

1

Clinical assessment of the woman
for assisted conception

Domenico Massimo Ranieri
Assisted Conception Unit, UCLH, London, UK

In the last four decades significant progress has been made in the diagnosis and treatment of infertile couples. It is currently estimated that about 90% of women will achieve pregnancy in the first year of trying to conceive and 95% within the second year, following which the chances of natural conception are lower. The remaining 5–10% can be defined as infertile and requiring investigation and treatment (WHO, 1992; ESHRE Capri Workshop, 1996). This timeframe can be shorter in women with risk factors such as previous history of pelvic inflammatory disease (PID), pelvic surgery, ectopic pregnancy, family history of premature ovarian failure and in women aged 35 years and over due to the natural age-related decline in fertility (van Noord-Zaadstra *et al.*, 1991). Increasing numbers of women are delaying childbearing to an age when they are more likely to encounter problems with conceiving, and public awareness of the scientific progress made in the field of assisted conception has led to an increased number of people seeking treatment.

The first consultation between an infertile couple and the clinician specializing in infertility is a crucial starting point for collecting the medical history, clinical examination and the evaluation of the appropriateness of a range of investigations to establish the cause of infertility, following which a strategy for treatment can be planned. When infertile couples present at tertiary assisted conception centres often they will have been referred by a general practitioner or gynaecologist and may already have completed basic infertility assessment. In this event it is often possible to discuss treatment strategies during the first consultation.

First consultation:

- Medical history.
- Clinical examination.
- Investigations:
 - cause of infertility;
 - strategy of treatment.

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2 **Domenico Massimo Ranieri**

Medical history

It takes about half an hour to glean a complete medical history and this should include the following areas.

Age and duration of infertility

Female fecundity declines with age, therefore reducing the chances of conceiving either naturally or with the help of assisted reproductive technologies (van Noord-Zaadstra *et al.*, 1991; ESHRE Capri Workshop, 1996).

Menstrual history

- Women with regular periods are likely to have ovulatory cycles (van Zonneveld *et al.*, 1999).
- Primary amenorrhoea can be caused by gonadal dysgenesis and/or chromosome abnormalities such as Turner syndrome and mosaicism (see Table 1.2).
- Secondary amenorrhoea can be caused by disturbances in the hypothalamic pituitary ovarian axis, most commonly polycystic ovary syndrome (PCOS), hyperprolactinaemia, premature ovarian failure or drastic weight changes and uterine abnormalities such as Asherman's syndrome.
- Severe dysmenorrhoea is often associated with endometriosis. Particular attention should be given to heavy periods, which can be caused by submucous fibroids.

Contraception

The absence of natural conception in sexually active women who have not used contraception may indicate a severe unidentified cause of infertility. If a woman has used contraception, it is important to focus on the previous form of contraception. The intrauterine contraceptive device (IUCD) can be associated with PID and tubal damage (Beerthuizen, 1996) and women who have had multiple partners without the use of condoms may be at higher risk of tubal damage caused by PID (Miller *et al.*, 1999).

Obstetric history

- Previous pregnancies should be discussed, particularly whether they miscarried, were terminations or ectopic pregnancies.
- Method of delivery and post delivery complications can be important. The necessity of antibiotic treatment for abdominal pain and high temperature after a delivery or termination of pregnancy can be suggestive of pelvic infection with subsequent tubal damage.
- Previous fertility is sometimes a good prognostic factor in women undergoing assisted conception (Stolwijk *et al.*, 2000).

3 Clinical assessment of the woman for assisted conception

Gynaecological history

A history of PID, endometriosis, fibroids and abdominal or pelvic surgery are of interest. Cervical cytology can be taken if the patient has not been screened in the preceding three years.

Past medical history

Details of the past medical history should be carefully analysed. Sometimes these are directly related to the cause of infertility, and can also reduce the chances of successful treatment, interfere with the pregnancy and worsen the clinical condition of the patient.

General physical condition

- The woman's body mass index (BMI) should be assessed. The normal range is between 20 and 30. Women who are underweight or obese can have either anovulatory cycles or an abnormal response to ovarian stimulation, and therefore lower chances of conceiving (Norman & Clark, 1998; Katz & Voellenhoven, 2000).
- Heavy cigarette smoking and excessive alcohol intake may be relevant. There is evidence that women who are heavy smokers have reduced fertility when compared to women who are non-smokers (Grodstein *et al.*, 1994; Bolumar *et al.*, 1997; Sharara *et al.*, 1998).
- Rubella status and, for women of specific ethnic origin, the possibility of Tay–Sachs (Jewish), sickle cell trait (Afro-Caribbean) and thalassaemia (Mediterranean) should be investigated.
- Couples should be routinely assessed for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) (Steyaert *et al.*, 2000).

Counselling

The end of the first consultation can be a good opportunity to discuss the advantage of having counselling sessions prior to commencing treatment for assisted conception, particularly for those who will undergo treatment with assisted reproductive technology (ART) (see Chapter 15).

Clinical examination

When the full history has been taken, a clinical examination must be performed. This should include firstly a general examination when any large pelvic masses can be detected at abdominal palpation, and breast examination should be routinely performed.

Vaginal examination is of fundamental importance, as information about the size, shape and position of the uterus can be obtained and sometimes fibroids

4 **Domenico Massimo Ranieri**

or adnexal masses (ovarian cysts or hydrosalpinges) can be found. When such abnormalities are detected a sonographic assessment of the pelvis is required to confirm the diagnosis, establish its correlation with the fertility of the patient and to decide on further investigations and treatment.

Investigations

In the last decade, the infertility investigation work-up has expanded (Campana *et al.*, 1995), but when a battery of tests is performed, the chances of false positive results can increase exponentially (Hatasaka *et al.*, 1997; Zayed & Abu-Heija, 1999). It has been suggested that abnormal tests define a cause of infertility only when the treatment of this cause enhances fertility in comparison with no treatment. Therefore, the usefulness of such extensive investigations remains controversial. To avoid unnecessary and expensive tests and treatment, the evaluation of infertile women can be based primarily on the assessment of ovulation and tubal patency (ESHRE Capri Workshop, 1996). As the number of infertile women of advanced reproductive age is increasing, it is also important to include in the preliminary investigations the assessment of the ovarian reserve (Leeton, 1992; Speroff, 1994). (Table 1.1.)

Assessment of ovulation

Subtle ovulation disorders such as anovulation, inadequately timed ovulation or ovulation of a follicle of reduced size are reported in only 4% of the women studied (van Zonneveld *et al.*, 1999). Patients with infertility and regular cycles usually have normal ovulatory cycles. Therefore, intensive hormone monitoring may not be necessary.

Measuring progesterone in the mid-luteal phase appears to be the best test for confirming ovulation (Crosignani & Rubin, 2000), and to predict ovulation, the detection of the LH (luteinizing hormone) surge in the urine can be informative (Martinez *et al.*, 1992). However, ovulation and LH surge may not correspond and false negatives have been noted (Crosignani *et al.*, 1993). Often infertile women will present with basal body temperature (BBT) charts following instruction by their general practitioner. BBT charts are a simple and inexpensive method for determining the production of progesterone and thus confirming ovulation. However, since the role of luteal phase defects as a cause of infertility has been challenged, because they do not necessarily recur in every cycle, the importance of BBT charts has been diminished (Dawood, 1994). Follicular tracking by ultrasound scan may not be cost-effective in women with regular cycles.

5 Clinical assessment of the woman for assisted conception

Table 1.1. Investigations for infertile women

<i>Ovulation</i>
Basal FSH/LH
Prolactin
Thyroid function tests
Temperature chart
Mid-luteal progesterone
Follicular tracking
<i>Ovarian reserve tests</i>
Static tests:
Basal FSH
Basal oestradiol
Inhibin-B
Dynamic tests:
Clomiphene citrate challenge test
GnRH-agonist stimulation test
FSH GnRH-agonist stimulation test
Ovarian volume
Ultrasound
<i>Tubal and Uterine Factor</i>
Chlamydia
Hysterosalpingography
Hysterosalpingo contrast sonography
Laparoscopy
Hysteroscopy

Note: FSH: follicle stimulating hormone; LH: luteinizing hormone;
GnRH: gonadotrophin releasing hormone.

Women with infrequent (oligomenorrhoea) or absent (amenorrhoea) menstruation often have anovulatory cycles and are infertile. Women with primary amenorrhoea in general have usually been evaluated previously, but these investigations are not usually in the context of infertility. Table 1.2 lists the most common causes of primary amenorrhoea:

Patients in this group who can benefit most from ART are those with chromosome abnormalities as, if the uterus is normally formed, egg donation is an option. For women with Rokitansky–Kuster–Hauser syndrome, surrogacy is an option. Kallmann’s syndrome can be successfully treated with the gonadotrophin releasing hormone (GnRH) analogue pump or with gonadotrophin (Imai & Tamaya, 1986; Chryssikopoulos *et al.*, 1998). Women with secondary amenorrhoea and

Table 1.2. Causes of primary amenorrhoea

<i>Hypothalamus</i>
Kallmann’s syndrome
Hypothalamic tumour or trauma
Hypothalamic amenorrhoea
Anorexia
<i>Gonads</i>
Streak gonads:
XO Turner’s syndrome
XX or mosaic
XY gonadal dysgenesis
Testicular feminization
Polycystic ovary syndrome
Galactosaemia
<i>Uterus</i>
Absent
Rokitansky–Kuster–Hauser syndrome
Testicular feminization
<i>Vagina</i>
Absent
Imperforate hymen
<i>Endocrine disorders</i>
Diabetes, thyroid and adrenal abnormalities

oligomenorrhoea are more likely to require investigations and further management because of anovulatory infertility (Table 1.3).

Clinical history and assessment of basal follicle stimulating hormone (FSH), LH and prolactin can be sufficient for the diagnosis of the majority of causes of anovulation listed.

FSH and LH

Hypothalamic dysfunctions related to weight loss, anorexia nervosa, or excessive physical exercise are caused by reduced secretion of luteinizing hormone releasing hormone (LHRH), with FSH and LH levels below the norm (<5 mIU/ml) and very low oestradiol levels (Lachelin & Yen, 1978; Rowe *et al.*, 1993). This condition can be self-limiting if the initiating factors are removed and weight is regained. When amenorrhoea persists for a prolonged time hormone replacement therapy (HRT)

7 Clinical assessment of the woman for assisted conception

Table 1.3. Causes of secondary amenorrhoea and oligomenorrhoea

<i>Hypothalamus</i>
Weight loss/anorexia
Stress, emotional trauma
Excessive physical exercise
Tumour, trauma, craniopharyngioma
<i>Pituitary</i>
Prolactin secreting
Failure: Sheehan's syndrome
<i>Ovaries</i>
Polycystic ovaries
Ovarian failure
Galactosaemia
Chemo-/radiotherapy
<i>Uterus</i>
Asherman's syndrome
<i>Endocrine disorders</i>
Diabetes, thyroid abnormalities

is required to prevent loss of bone density (Drinkwater *et al.*, 1984; Rigotti *et al.*, 1984). If pregnancy is desired, ovulation can be successfully stimulated with a GnRH pump or gonadotrophins. Sometimes FSH, LH and oestradiol levels are within the normal ranges and in this case the woman can benefit from the administration of clomiphene citrate.

Premature ovarian failure is defined as the cessation of ovarian activity in women aged <40 years and is caused by exhaustion of the ovarian reserve, with FSH and LH levels of >20–40 mIU/ml. This can be idiopathic, familial in a few cases (Davis *et al.*, 2000), or caused by autoimmune disorders and chemotherapy. In women aged <30 years it is often associated with chromosome abnormalities. When a Y chromosome is identified, the gonads must be surgically removed as there is a 25% risk of malignant tumour formation (Speroff *et al.*, 1989; Conway *et al.*, 1996). Women with ovarian failure need to start HRT immediately. When pregnancy is desired and the uterus is normally formed, oocyte donation is the only option for assisted conception (Serhal & Craft, 1989).

Polycystic ovary (PCO) is a heterogeneous condition that can be associated with endocrine or metabolic disturbances. About 38% of the women with polycystic ovaries are obese, 66% have menstrual disorders, 48% have signs of hyperandrogenism and 73% are infertile because of anovulatory cycles. However, 20% are

8 **Domenico Massimo Ranieri**

completely asymptomatic and may be first diagnosed with PCO during their attendance at a fertility clinic when ultrasonography reveals the typical ultrasound appearance of PCO (Polson *et al.*, 1988). In 40% of women with PCO, LH levels can be elevated and when it is >10 mIU/ml it is more likely to be associated with a history of infertility and a higher miscarriage rate (Regan *et al.*, 1990).

Therefore, in women with PCO, infertility needs to be approached by ovulation induction in the first instance, and the first line of treatment should be with clomiphene citrate. If ovulation is not achieved gonadotrophins can be used (Lachelin, 1991). However, the risk of over-response is higher and often the treatment cycle is abandoned because of the risk of multiple pregnancy and hyperstimulation (Jacobs, 1987). In these women or when the LH levels are very high, laparoscopic ovarian diathermy (LOD) is an alternative method of treatment (Farquar *et al.*, 2000).

In vitro fertilization (IVF) finds its place in the treatment of PCO patients when the above methods fail to achieve pregnancy or there are other associated causes of infertility. Women with PCO who need controlled ovarian stimulation for IVF are an unusual group of patients. They need a profound down-regulation with GnRH-analogue, which may result in lower LH levels with improved oocyte quality, higher fertilization rate and significantly reduced miscarriage rate. They also have a high sensitivity to gonadotrophin, which must be used at a lower dose than for non-PCO patients, to reduce the risk of ovarian hyperstimulation syndrome (Balen *et al.*, 1999).

Prolactin

The normal cut-off level for prolactin is 700–800 mIU/l (Lenton *et al.*, 1982) but levels up to 1000 mIU/l are unlikely to be due to a pathological cause as prolactin levels can vary from one assay to another and can be increased by stress (Jeffcoate *et al.*, 1986). Often a rise in prolactin can be driven by psychotherapeutic drugs and high oestrogen levels such as with PCO, oestrogen therapy (pill), or a perimenopausal state. When a second blood test confirms abnormal levels of prolactin, thyroid function must be checked by measurement of thyroid stimulating hormone (TSH) and thyroxine levels, as primary hypothyroidism that can cause hyperprolactinaemia is not always an easy condition to diagnose clinically (Heyburn *et al.*, 1986). Pituitary adenoma can be diagnosed by magnetic resonance imaging (MRI) (Stein *et al.*, 1989). Microadenoma (<1 cm) can benefit from medical treatment with bromocriptine or cabergoline. Macroadenoma (>1 cm) can be treated medically and/or surgically.

It is important to remember that non-prolactin-secreting pituitary tumours may also be associated with increased prolactin levels because of obstruction of the

9 Clinical assessment of the woman for assisted conception

portal vessels and interference with the control of prolactin release. Therefore, acromegaly and Cushing syndrome must also be looked for. Galactorrhoea may be present in only one-third of women with hyperprolactinaemia and only one-third of women with galactorrhoea will have hyperprolactinaemia (Sakiyama & Quan, 1983). Women planning a pregnancy can be reassured, as there is no evidence of increased risk of miscarriage or malformations if conception occurs when taking bromocriptine (Turkalj *et al.*, 1982). However, it would be prudent to stop the drug when pregnancy is confirmed and commence close follow-up of the patient. When evidence of regrowth of an adenoma occurs, the treatment should be recommenced (Tan & Jacobs, 1986).

Ovarian reserve tests

Ageing of the ovary is characterized by reduction in the number of primordial follicles and a progressively reduced response to exogenous gonadotrophin. The recruitment of a sufficient number of follicles during ovarian stimulation is a crucial factor in the success of ARTs. A good ovarian response yields a larger number of oocytes and provides a wider choice of embryos for transfer (Loumaye *et al.*, 1990; Roest *et al.*, 1996). Failure of the ovaries to respond to gonadotrophin stimulation is a negative prognostic factor because it indicates reduced ovarian reserve. Although this is usually an age-related problem, its onset is highly variable and difficult to detect (Fahri *et al.*, 1997). Age and regularity of cycles are unreliable ways to predict ovarian reserve. The availability of an accurate screening test to identify patients who will respond poorly to ovarian stimulation has always been an attractive proposition to clinicians as it would provide a valuable means to select appropriate fertility treatment. A variety of screening tests to assess ovarian reserve and predict response to gonadotrophin stimulation have been developed.

Static tests

- Basal FSH
Diminishing of the number of follicles stored in the ovaries is followed by an increase in the FSH level. The measurement of basal FSH has been widely studied and found to be reliable (Muasher *et al.*, 1988; Toner *et al.*, 1991). It is simple and inexpensive and is the most widely used screening test for infertile women (Scott & Hoffman, 1995). However, women with normal basal levels of FSH do not always respond well to ovarian stimulation (Fahri *et al.*, 1997).
- Basal oestradiol (E₂)
Women with reduced ovarian reserve may have a shorter follicular phase with more advanced follicular recruitment and a higher basal E₂ level. Therefore,

10 Domenico Massimo Ranieri

Licciardi *et al.* propose basal E₂ as an accurate predictor of ovarian reserve and IVF outcome (Licciardi *et al.*, 1995), but the accuracy of this test is controversial (Phopong *et al.*, 2000).

- Inhibin-B

Inhibin-B is a glycoprotein released by granulosa cells, controlling the pituitary secretion of FSH with negative feedback. Low levels of inhibin have been correlated with a reduced ovarian reserve and poor IVF outcome (Seifer *et al.*, 1997) but this is not confirmed in more recent studies (Corson *et al.*, 1999).

Dynamic tests

Dynamic tests have been proposed to reveal poor ovarian reserves in women with an apparently normal static test such as basal FSH.

- Clomiphene challenge test (CCT)

This is based on the evaluation of the change of FSH levels from days 3 to 10 after administration of clomiphene citrate 100 mg from cycle days 5 to 9 (Navot *et al.*, 1987). When the Δ FSH is >20 there is an increased chance of low ovarian response to stimulation and poor IVF outcome (Scott *et al.*, 1993; Fahri *et al.*, 1997).

- GnRH agonist stimulation test (GAST)

The administration of a GnRH-a on cycle days 2 and 3 induces an initial surge of FSH, LH, and E₂ (flare-up), followed by pituitary desensitisation. The E₂ response to stimulation reflects the functional integrity of the ovarian follicles. A low E₂ response can be regarded as a consequence of dwindling cohorts of secretory follicles. Therefore, it is a poor prognostic factor for patients undergoing ovarian stimulation for ART (Padilla *et al.*, 1990; Winslow *et al.*, 1991).

- FSH GnRH agonist stimulation test

Simultaneous evaluation of basal FSH and E₂ response to GnRH-analogue administration (F–G-test) enhances the possibility of predicting ovarian reserve. This was first proposed in 1998 and compared to other tests it has the highest correlation with the ovarian response to stimulation (Ranieri *et al.*, 1998). The importance of this test with the additional evaluation of inhibin was confirmed by Ravhon *et al.* (2000). Recently it has been shown that the F–G-test can be used to individualize the drug regimen in women undergoing ovarian stimulation for IVF (Ranieri *et al.*, 2001).

Ovarian volume

A reduction of ovarian volume and number of antral follicles measured by transvaginal ultrasound scan have been noticed in older women. These changes may be observed earlier than a rise in FSH levels and are correlated with poor response of