

ABNORMAL LABORATORY RESULTS

Fertility testing

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SYNOPSIS

Hormone testing is helpful in the investigation of infertility, but excessive testing is rarely valuable. The history of infertility and examination of both partners usually enables a simple approach to testing. Tests of ovulation rely on measuring serum progesterone seven days before an expected period. Measurement of serum testosterone is sufficient to exclude ovarian or adrenal tumours as a cause of hyperandrogenism, while prolactin and thyroid stimulating hormone may be valuable in women with irregular periods. Semen analysis is essential in the infertile male.

Index words: infertility, progesterone, testosterone.

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Introduction

The general practitioner is usually the first person to see the 10–15% of couples who are concerned about their fertility. At some time in their lives, approximately half of these couples will seek medical advice. A third of these people will need to be referred to a specialist or assisted reproductive technology unit. In a third of infertility cases there is a female factor, in another third a male factor and in the remaining third there will be a combination of both, or no detected cause. The investigation by the general practitioner depends upon the couple's history, their ages and the findings on examination (Fig. 1). Patients who present with less than 12 months of infertility should have minimal testing unless a clear cause is found from clinical assessment. Selection of tests after this will depend on the potential cause of infertility indicated by the history and examination.

Female infertility

A detailed history of the menstrual cycle often provides a clue to problems such as anovulation or ovarian failure. A general examination should be carried out, in addition to a pelvic examination, to look for problems such as hypothyroidism or hirsutism.

Issues to consider when measuring female hormones

The concentrations of most hormones fluctuate during the menstrual cycle, and in the case of luteinising hormone (LH) and follicle stimulating hormone (FSH) there is also a minute by minute pulsatile variation. Most hormones should be measured in the first seven days of the cycle when there is little

fluctuation in their concentrations, but the pulsatile release of hormones such as LH may lead to quite variable results between specimens. The measurement of hormones such as prolactin can be significantly affected by stress and medication. Progesterone and 17-hydroxyprogesterone vary substantially between the follicular and luteal phase of the cycle. In the perimenopause, the concentrations of FSH can fluctuate markedly as the ovarian sensitivity to gonadotrophins varies.

Tests for detection of ovulation

The most appropriate test for detecting ovulation is a serum progesterone concentration. This is performed approximately seven days before the predicted date of a menstrual period (day 1). The day can be calculated on the basis of a 14 day luteal phase so if the menstrual cycle is 28 days, test on day 21. Test on day 23 of a 30 day cycle, and day 25 of a 32 day cycle.

A progesterone concentration above 20–25 nmol/L confirms ovulation occurred in that cycle. Lower values mean either anovulation or inappropriate timing of the blood test. A low concentration can be checked by taking two measurements of progesterone a week apart in the next cycle or alternatively recalculating the day of testing.

Urinary dip sticks for LH are also widely used for ovulation detection, but are expensive, open to problems of interpretation and are only of value when periods are regular. Blood or urinary LH tests are of no value in general practice.

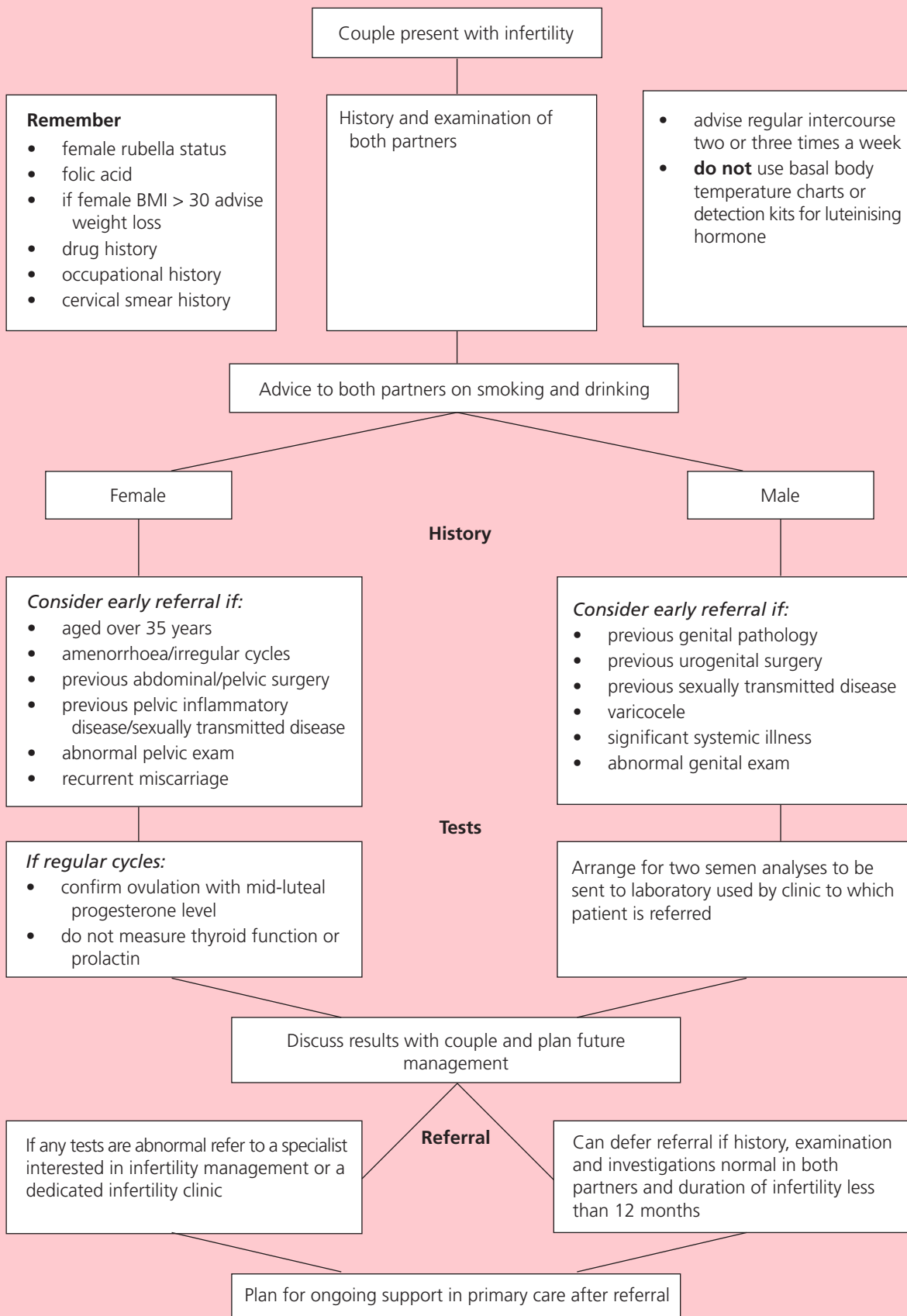
Tests for hirsutism

The commonest cause of hair growth in women with abnormal periods is polycystic ovary syndrome. The most appropriate test for hyperandrogenaemia is a serum total testosterone. This will normally be below 2 nmol/L but can vary from laboratory to laboratory and also during the menstrual cycle. Values of testosterone above 10 nmol/L are suggestive of a testosterone producing tumour of the ovary or adrenal. As testosterone is bound to sex hormone binding globulin, an estimate of free androgen can be obtained by calculating the ratio of testosterone to sex hormone binding globulin (the free androgen index). Direct measurement of free testosterone is technically flawed and a useless test.

Tests for other androgens, such as androstenedione and dehydroepiandrosterone, are of little value in general practice. The commonly used LH:FSH ratio is also of little value although a raised LH with a normal FSH is helpful in the diagnosis of polycystic ovary syndrome. Measurement of 17-hydroxyprogesterone is occasionally helpful where late

Fig. 1

The investigation and management of the infertile couple by the family doctor



onset congenital adrenal hyperplasia (an inherited condition affecting one of the enzymes in the adrenal gland) is suspected.

Many women with polycystic ovary syndrome will develop diabetes. When the syndrome is diagnosed in an overweight patient, diabetes mellitus and hypertriglyceridaemia should be excluded.

Tests for early menopause

The only test of any value where the diagnosis is uncertain is serum FSH. The concentration may be raised above 20–30 IU/L, but this test should be repeated on several occasions as the condition of ovarian failure fluctuates remarkably. There is no place for measuring oestradiol or LH in this situation.

Tests for early pregnancy

Human chorionic gonadotrophin is the best test for early pregnancy. Values over 25 U/L in the blood or urine are usually diagnostic of pregnancy. Concentrations below this are reported as equivocal or negative. If the result is equivocal it can be repeated two days later and should have at least doubled in value. While modern laboratory assays for human chorionic gonadotrophin are reliable, urinary home pregnancy tests are often less satisfactory. There is usually a 1:1 relationship between concentrations of human chorionic gonadotrophin in blood and urine. However, blood testing is more reliable and is positive 1–2 days earlier.

Tests for menstrual irregularity

Where abnormal periods are present, measurement of serum prolactin is of value. Prolactin concentrations are increased by stress, hypothyroidism, dopamine depleting drugs and microadenoma of the pituitary as well as by pregnancy and lactation. When periods are irregular, measuring thyroid stimulating hormone is important to exclude primary hypothyroidism. Routine measurement of FSH, LH and oestradiol for infertility is of little value except in early menopause. Chromosome analysis is needed in cases of primary amenorrhoea.

Male infertility

After a history and examination, semen analysis is the essential test.

Semen analysis

Infertility in a couple requires analysis of a sample of semen. A semen specimen should be produced, after three days abstinence from ejaculation, into a clean wide-topped jar and delivered to the laboratory within 20 minutes. Previous illness and some drugs (e.g. anabolic steroids, testosterone) can seriously affect the amount and motility of the sperm.

Analysis required

The volume, concentration, motility and morphology of the seminal specimen are measured. Sperm numbers should be above 20×10^6 per mL, their motility should be at least 50% and their morphology should be above 20% normal. Morphology is poorly assessed by most laboratories other than those routinely dealing with infertility, but it predicts the chances of fertility. Single, double or triple defects necessitate

the measurement of a second specimen in a specialist laboratory and probable referral to a specialist.

Other tests

In patients with azoospermia, small testes and a high FSH, chromosome analysis may be required to exclude conditions such as Klinefelter's syndrome (XXY). Other disorders of semen analysis may require the measurement of FSH and LH to show whether the defect is in the testis (high result) or in the hypothalamus or pituitary (low result). Serum testosterone is normally well above 10 nmol/L and low values may necessitate testosterone replacement or injection of human chorionic gonadotrophin depending on the cause and desire for fertility. Occasionally, microadenomas of the pituitary can present with high prolactin values and male infertility. Sperm antibody testing is important in specialist practice but not in primary care as a routine investigation.

Conclusion

Infertility is a condition initially best dealt with by the general practitioner. After history and examination, selective testing of hormones is helpful for making the diagnosis and for decisions regarding referral. Inappropriate hormone testing is expensive and a waste of resources.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 47)

5. Measurement of oestradiol is a valuable test in infertility and early menopause.
6. Day 21 progesterone is the best test for ovulation in a 28 day cycle.

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