The subfertile couple

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Abstract

Subfertile couples by definition require medical help to get pregnant after trying unsuccessfully for a variable period of time. Although the term subfertility is also occasionally used in the context of women who can conceive, but suffer recurrent miscarriages, this broad aspect is outside the scope of this chapter. Subfertility can seriously affect mental and social well-being, although not generally viewed as a disease that significantly causes physical ill health. On the contrary, subfertility may in fact be the early manifestation of serious co-existing disease. Advances in assisted reproductive technology in the last 25 years have simplified and diversified treatment options, thereby rendering the terms infertility and sterility unfashionable. As a result, there is now an unfortunate trend for couples to be subjected to superficial medical history and only perfunctory physical examinations, occasionally missing the presentations and implications of associated co-morbidities, with devastating implications. There are now many guidelines on the initial investigations and subsequent management of the subfertile couple. It is therefore now relatively easy to assist a couple to achieve a pregnancy. However, dealing with the devastating news of causative factors like azoospermia, genetic disease, congenital anomaly or premature ovarian failure can be very difficult. To discuss these sympathetically, professionals require interpersonal skills in breaking bad news. Finally, a multidisciplinary team approach should be adopted to cater for the long-term health consequences, whenever co-morbidities are detected.

Keywords anovulation; azoospermia; fallopian tube diseases; hydrosalpinx; infertility; IVF; oligospermia; PCOS

Subfertility affects approximately one in seven couples. One of the measures of fecundity (ability to reproduce) is fecundability (the monthly probability of pregnancy); which is only about 15%. Theoretically therefore, 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 one year and 95% by the end of the second year. Other factors can affect these rates however; including age of female partner over 36 years and presence of co-morbidity. The distribution of causative factors varies slightly from one region to another. In the UK about 25% of cases, have no identifiable causes (unexplained), whereas male factors can account for up to 30%. The breakdown of female factors is shown in Figure 1. In about 20% of cases, both male and female factors may co-exist.

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The management of a subfertile couple starts in primary care with a detailed medical, gynaecological, social and family history followed by a general and pelvic examination. Other pathologies are occasionally present and it should always be borne in mind that subfertility might present the opportunity to detect and treat serious or life-threatening co-morbidity. For example, azoospermia or severe oligozoospermia may be the presentation of a testicular or adrenal androgen-secreting tumour; or side effects of medications (Table 1). Similarly, gonadal or adrenal tumours may rarely present with anovulatory subfertility, particularly if associated with a high blood testosterone levels and rapidly progressive features of hyperandrogenisation or virilisation in younger women. Pelvic endometriosis may present with chronic pain and subfertility from severe tubo-ovarian disease, the surgical treatment of which may predispose to premature menopause. Tuberculosis is becoming more common in the UK with the increase in human migration. This disease may present for the first time with chronic tubal disease in a subfertile couple.

General lifestyle advice should be offered on the effects of obesity, cigarette smoking, occupational hazards, alcohol or recreational drug misuse on fertility. Baseline tests include semen analysis, cervical smear test, screening for chlamydia, tests of ovulation and tubal patency. Semen analysis should ideally be performed in dedicated andrology laboratories with semen parameters measured against the World Health Organisation (WHO) reference values (Table 2). Semen analysis should be repeated approximately three months after an abnormal result. If severely abnormal, further tests are mandatory as shown in **case 1**. Occasionally a very low ejaculate volume may be associated with azoospermia, or severe oligozoospermia, in which case the diagnosis of retrograde ejaculation should be suspected, leading to the analysis of a post-ejaculate urine sample.

The majority of regularly menstruating women are ovulating, therefore a single assay of mid-luteal phase progesterone is an adequate test of ovulation in the UK. However, in women with irregular menstrual cycles, it can be difficult or impossible to time a mid-luteal progesterone assay. For this group, anovulation should be suspected therefore, assays of follicle stimulating hormone (FSH) and luteinising hormone (LH) should be obtained in the basal (proliferative) phase of the menstrual cycle. For women older than 37 years, it may be prudent to assay FSH as a baseline test of ovarian reserve. Unless indicated by suspicions of co-morbidities from the history, assays of prolactin, or thyroid function tests are not routine part of basic subfertility investigations (Table 3).

The default test for tubal patency is hysterosalpingogram (HSG). Other credible alternatives, where the skills are available, are selective salpingogram and tubal catheterisation, and hysterosalpingo-contrast-sonograpgy (HyCoSy). However, diagnostic laparoscopy and dye test is the preferred choice, if there are clinical suspicions of pelvic inflammatory disease, endometriosis, previous pelvic surgery or ectopic pregnancy.

Subfertility and its management can present the couple with significant stress and anxiety, which may adversely affect their physical relationships. They should therefore be offered counselling services at any stage of their management, particularly if any assisted conception treatment is being considered. There is a

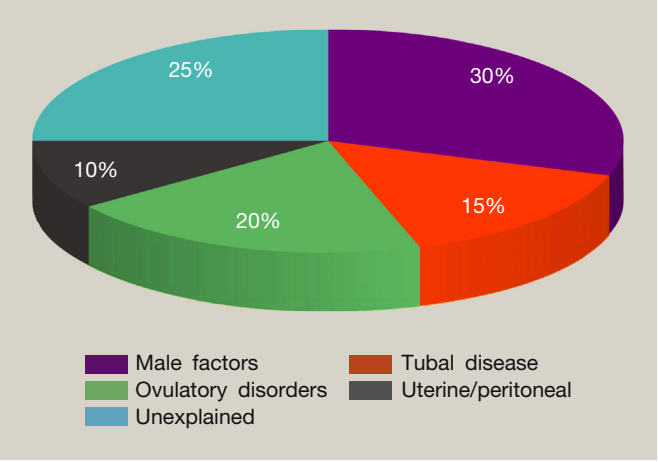

Figure 1 Causes of subfertility.

very wide spectrum of treatment options for subfertility, depending on mode of presentation, the duration of onset, age of the female partner and type of co-morbidity. It is not possible to deal with all treatment options of subfertility in this chapter; however the following cases are presented to illustrate the clinical presentations of a spectrum of subfertile couples.

Classification of azoospermia by causation or co-morbidity

Pre-testicular (hypogonadotropic hypogonadism) azoospermia
- Use of anabolic steroids (blood testosterone may be high if Sustanon is used)
- Extra-gonadal androgen producing tumours
- Pituitary tumours e.g. prolactinoma, craniopharyngioma, cancer
- Kallman's syndrome
- Haemochromatosis (iron overload)

Testicular azoospermia
- Trauma, torsion,
- Undescended testes (Cryptorchidism)
- Chromosomal (aneuploidies)
  - Klinefelter's syndrome
- Genetic disorders/mutations
  - 5 Alpha reductase deficiency
  - Androgen insensitivity syndromes
  - Sertoli only syndrome
- Infection involving the testes (mumps orchitis)
- Androgen producing testicular tumours
- Iatrogenic
  - Surgery, radiation or chemotherapy

Post testicular azoospermia
- Post infective: chlamydia, gonorrhoea, tuberculosis
- Iatrogenic: post hernia or hydrocoele surgery, vasectomy
- Genetic mutations
  - Cystic fibrosis
  - Congenital bilateral absence of the vas deferens
- Ejaculatory failure or retrograde ejaculation

Table 1

Case 1

Miss NW, aged 34 years and her partner Mr JG, aged 41 years, were referred to the local teaching Hospital from the district Hospital on account of secondary subfertility due to tubal disease of 12 months duration. They had been together for over two years. Coital frequency was at best twice a week because of the association with deep dyspareunia. Miss NW had a child aged 10 years from a previous relationship who lived with them. She had separated from her previous partner because of infidelity resulting in Chlamydia pelvic inflammatory disease, which was eventually treated after some delay in diagnosis. She was on folic acid, immune to Rubella, up to date with her cervical smear tests and had been advised to cut down on alcohol and her 25 cigarettes per day habit. Hysterosalpingogram (HSG) performed at the referring hospital showed bilateral large hydrosalpinges, with no peritoneal spillage on either side. All other fertility tests were normal. The couple had been told by the referring doctor that she had two options of definitive treatment; either tubal surgery or in-vitro fertilisation (IVF).

- What initial advice would you give to this couple?
- What is your opinion about the choice of tubal patency test in this case?
- What are the treatment options?

Pre-conception advice about diet, weight reduction, sensible use of alcohol, cigarette cessation and prophylactic folic acid is good practice during the first visit. Many couples also need to be advised on a coital frequency of about 3 times a week, not timed to ovulation unless medically indicated.

Most gynaecologists will disagree with the choice of HSG as the test of tubal patency for this patient. Whenever there is a reliable history of sexually transmitted disease (STD), or there was co-existing pelvic pain or dyspareunia, diagnostic laparoscopy and dye test is certainly a better choice as it allows assessment of the extent of tubal damage and inspection of the peritoneum for adhesions or endometriosis. Diagnostic laparoscopy allows staging of the degree of tubal disease in order to formulate a prognosis. For stage 1 (thin-walled with little or no fibrosis) and 2 (thick-walled with good mucosa), laparoscopic adhesiolyses and cuff salpingostomies performed at the same time could offer a clinical pregnancy rate (CPR) of up to 50% over three years; whereas, for stages 3 (thick-walled with marked mucosal damage, or a thick fibrous endosalpingeal adhesion) and 4 (tubo-ovarian mass or fibrosis, or an adherent hydrosalpinx with incarcerated ovary and/or isthmic damage), the rates over the same period were less than 12%. Furthermore, ectopic pregnancy rates after tubal surgery for stages 3 and 4 were as high as 25%.

The other treatment option was IVF. However, there is evidence that untreated hydrosalpinges or unilateral tubal disease, which communicates with the uterine cavity, could significantly reduce clinical pregnancy rates. Hydrosalpinges adversely affect endometrial receptivity, thereby decreasing the implantation rate and increasing the risk of early miscarriages. There is also evidence showing that laparoscopic salpingectomy or salpingectomies could more than double the live birth rate following IVF to about 30% per cycle in good centres.

She underwent diagnostic laparoscopy and staging of tubal disease, with additional consent to proceed to either adhesiolysis