

Review of the Management of Female Infertility: A Primary Care Perspective

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Abstract: Each GP sees approximately two infertile couples each year. Despite the relative lack of opportunity to rehearse the skills necessary to manage infertile couples a basic understanding will assist in the GPs advocacy role. Broadly the causes can be classified as male factors, ovulatory disorders, tubal disorders or unexplained infertility. The initial investigations commonly performed by GPs include semen analysis, serum mid-luteal progesterone and serum follicle stimulating hormone. The introduction of tubal assessment with open access hysterosalpingography (HSG) has given GPs the opportunity to manage the initial stages of infertility more effectively. Management strategies for the GP include optimising general health, weight loss for obese infertile women, ovulation induction with clomifene and expectant management for young women with no identified cause for their delayed fertility. Referral of couples with semen problems or tubal disorders should be to dedicated specialist fertility units capable of delivering the treatment necessary, typically in-vitro fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI) for this cohort. Current guidelines fail to address the impact of a full fertility assessment in primary care and the effect upon subsequent management and referral from primary care. This review focuses on the assessment and management of female infertility from a UK perspective.

Keywords: infertility, primary health care, family practice, hysterosalpingography, obesity, clomifene

Clinical Medicine Reviews in Women's Health 2010:2 11–23

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Introduction

In the UK, infertility affects approximately one couple in seven during their lifetime.¹⁻³ Comparable societies report similar rates between 8% and 20%.⁴⁻⁶ The annual incidence of infertility is estimated at approximately 1 couple per 1000 total population which has remained unchanged over the last 25 years,^{1,7} so a British GP with an average list size of 1,800 patients can expect to see 2 new infertile couples presenting each year among his/her 6000 consultations performed in that year. As the patients' advocate and someone who sees infertile couples relatively infrequently, the GP's challenge is to ensure that the necessary treatment is given in a timely manner. This requires preliminary investigations, use of appropriate therapeutic options and referral to a fertility centre that can deliver the treatment required for that couple.

Help-seeking behaviour among infertile couples varies, with an estimated 44% of couples not seeking medical assistance at all.⁶ GPs will commonly begin investigating a couple who are having difficulty conceiving after 12 months of regular unprotected intercourse. This is based upon population estimates of normal fertility where 84% of 'normal' couples will achieve a pregnancy within one year and a cumulative conception rate of 92% in the second year (Fig. 1).⁸ Infertility however is defined as a failure to conceive within two years of regular unprotected intercourse.^{8,9}

In this review we will consider the management of infertility from a GP perspective. Although infertility is a 'couple problem', this review will focus predominantly on the causes of female infertility, the

investigations of those causes, therapeutic options available in primary care, referral options, finally giving an international perspective. A detailed analysis of male factor infertility is beyond the scope of this review. This paper has been prepared from a UK perspective.

Aetiology

An understanding of the causes of infertility will help GPs to investigate their infertile couples and recommend appropriate treatment. True infertility i.e. absence of gamete or of female reproductive tract is a rare event, therefore for most couples the issue is more of a decrease or delayed fertility. Whilst acknowledging that understanding of human infertility is somewhat limited, researchers have codified contributing factors. These are traditionally classified as male factors, female factors, unexplained or other conditions. Male infertility is identified as a cause in 19%–57% of all infertile couples.^{1,3,7,9} Semen analysis is the main diagnostic tool with method of analysis and normal value ranges outlined by the World Health Organisation (WHO). The demonstrated absence of standardization and strict quality control for semen analysis undermines the diagnostic and prognostic value of the test.¹⁰

Female factors include ovulatory defects, tuboperitoneal disorders and uterine disease. Disorders of oocyte production and ovulation are among the commonest causes of female infertility, the estimated prevalence varying from 21 to 32%.^{1,3} The WHO offers a treatment oriented 'group' classification

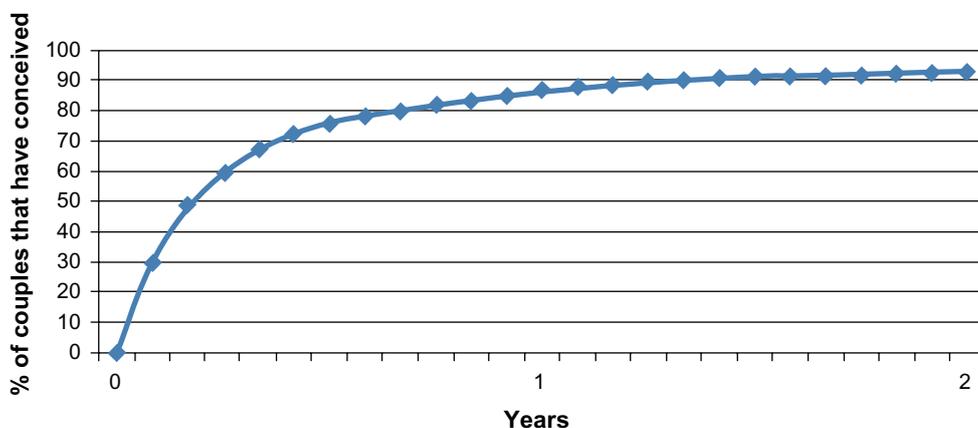


Figure 1. Population estimates of cumulative conception rates.

Source: <http://www.statistics.gov.uk/hub/population/births-and-fertility/conception-and-fertility-rates/index.html>



based on the measurement of three endocrine serum markers: prolactin, gonadotrophins (LH, FSH) and oestrogens.

Group I

Hypothalamic pituitary failure (hypothalamic amenorrhoea, hypogonadotrophic hypogonadism) accounts for less than 10% of ovulatory disorders.^{1,3} The gonadotrophin deficiency could be isolated (Kallman syndrome) or more commonly functional, secondary to stress, strenuous exercise, excessive weight loss, chronic illness CNS disorders and pituitary surgery (Craniopharyngioma).¹¹

Group II

Hypothalamic-pituitary dysfunction (normogonadotrophic ovulatory dysfunction) is associated with polycystic ovarian syndrome (PCOS) and accounts for 85% of ovulatory disorders (FSH may be normal or low).¹²

Group III

Ovarian failure (hypergonadotrophic hypogonadism) accounts for 4% of ovulatory disorders. The causes include genetic abnormalities (Turner syndrome 45, XO), chemotherapy, radiotherapy, pelvic surgery and premature menopause.

Group IV

Hyperprolactinaemic ovulatory dysfunction may be idiopathic, iatrogenic (drug related: SSRIs, metoclopramide, neuroleptics and some PPIs) or related to space-occupying lesions in the hypothalamic-pituitary region.

Tubal disease accounts for 14% to 26% of couples referred to fertility clinics.^{1,7} It is commonly associated with chlamydia infection and tubal sterilisation. Adhesions involving fallopian tubes and ovary (post-surgery, perforated appendicitis, endometriosis) also contribute to tubal dysfunction. The risk of tubal infertility after a single episode of pelvic inflammatory disease is 12%. That figure rises to 23% at the second episode and 54% at the third.¹³ However in most cases (>50%) of proven tubal disease there are no identifiable risk factors.¹⁴

Unexplained infertility is an unsatisfactory diagnosis of exclusion when a cause of infertility cannot be found.³ Its prevalence varies between

8 to 38% depending on the type of investigation performed.^{1,3,9,12,15} In approximately one third of infertile couples more than one cause is identified.¹

Endometriosis is found in approximately 5% to 6% of infertile couples.^{1,9} and is thought to exert its effect predominantly through tubal damage but also through its negative effect upon oocyte quality and impairment of fertilisation and implantation.^{16,17}

Obesity,¹⁸ increasing age and chronic illness have a significant detrimental effect upon female fertility. All have a direct or indirect impact on oocyte production and quality. With obesity now affecting over half of the population in developed societies¹⁹ and an estimate of 20% of women starting to try for their first pregnancy after the age of 35,²⁰ these factors are likely to play a significant role in future female fertility.

Management of Female Infertility in Primary Care

Historically, GPs have undertaken varying degrees of investigation and been mediators for referral of infertile couples to fertility specialists.²¹⁻²³ Since its development 30 years ago, IVF has become almost routine in clinical practice and is the treatment endpoint for over half of all infertile couples presenting to their GP.⁷ However not all couples require IVF in a dedicated specialist IVF unit. The role of primary care in fertility management in countries with a gate-keeping primary care function is four fold: 1) to evaluate the couple's fertility status; 2) to optimise general and reproductive health; 3) ovulation induction where clinically indicated; and 4) to ensure appropriate and timely referral to specialist services for further investigation and/or treatment. This section reviews the investigation and management of infertile couples in primary care.

Investigation and diagnosis

The UK Royal College of Obstetricians and Gynaecologists guidelines (1999) clearly describe the initial investigations that should be carried out in general practice.²⁴ The UK National Institute for Clinical Excellence guidelines (NICE 2004)⁸ describe the initial management of the infertile couple but do not ascribe roles to professional groups. A summary of the guidelines applicable to general practice is given Table 1. Similarly, the ASRM (American Society for Reproductive Medicine) and ESHRE (European



Table 1. Summary of NICE Guidelines applicable to general practice. *Summary of RCOG guidelines applicable to general practice.*

Key recommendations

- Screening for chlamydia trachomatis should be offered before uterine instrumentation.
- Woman aged 23–39 years with a diagnosed cause of infertility of any duration or unexplained infertility of at least three years duration, should be offered 3 complete IVF cycles and informed of the risk of multiple births.
- For the assessment of tubal damage, women not known to have co-morbidities (pelvic inflammatory disease (PID), endometriosis or previous ectopic pregnancy) should be offered hysterosalpingography (HSG) or hysterosalpingo-contrast-ultrasonography (HyCoSy).

Human reproduction and fertility

- Infertility is defined as ‘failure to conceive after regular unprotected intercourse for two years’.
- Couples should be informed that 82% of couples will conceive within one year and 92% by 2 years.
- People who have not conceived after 1 year of unprotected intercourse should be offered further investigation.
- If there is a history of predisposing factors for infertility (such as pelvic inflammatory disease, oligomenorrhoea, amenorrhoea, undescended testes) investigation should begin immediately.

Principles of care

- The management of infertility should involve the couple. *Infertility management should involve the couple.* The care should be sensitive, informed, backed by patient information literature and couples should be informed of a patient support group. *A detailed history should be taken and the couple examined, with explanation and support.*
- A specialist team should treat couples. *Couples should be referred to an appropriate specialist centre.* An expert not directly involved with the infertility management should offer counselling before, during and after treatment.

General advice

- Intercourse should be at least every 2 to 3 days. *Couples should be advised to have regular intercourse throughout the cycle.*
- Couples should be advised to limit the use of alcohol. *Both partners should be advised to limit the use of alcohol.*
- Couples should be advised to stop smoking. *Both partners should be advised to give up smoking.*
- Couples should be offered specific advice in relation to recreational drug use where appropriate. *A detailed drug history, including drugs of abuse, should be taken from both partners.*
- Men should be advised to avoid tight fitting underwear and avoid testicular hyperthermia. *Men with poor sperm quality should be advised to wear loose fitting underwear and avoid testicular hyperthermia.*
- Women should be advised to lose weight if their BMI > 29 kg/m². *The woman’s BMI should be calculated and if >30 kg/m² weight reduction should be advised.*

Preconceptual advice

- Women should be advised to take 400 mcg of folic acid before conception and up to 12 weeks gestation. *The woman should be advised to take 400 mcg of folic acid while trying to conceive and during the first 12 weeks of pregnancy.*
- Rubella status should be determined and if seronegative offer immunisation and avoid pregnancy for one month. *The woman’s rubella status should be determined: if seronegative, rubella vaccination should be offered and the woman advised not to become pregnant within one month of immunisation.*

Initial assessment

- Semen analysis should be performed on behalf of all couples presenting with infertility. If the first is abnormal repeat a second sample three months later. *Two semen samples should be sent to the laboratory to which the GP may ultimately refer.*
- For the assessment of ovulation a menstrual history should be taken. If women have regular menses, they should be informed that they are ovulating. Confirm ovulation with mid-luteal progesterone. *Mid-luteal progesterone should be performed to confirm ovulation.* Temperature charting is not recommended. *Avoid using temperature charts or urine luteinising hormone (LH) detection kits, as there is no evidence that their use improves outcome.*
- Women with irregular cycles should have serum FSH and LH measured; high levels may indicate ovarian failure.
- Women who have symptoms of thyroid disease should have their thyroid function estimated. *Measurement of thyroid function has no role in women without symptoms of thyroid disease.*
- Women who have galactorrhoea should have their serum prolactin measured. *Measurement of prolactin has no role in women without galactorrhoea.*
- Before undergoing uterine instrumentation, women should be offered chlamydia trachomatis screening and treatment where necessary.
- For the assessment of tubal damage, women who are not known to have co-morbidities (such as PID, previous ectopic pregnancy or endometriosis) should be offered HSG or HyCoSy. Women with co-morbidities should be offered laparoscopy and dye as other pelvic pathology can be assessed at the same time.



Society of Human Reproduction and Embryology) also describe the management process linked to professional competence.

GPs believe that the initial management of the infertile couple should take place in primary care.²⁵ This is evidenced by the activity of over half of GPs performing initial investigations.^{21–23,26} Prior to investigations, a thorough history should be taken, including medical, surgical, drug, sexual, coital, lifestyle, social and family history, for both partners, and combined with a clinical examination. This will guide the need for subsequent tests which are semen analysis, mid luteal progesterone and tubal patency testing. Although commonly done, the predictive value of ovarian reserve (basal FSH) for spontaneous pregnancy is unclear.^{27,28} While a significant proportion of couples have their semen analysis, mid-luteal progesterone and follicle stimulating hormone (FSH)

estimated, it is disappointing to see only one fifth of couples having their rubella status recorded and evidence shows that pre-pregnancy advice is rarely recorded (Table 2). Full blood count, thyroid function tests and serum prolactin continue to be popular investigations despite recommendations that these should not to be used as screening tests. These should only be performed when patients present with symptoms of the associated clinical condition.

A synthesis of available guidelines, published evidence of GP recorded activity and recent innovations have led to the authors compiling a contemporary plan for the GP investigation and management of infertility (Box 1).

The newest innovation for the NHS is the development of open access hysterosalpingography (HSG), which is now advocated as a first line investigation for the infertile couple.

Table 2. GP management of infertility.

Study	How GPs manage infertility (recorded activity:%)					How GPs perceive they should manage infertility (%)
	A	B	C	D	E	F
Advice						
*BMI	–	2	38	–	1	a
*Folic Acid	–	9	33	–	36	74
*Smoking	–	19	56	–	14	a
*Alcohol	–	8	12	–	10	a
*Recreational drugs	–	12	–	–	1	a
Investigations						
*Semen analysis	54	47	33	34	53	60
*Mid-luteal progesterone	66	40	12.5	51	70	84
*FSH/LH	33	30	–	–	58	b
*Rubella status	18	12	21	20	20	75
FBC	42	12	–	–	39	b
TFT	51	21	–	–	49	b
Prolactin	58	23	–	–	24	b
Oestrogen	13	–	–	–	4	b
SHBG/Testosterone	13	2	–	–	9	b
Chlamydia	4	–	–	–	13	b
RBG	4	–	–	–	15	b
Hep B	–	0	–	–	–	b
HIV	–	0	–	–	–	b

A: (Wilkes & Jones 1995).¹⁵

B: (Nicolopoulos & Croucher 2003).²²

C: (Das & Chin 2003).²¹

D: (Morrison et al 2007).²⁶

E: (Wilkes 2009).²³

F: (Souter, Penny and Gorman 1997).²⁵

*: Key recommendations from NICE for the initial management of the infertile couple.

a: 81% GPs agree a full medical, social and sexual history should be taken.

b: 19% GPs agree no other tests should be carried out by the GP.

**Box 1.** GP management of female infertility.

Task	Rationale
	History
Infertility history	Helps determine where the likely cause may be e.g. secondary may be more likely to be tubal or other union may indicate male factor infertility.
Length of infertility	Investigate after no contraception for 1 year.
Previous pregnancy	May inform treatment exclusion criteria.
Medical disorder affecting fertility	Hypo/hyperthyroidism, prolactinoma, PCOS, Hypothalamic pituitary disease, anorexia, weight loss, Cushing's disease, premature ovarian failure, ovarian dysgenesis.
Surgical disorder affecting fertility	Tubal damage (abdominal operations, adhesions etc), endometriosis.
History of PID/STI	Potential for tubal damage.
Current menstrual history	Helps to determine if we are likely to be dealing with an ovulation problem.
Smoking, alcohol and drugs	Detrimental effect upon fertility.
Coital and social history	Important to ensure frequent unprotected intercourse.
	Examination
General examination	Features of thyroid disease, PCOS, weight problem, Cushing's disease.
Pelvic examination	Not necessary especially if doing HSG/HyCoSy.
BP	Good practice, pre-pregnancy baseline.
BMI	Anorexia and amenorrhoea. Obesity and PCOS.
	Initial Investigations
Semen analysis	2 samples unless 1st is good. WHO values for 'normal' semen analysis: Volume (2–5 mls); Concentration (>20 million/ml); Motility (>50% progressive motility); Morphology (<30% abnormal forms).
Mid-luteal progesterone	Helps to determine ovulatory and anovulatory cycles. >20 nmol/l can be taken as proof of ovulation. A value <5 nmol/l tells us there is little or no luteal function.
Day 2–5 FSH	Assessment of ovarian function.
Open access HSG/HyCoSy	Tubal status. Rubella and Chlamydia screening (plus tests above) are pre-requisite tests for HSG.
	Additional investigations; oligomenorrhoea, amenorrhoea
TSH	Hypo/hyperthyroidism.
Prolactin	Prolactinoma.
FSH and LH	High FSH and low oestradiol implies premature ovarian failure. Low FSH, LH and oestradiol implies hypothalamic/pituitary disease. LH/FSH ratio >2:1 in PCOS (with FSH normal or low).
Oestradiol	High FSH and low oestradiol implies premature ovarian failure.
Testosterone	Raised in PCOS.
DHEAS	A metabolite of cortisol which will be elevated in PCOS.
17aOH Progesterone	Elevated in congenital adrenal hyperplasia.
SHBG	Low in PCOS.
FBC, U&E, ESR	Anaemia, general wellbeing, chronic disease etc.
Karyotype	Turners syndrome (45XO), Triple X (48XXX) if primary amenorrhoea.
	Management
	Abnormal semen analysis and/or tubal occlusion will require referral to a specialist IVF unit.
	Abnormal assessment of ovulation will require referral to a fertility specialist or GP management below.
	Normal initial investigations suggest unexplained infertility and managed as per NICE guidance.

(Continued)

**Box 1. (Continued)****Ovulation induction in general practice**

Appropriate for WHO group II (mainly PCOS)

Clomifene treatment may be started after the cause of anovulation has been fully investigated. Semen analysis must have been carried out and adequate coital technique ensured before starting treatment. Tubal patency test by HSG/ HyCoSy scan ideally should be performed prior to ovulation induction with Clomifene. Clomifene is not indicated when spontaneous ovulation is occurring as indicated by regular menstruation or a mid luteal progesterone >20 nmol/l.

Couples must be informed of the risks and side effects of the drug before starting treatment, i.e. multiple pregnancy, OHSS, ovarian cysts and visual disturbance.

Clomifene is started on Day 2 of a spontaneous cycle or a progesterone induced withdrawal bleed. The starting dose is 50 mg daily for 5 days. She is asked to attend for blood tests at weekly intervals from Day 21 of the cycle for progesterone estimation. She should attend for follow up 1 month later to review the results.

If there is satisfactory luteal function (Progesterone >20 nmol/l), restart clomifene on the same dose. If there is no progesterone rise, start a second course with clomifene dose increased by 50 mg daily. Blood is again taken on Day 21 and weekly thereafter until menses or review 1 month later. The cycle then restarts from.

The maximum dose used is 150 mg and the maximum number of Clomifene cycles will be three. Thereafter specialist referral and advice on further management will be sought.

Progesterone induced withdrawal bleed:

Day 1 Norethisterone 10 mg daily for 5 days.

Day 7 Clomifene 50 mg daily for 5 days.

Day 21 Progesterone estimation.

Day 28 (if no menses) progesterone estimation.

Review in 6 weeks

Source: Wilkes, S. 2007, Evaluation of open access HSG in the initial management of infertility in primary care: PhD Thesis, University of Sunderland.

NICE 1.4.4.1. Women who are not known to have co-morbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered hysterosalpingography to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion, and it is less invasive and makes more efficient use of resources than laparoscopy.⁸

Together with semen analysis and endocrine blood tests, this completes the initial stages of investigation for the infertile couple and evaluates the main possible causes, i.e. male factor, ovulatory dysfunction and tubal occlusion. The introduction of open access HSG in the NHS has been as a criterion-driven open access investigation. The criteria defining access to the investigation are summarised in Box 2. A couple who have an abnormal semen analysis are likely to require treatment with Intra-cytoplasmic sperm injection (ICSI) thus rendering the open access HSG investigation of limited value. Similarly, if a woman is discovered to have an ovulatory disorder, the focus will then be to diagnose and treat that disorder, usually with ovulation induction strategies. The debate

is whether she should also have tubal assessment with HSG prior to ovulation induction to ensure tubal patency. Women with oligomenorrhoea will require full assessment of their ovulatory function (Box 1). To date, open access HSG is not widely available in the NHS and its place in fertility management in primary care is slowly evolving as Primary Care Trusts (PCTs) re-evaluate their fertility care pathways.

Optimise general and reproductive health

General Practice has a significant contribution to make to the management of obesity related female infertility. Among the US, UK, European and Australian populations approximately one-third are overweight (BMI 25–29.9 kg/m²) and one-quarter are obese (BMI 30 kg/m²+).¹⁹ Most women with PCOS are overweight, with approximately half being obese.^{29,30} Simple obesity and PCOS are associated with the development of hyperinsulinaemia and hyperandrogenism,³¹ and associated chronic anovulation leading to decreased fertility.³²



Box 2. Criteria for open access HSG.

- The couple must have been trying to conceive for one year
- Normal semen analysis
- Normal coital function
- Female aged < 40 years
- Regular menstrual cycle (< 6 weeks)
- Day 2–5 FSH <10 IU/l
- Mid luteal progesterone > 20 mmol/l
- No history of tubal disease
- No known uterine or cervical abnormality
- Negative endocervical swabs for chlamydia and gonococcus
- Rubella status checked
- Female in receipt of folic acid

Source: Wilkes et al. Open Access Tubal aSessment for the initial management of infertility in general practice (the OATS trial): a pragmatic cluster randomised controlled trial. *British Journal of General Practice*. 2009;59:329–335.

Obese women have reduced fertility and experience lower success rates per cycle when compared with their lean counterparts,³³ and the success of ART is also reduced.^{34,35} The most effective form of treatment for obese infertile women is weight reduction. In a small cohort study of 13 obese infertile women, a weight loss of 14 lbs, or a 5–10% reduction in BMI, was associated with resumption of ovulation in some anovulatory women and an increase in pregnancy rate.³⁶ A similar observation occurs with weight loss in obese women with PCOS.^{36,37} This is best achieved with lifestyle

modification and hypo-caloric dieting,^{31,38} aiming for a 500 calories per day reduction with less than 30% of daily calories from fat.³⁹ Primary care is well placed to manage obesity and GPs are experienced in the use of drug therapy with orlistat but this should be reserved for second line adjunctive therapy. Sibutramine and Rimonobant are not recommended for women trying to conceive and the role of metformin in anovulatory PCOS remains unclear.^{40,41} The British Fertility Society (BFS) recommend that women should aim for a BMI of 30 kg/m² or less to increase their chances of success and reduce the risk of congenital anomalies and maternal mortality.⁴⁰ This does however present an ethical dilemma. Denying treatment to obese infertile women, who can rationalise the risks presented to them, may be prejudiced when normally fertile obese women can and do become pregnant. However, there are three compelling reasons for obese women to lose weight: firstly women will have increased natural fertility; secondly assisted reproduction is more likely to succeed; and thirdly foetal morbidity and maternal mortality will be reduced.

The initial consultation in general practice offers an ideal opportunity to address cigarette smoking, alcohol and caffeine consumption as well as recommending folic acid supplementation and review of non-prescription and prescription drugs. Tobacco exposure reduces fecundability and success rates for IVF,⁴² and smoking cessation should be recommended.

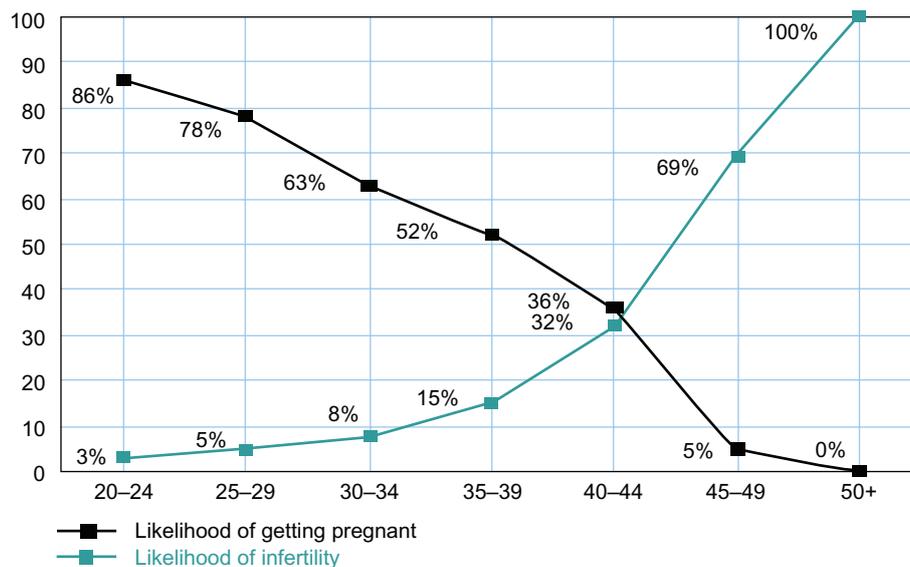


Figure 2. Age-related conception rates. Adapted from Menken J, Trussell J, Larsen U. Age and infertility. *Science*. 1986;23:1389.



In the UK, some PCT commissioners describe a non-smoking status as a pre-condition to allow funding of fertility treatment.⁴³

Alcohol consumption also has a detrimental effect on female fertility and it is probably dose dependant.⁴⁴ Current guidelines suggest avoiding alcohol all together or limit it to 1–2 units per week.^{8,24} High caffeine intake (>500 mg/day) has also been associated with delayed conception.⁴⁵ Low BMI (<18 kg/m²) commonly results in subfertility due to amenorrhoea, and management of the underlying illness, whether an associated eating disorder or chronic illness, is required.

Ovulation induction in primary care

Ninety per cent of ovulation disorders are PCOS related.³⁰ The definition of PCOS has been outlined by the Rotterdam consensus in 2003 (ESHRE/ASRM Workshop).⁴⁶ It stated that the diagnosis could be made if two out of three criteria were met. Those criteria are oligo/amenorrhoea and/or anovulation, biochemical or clinical hyperandrogenism and polycystic ovaries on ultrasound scan. Other endocrine disorder should be excluded but essentially this diagnosis can be made in primary care by the GP. Key and common features of PCOS are obesity and insulin resistance. The first therapeutic option for obese infertile women with PCOS is weight loss, which is best achieved with a combination of diet and exercise.¹⁸ Even a modest weight loss of 5%–10% may be enough to restore normal ovarian function.³⁷ Adjuvant use of bariatric surgery and pharmacological weight loss is recommended for the treatment of morbid obesity in PCOS.⁴⁷ For lean women with PCOS or women who remained anovulatory despite optimisation of their weight, ovulation with clomifene citrate is the first line of treatment. Clomifene citrate is a selective estrogen receptor modulator, which inhibits the action of the oestrogens at the level of the hypothalamus and, through negative feedback, leads to an increase of FSH and LH release. The medication is usually well tolerated but patient should be warned about common potential side effects such as hot flushes, irritability, abdominal discomfort, visual blurring (dose-dependent), and/or reversible ovarian enlargement and cyst formation. The starting dose is 50 mg/day with a maximum daily dose of 150 mg for 5 days starting on day 2 or 3 of the menstrual

cycle. The recommended duration of treatment is 6 ovulatory cycles. On an individual basis, it could be extended to a maximum of 12 cycles.⁴⁷

Ovulation induction in primary care, with clomifene, is supported by some authors.^{4,48,49} Only 65% of GPs believe that the treatment of anovulation with clomifene should always be initiated by a specialist hospital clinic rather than in general practice.²⁵ Also, a recent study showed that ovulation induction with clomifene was initiated in general practice for 9% of patients who had an ovulatory disorder.⁷ Ovulation induction in primary care is not described in any authoritative guidelines.^{8,24} Ovulatory infertility represents the easiest form of infertility to correct,^{48,50} with clomifene therapy inducing ovulation in 70% of women with PCOS resulting in a conception rate of approximately 50% and an incidence of twin pregnancies of around 10%.⁵¹ Monitoring of clomifene treatment is controversial with some authors suggesting that monitoring by ultrasound is not essential to a good outcome.⁵² Ultrasound monitoring of clomifene cycles is recommended by NICE.⁸

NICE 1.6.1.4 Women undergoing treatment with clomifene citrate should be offered ultrasound monitoring during at least the first cycle of treatment to ensure that they receive a dose that minimises the risk of multiple pregnancy.⁸

But there is no evidence to suggest that ultrasound monitoring reduces the chance of multiple pregnancies which occur at a rate of approximately 8%–10% with clomifene therapy.⁴⁸ Furthermore, the risk of Ovarian Hyperstimulation Syndrome is rare (<1%).⁵¹ The rationale for the use of ultrasound monitoring is to allow tracking of multiple follicular development and subsequent abandonment in those cycles. This is possible for IVF cycles where treatment can be stopped but there is no evidence that couples who have received clomifene, are desperate for a child and who are also aware of the risks of multiple pregnancy, will refrain from having intercourse. Monitoring of clomifene treatment cycles with mid-luteal progesterone remains common practice.^{48,49}

Referral

The referral process in a managed health care system such as the NHS is often dictated by local commissioning arrangements and not necessarily by the needs of the patient. The quality of referrals from general



practice varies with some GPs referring immediately upon first consultation whilst others perform the requisite investigations prior to referral. A prompt referral upon initial consultation with little GP involvement may be seen as an uninterested GP or conversely a GP avoiding delays in seeking specialist help. Care pathways and clinical guidelines embedded within structured referral proformas may increase the quality of information received upon referral.^{53,54}

In the UK, fertility treatments are licensed by the Human Fertilisation and Embryology Authority (HFEA) and assisted reproduction in the NHS is delivered in both secondary care and tertiary care centres. Broadly, tertiary care centres are HFEA licensed units that deliver a full range of services including IVF and ICSI whereas secondary care services are often non-HFEA licensed centres and are often limited to ovulation induction alone. There is a risk that un-investigated couples in primary care with undiscovered semen or tubal problems may be referred to a secondary care unit that cannot deliver the treatment required. We know that approximately 38% of couples referred to secondary care have either

a semen or tubal problem.⁷ Hence, there is potential for wasted time and resources for these *mis-directed* referrals, stemming from a lack of investigation in primary care. A simplified management algorithm can help prevent some of these *mis-directed* referrals (Fig. 3). We also know that 51% of couples presenting to their GP require IVF or ICSI, that approximately 5% of couples are referred from general practice for private treatment,⁷ and that approximately 70% of IVF cycles in the UK are delivered privately,⁵⁵ demonstrating that a significant proportion of couples are referred on from NHS secondary or tertiary care to private practice. These *inappropriate* referrals from primary care result from a lack of interpretation of restrictive clinical and social criteria which govern access to NHS funded assisted reproduction. Additional and common restrictive clinical criteria in the NHS include age, smoking status and BMI, while the most common and contentious social exclusion criterion is to deny treatment to couples who have a child from a previous relationship.⁵⁶ The latter affects 26% of couples seeking help⁷ and is imposed by 68% of PCTs.⁵⁷ The application of these criteria,

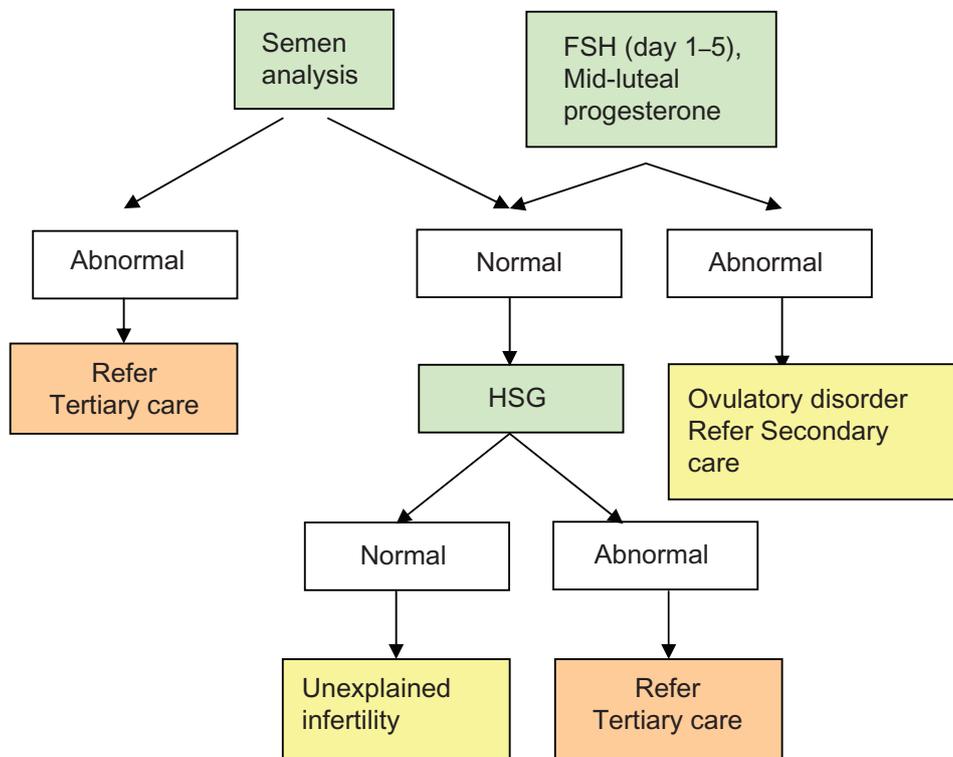


Figure 3. Simplified GP management algorithm (based on NICE algorithm 2004).
 Green shaded boxes: initial GP investigations.
 Yellow shaded boxes: management strategies for GPs to consider.
 Orange shaded boxes: referral to a specialist IVF unit is required.



and hence availability of NHS fertility treatment, varies from one PCT to the next. The British Fertility Society and patients' charity Infertility Network UK have suggested national unification of clinical and social exclusion criteria to end the 'post-code' lottery of NHS treatment provision.

Referral of couples with no apparent cause for their infertility, following initial investigations, deserves further elaboration. Unexplained infertility is an unsatisfactory diagnosis reached when investigations reveal no apparent cause for the couples' difficulty conceiving. The extent of investigation that leads to this diagnosis is also poorly defined. For a primary care professional such a diagnosis is useful as a prognostic tool. For a woman aged less than 35 with normal mid-luteal progesterone, HSG and semen analysis for her partner, their chances of achieving a pregnancy within the next 2 years remain good and are approximately 46%.⁵⁸ Following 3 years of infertility it is then appropriate to offer assisted reproduction with IVF.⁸ Early studies suggested that there was a benefit using clomifene for couples with unexplained infertility with a doubling of their chance of pregnancy (OR 2.5, 95% CI 1.35–4.62)⁵⁹ and a two year conception rate of 88%.⁵⁰ However, an updated Cochrane review has shown no difference in live birth rate when expectant management was compared to clomifene citrate or unstimulated IUI.⁶⁰

In summary, full initial assessment in primary care can lead to more appropriate management and referral for infertile couples.

International Perspective

Infertility management varies not only within health care systems but also between systems. In the insurance based system of America, infertility is not recognised in the Americans with Disabilities Act (ADA) and couples are unable to gain financial support for assisted reproduction.⁶¹ In such circumstances we see primary care physicians doing all they can for their patients including ovulation induction with clomifene.^{5,62} In societies such as Germany, where the primary care gate-keeping role is less evident, GPs feel dis-empowered and less confident and consider that it is not within their remit to manage infertile couples.⁶³ In many developing countries there are no primary care physicians and access to specialist

services is poor. In sub-Saharan Africa, childlessness is associated with social stigma, ostracism and marital difficulties, with an estimated 2% of women remaining permanently childless.⁶⁴ In health care systems where primary care acts as the gatekeeper, it is incumbent upon the primary care physician to investigate the couple, manage those in primary care for whom it is appropriate and avoid mis-directed or inappropriate referrals. Appropriate referral, whether private, or to secondary or tertiary level services, is key if the health system is to achieve cost-effective management of the infertile couple. Infertility presents a unique set of problems for the primary care physician where not all couples need to be referred; a proportion can be managed in primary care and referral needs to be tailored to the couples' individual fertility needs.

Conclusions

GPs feel they are an important source of information and advice and believe they should manage the initial stages for infertile couples.^{26,65} This view is also held by fertility specialists.^{48,49,66–68} However, some GPs feel they lack the expertise and the management of infertile couples lies within the domain of the fertility specialist.⁶³ The initial investigation of the infertile couple is essentially simple and includes assessment of ovulation with mid-luteal progesterone 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 35 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.

Acknowledgements

Thank you to Professor Alison Murdoch, Fertility Centre at Life, Newcastle upon Tyne, who provided helpful comments on drafts of this paper and Sally Black MBE who proof read the manuscript.

Ethical Approval

Not required.



Competing Interests

None declared.

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