



## **Fertility Treatment: what the GP needs to know**

A GP with an average list size of 1800 patients in the UK can expect to see approximately two infertile couples each year. The most important role for the GP is that of advocacy ensuring that couples receive the correct advice, investigations, management and referral.

## **Causes of infertility**

Broadly, the causes of infertility may be expressed as sperm problems, disorders of ovulation, tubal problems and unexplained infertility. Estimates of the prevalence of each cause vary between studies, but are approximately 25% for each.

The majority (approximately 90%) of women with an ovulatory disorder will have polycystic ovary syndrome (PCOS) and many women with PCOS are overweight or obese.

The initial assessment and investigation in primary care is aimed at evaluating the main causes of infertility.

## **Initial assessment**

History:

- Current menstrual history will help to determine the likelihood of an ovulation problem.
- The GP should be mindful of certain medical disorders that affect female fertility. These include: hypo/hyperthyroidism, prolactinoma, PCOS, hypothalamic pituitary disease, anorexia, weight loss, Cushing's disease, premature ovarian failure and ovarian dysgenesis.
- Tubal damage can be associated with abdominal operations, a history of pelvic inflammatory disease, sexually transmitted infections, endometriosis and adhesions.
- Smoking, alcohol and drugs can have a detrimental effect upon fertility and pregnancy.
- Male fertility can be adversely affected by testicular hyperthermia, certain drugs (sulphasalazine, nitrofurantoin, tetracyclines, cimetidine, ketoconazole, colchicine, allopurinol, alpha-adrenoceptor-blocking agents, propranolol, chemotherapeutic alkylating agents, cannabis, cocaine and anabolic steroids) as well as any other concurrent illness.
- Coital and social histories are important to ensure frequent unprotected intercourse.

Examination:

- General examination looking for features of thyroid disease, PCOS, weight problem and Cushing's disease.
- A pelvic examination is usually not necessary especially if requesting an HSG.
- Recording female BP is good clinical practice as well as giving a pre-pregnancy baseline.
- Recording female BMI is essential particularly in relation to anorexia, amenorrhoea, obesity and PCOS. A high BMI may also restrict access to some complex treatments.

### Investigations and diagnosis

Conception usually occurs after two years of regular unprotected intercourse. This statement is based on 'normal' population conception rates of 84% at one year and 92% at two years. Couples who have failed to conceive after one year of unprotected intercourse should be offered further clinical assessment and investigation. However earlier assessment should be offered where the woman is 36 years or more or if there are known causes of infertility.

The investigations that can usefully be performed in general practice are aimed at identifying the causes described above.

Initial investigations:

- Semen analysis. Two samples, three months apart unless the first sample is normal.
- Day 2-5 FSH (Follicle Stimulating Hormone) and LH (Leutinizing Hormone). Where available, AMH (anti-Müllarian hormone) is considered to be a better estimate of ovarian reserve and it can be taken at any time of the month.
- Mid-luteal progesterone. Helps to determine ovulatory and anovulatory cycles.

Assessment of tubal status:

- HSG (Hysterosalpingography). In some areas GPs have direct access to HSG for women not known to have co-morbidities such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis.

Additional investigations:

- Serum prolactin. Offered to women who have oligo/amenorrhoea, galactorrhoea or a pituitary tumour.
- Thyroid function tests. Offered to women with symptoms of thyroid disease.
- Serum testosterone. Raised in PCOS.
- SHBG (sex hormone binding globulin). Offered to women with oligo/amenorrhoea to assist with the diagnosis of PCOS. Low in PCOS.

- Oestradiol. High FSH and low oestradiol implies premature ovarian failure. Low FSH, LH and oestradiol implies hypothalamic/pituitary disease.
- DHEAS. A metabolite of cortisol which will be elevated in PCOS.
- 17aOH Progesterone. Elevated in congenital adrenal hyperplasia.
- USS (ultrasound scan) to assist with the diagnosis of PCOS and assess the uterus.
- FBC, U&E, ESR and random blood sugar to exclude concomitant disease.
- Karyotype. Turners syndrome (45XO), Triple X (48XXX) if primary amenorrhoea.

### **Obesity and female fertility**

Female obesity and its effect upon fertility is an increasing problem encountered in general practice. Obese women with or without PCOS have reduced fertility and lower success rates with assisted reproduction when compared with non-obese women.

Women with PCOS or simple obesity with a BMI greater than 29kg/m<sup>2</sup> should be advised that weight- loss may restore ovulatory function and natural fertility. Additionally the risk of congenital anomalies and maternal mortality is reduced with weight loss as well as seeing improved success rates of any subsequent assisted reproduction. Hence the first therapeutic option applied in general practice is a hypo- caloric diet.

### **Ovulation induction**

Ovulation induction in primary care remains a subject of debate.

Women with WHO group II anovulatory infertility (predominantly PCOS) can be offered clomifene, metformin or a combination of both. Treatment with clomifene is usually for a maximum of six cycles and NICE recommends offering ultrasound monitoring during at least the first cycle to minimise the risk of multiple pregnancies.

Risks associated with clomifene use include multiple pregnancies (10% chance of twins), ovarian hyperstimulation syndrome. There is a theoretical increased risk of ovarian cancer although this is not supported by evidence.

### **Referral**

An important advocacy role for the GP is to ensure appropriate referral for infertile couples. Appropriate referral can be achieved following initial assessment, investigation and diagnosis.

A couple with identified tubal infertility or male factor infertility will require referral to a specialist fertility centre for in-vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) treatment.

Some ovulation disorders may be managed in general practice. For couples requiring referral this will be dictated by local commissioning arrangements and may be to a local secondary care gynaecology service or specialist fertility centre.

Unexplained infertility. A working diagnosis of unexplained infertility may be reached in primary care for a woman aged less than 36 years with normal mid-luteal progesterone,

HSG, and semen analysis for her partner. Although it is an unsatisfactory diagnosis with no agreed diagnostic threshold, the couple's chance of achieving a pregnancy in the next two years is about 46%. Referral for IVF after two years of infertility is then appropriate.

For NHS referrals, the GP needs to be aware of local clinical and social exclusion criteria for assisted conception. Commonly these are female age, female BMI and whether the couple have a child in the current or a previous relationship. The majority of IVF cycles in the UK are delivered privately, commonly as a result of couples failing to meet social and/or clinical criteria to allow access to NHS funding.

### **Assisted reproduction**

Intrauterine insemination has a diminishing role in the latest NICE guideline. It is still considered for couples using partner or donor sperm, same sex couples and following sperm washing in HIV positive men.

Tubal surgery is still an option for women with mild tubal disease.

IVF is the mainstay treatment for women with tubal infertility or women with unexplained infertility who have not conceived after two years of regular unprotected intercourse. ICSI remains the treatment of choice for male factor infertility.

Currently NICE recommends single embryo transfer in an IVF cycle for women under 37 years. Double embryo transfer is considered in older women or additional IVF cycles.

### **Summary**

GPs continue to be the first point of contact for couples struggling to conceive. The initial investigation of the infertile couple can be performed in general practice and is essential to ensure appropriate management and onward referral. These include assessment of ovulation with mid-luteal progesterone and/or AMH and day 2–5 FSH, male factor with semen analysis and tubal status with HSG. Management strategies for primary care include obesity management and may include ovulation induction for a small cohort of infertile couples. Watchful waiting is appropriate for women aged less than 36 years and where no cause for infertility has been identified following initial investigations described above. Following initial assessment couples with male factor infertility or tubal infertility should be referred to specialist units that can deliver IVF/ICSI treatments.

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