expectant management is appropriate for young couples where an endometrioma is identified with no suspicion of malignancy. The decision to operate should be individualized bearing in mind the potential for damage to the ovarian cortex. Surgery should be considered for patents with significant pain and for cysts greater than 3 cm in size.

For moderate or severe cases, or where conception fails following surgical management, IVF remains the mainstay of management for subfertile women with endometriosis.

Conclusion

Failure to conceive is common and has a negative impact on psychological and emotional wellbeing. Treatment for infertility is also extremely stressful. All staff involved in the management of infertile couple should be sensitive to this. Formal counselling services should be available.

Female and male factors contribute almost equally in the failure to conceive. and both should be investigated. Expectant management and lifestyle changes should be advised where appropriate.

Surgery for minor degrees of endometriosis improves conception rates. Patients with endometriomas greater than 3 cm and significant pain symptoms should be considered for surgery by suitably trained gynaecologists. ◆

FURTHER READING

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Practice Points

- All subfertile couples should be encouraged to address lifestyle factors as part of general health measures, and to improve fertility
- Counselling should be considered to address the emotional and psychological effects of infertility
- When and how to investigate the subfertile couple should be individualized
- Male and female factors should be investigated
- Medical treatment of endometriosis does not improve fertility