Chapter 4
Preliminary Assessment Prior to Oocyte Cryopreservation

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Introduction

It has been estimated that around 90% of primordial follicles are lost by the age of 30 years, which is an average age of women starting family in most western countries [1, 2]. This suggests most women start trying to conceive in a state of depleted ovarian reserve; consequently, in some this leads to infertility and childlessness. Therefore, availability of Fertility Preservation Services is emerging as a basic health necessity for some women. Owing to recent advances in techniques for oocyte vitrification an option of effective fertility preservation, long before women have made reproductive decisions, has become available. However due to a range of factors which include lack of societal acceptance, inadequate awareness among patients as well as health care professionals, the economic cost and the organisational challenges, Fertility Preservation services are not readily accessible.

In principal, care pathway of Oocyte Cryopreservation can be divided into four distinct stages: (1) preliminary assessment, (2) controlled ovarian stimulation, (3) oocyte recovery and cryopreservation and (4) post treatment counselling. Preliminary assessment is of paramount importance, given that the effectiveness of subsequent stages of the management are largely determined by this evaluation. In addition, pre-treatment consultation provides an excellent opportunity to develop an understanding with the patient which can be invaluable in care of patients undergoing a potentially stressful treatment.

In this chapter, the interventions for the preliminary assessment prior to oocyte cryopreservation has been discussed in a stepwise manner reflecting the patient

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journey in real clinical conditions. The merit of each intervention has been appraised in the light of availability of the scientific evidence on its effectiveness. More importantly the quality of the evidence itself has been subjected to a robust interrogation, providing in depth analysis of the whole process.

A thorough preliminary assessment should include following stages: (1) history taking; (2) physical examination, (3) pelvic ultrasound scanning, (4) assessment of ovarian reserve, (5) genetic testing and (6) pre-treatment counselling.

History Taking

It is important to note, that the choice of treatment interventions may vary according to patient characteristics and expectations. Therefore, the reason for requesting oocyte cryopreservation and the outcome patient expects from the treatment ought to be established. For instance, the treatment pathway of a young patient wishing fertility preservation prior to achieving career goals may differ to that of someone with a family history of premature ovarian insufficiency. Consequently, achieving an understanding of the reason behind the need for oocyte cryopreservation is of importance.

History on general health should be established to evaluate safety of ovarian stimulation and oocyte recovery procedures as well as implications of a future pregnancy on patient's health. Reproductive history includes, age at menarche, duration of menstrual cycles, the date of last menstrual cycle, use of contraceptives, previous gynaecological pathologies and previous obstetric history. As part of a social history clinicians may seek if the patient is in a stable relationship, patient's plans for future fertility and if there are any relevant social issues that may affect future plans for starting a family.

Importantly, by way of directed history taking, risk factors for loss of ovarian reserve should be ascertained. Ovarian reserve is determined by assembly of primordial follicles during embryonic and fetal period as well as subsequent rate of loss of oocytes, both of which appear to be largely under the influence of genetic, environmental, life style and medical factors [3, 4]. Studies have demonstrated that there is a significant association between maternal age at menopause and the ovarian reserve of a woman [5]. Therefore, establishing this and reproductive history of the patient's mother and sisters provide important insight into a genetic predisposition of the patient to premature ovarian insufficiency (POI). The effect of environmental factors on ovarian reserve is not fully explored. However, there is convincing evidence on detrimental impact of certain agents such as radiation and gonadotoxic chemicals. Similarly, some life style factors such as smoking affect the patient's ovarian reserve as well as reproductive performance in general. The role of certain medical factors on the ovarian reserve have been studied in depth which can largely be divided into three broad medical modalities: Radiotherapy, Chemotherapy and Surgical Intervention on ovaries. Although all these interventions appear to have

detrimental effect on ovarian reserve, there is considerable variation between the effect of individual treatments. For instance, some chemotherapeutic agents display a potent gonadotoxic effect whilst others may result in mild and temporary cessation of the patient's reproductive performance [6]. Similarly, the duration as well as dose of chemotherapeutic agents are also recognised determinants of subsequent ovarian reserve. Therefore obtaining detailed history on exposure to Genetic, Environmental, Life Style and Medical Factors for accelerated loss of ovarian reserve provides important insight into the patient's current and future fertility, which is instrumental in counselling an individual patient with regards to their fertility preservation.

In contrast, the role of other factors on the ovarian reserve is less understood. For instance, findings of studies on the role of ethnicity with ovarian reserve is conflicting. Some studies reported significant association between patient's ethnicity and AMH levels [4, 7] whilst other did not find any correlation of AMH with ethnicity [8]. Similarly, a recent study which compared all three main markers (AMH, AFC, FSH) in a large cohort of infertile women (n = 2946) found that the effect of ethnicity on the markers of ovarian reserve was weak; suggesting prediction of the decline of ovarian reserve of individual patients on the basis of ethnicity is not feasible [9].

Physical Examination

Basic anthropometric measurements such as height, weight and body mass index allows to evaluate overall wellbeing of the patient. However, the role of BMI in understanding of individual patient's ovarian reserve is less understood. Whilst some report that higher body weight is associated with lower AMH [7, 10, 11], other studies found obese women have significantly higher AMH, AFC and lower FSH measurements levels suggesting direct correlation between weight and ovarian reserve [12].

Ultrasound

Pelvic pathology may have significant impact on both oocyte cryopreservation cycle and future fertility treatment. Therefore presence of uterine, tubal and ovarian pathologies should be ruled out prior to oocyte cryopreservation treatment cycle. Consequently, ultrasound scanning should be utilised as a tool for screening. In addition ultrasound scan offers one of the best tools for assessment of ovarian reserve, antral follicle count (AFC), which has a number of advantages compared to that of other markers of ovarian reserve which as discussed below.

Assessment of Ovarian Reserve

The biological ovarian reserve is defined as the number of primordial and growing follicles left in the ovary at any given time and therefore, establishment of a true biological ovarian reserve is clearly not feasible in clinical setting. However, ovarian reserve can be estimated using various biomarkers, such as Chronological Age, Follicle stimulating hormone (FSH), Anti-Mullerian Hormone (AMH) and Antral Follicle Count (AFC). Although these markers provide best available representation of patient's ovarian reserve, it is important to appreciate the strengths and the limitations of these markers so that they are interpreted within the context of overall characteristics of the tests rather than in absolute numbers. Therefore in order to provide in depth understanding; we first provide a brief review of the biology of ovarian reserve, then discuss technical performance of the tests in light of latest available evidence.

Ovarian Reserve

An ovarian reserve is determined by the size of the oocyte pool at birth and the decline in the oocyte number thereafter. Both of these processes are largely under the influence of genetic factors although environmental and life style factors appear to play a role [13, 4]. Folliculogenesis in women of reproductive age consists of two stages (a) the initial non-cyclical recruitment of primordial follicles leading to the formation of primary and pre-antral follicles and (b) the cyclical development of antral follicles with a subsequent selection of a single dominant follicle (Fig. 4.1). The mechanism of the initial recruitment of the oocytes is not well understood, but it is clear that the process is independent of the influence of the pituitary gonadotrophins and appears to be governed by the genetically pre-programmed interaction of

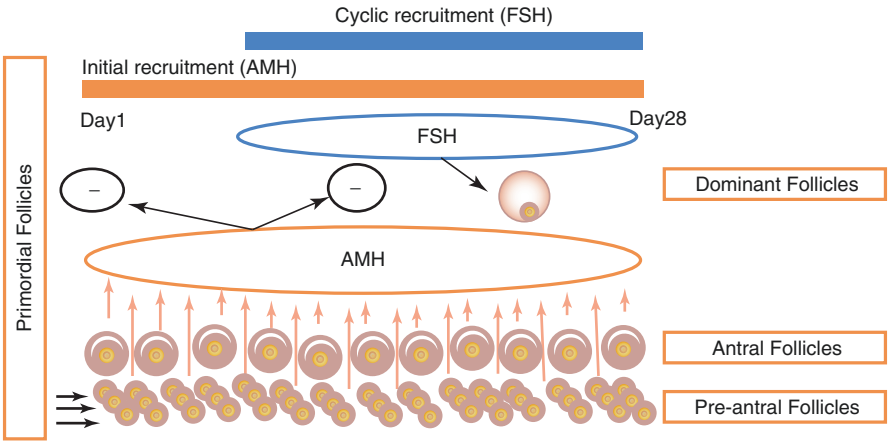

Fig. 4.1 Initial and cyclic recruitment of oocytes: the role of AMH and FSH

the oocyte with local growth factors, the most important of which appears to be anti-Müllerian hormone, and cytokines [3]. Anti-Müllerian hormone appears to be the main regulator of the size of the primordial follicle pool by its inhibitory effect on the recruitment of the primordial follicles [14]. The cyclical phase of development of oocytes is characterised by the transformation of secondary follicles into antral follicles and subsequent growth of the antral follicles into pre-ovulatory stages. In general, the process of cyclic recruitment starts from puberty under the influence of rising levels of pituitary follicular stimulating hormone (FSH). Interestingly, in addition to its inhibitory effect to the resting follicles, AMH also suppresses the development of the growing follicles and it appears that AMH inhibits FSH-induced follicle growth by reducing the sensitivity of growing follicles to FSH [15]. Thus AMH and FSH play a central role in recruitment and growth of follicles which is underpinned by the state of ovarian reserve at given time that is largely determined by the woman's age. Consequently measurement of these parameters, namely AMH, FSH, follicle count (AFC) and age, provides a window into the state of ovarian activity as well as overall reserve of the ovaries in women.

Chronological Age

Owing to the biological age-related decline of the quantity, and arguably the quality, of oocytes the chronological age can be used as a marker of ovarian reserve. Studies have demonstrated that ovarian reserve [2, 16], natural fecundity and outcomes of ART [17, 18] decline significantly from age of 35 when it is believed the ovarian reserve undergoes accelerated decline. Although there is a strong association between chronological age and reduction in fertility, evidently there is a significant variation in age-related ovarian reserve indicating chronological age alone may not be sufficient to estimate the individual woman's ovarian reserve reliably [19].

Basal FSH

Basal FSH was one of the first endocrine markers introduced in assessment of fertility and is still utilised in many fertility clinics, albeit in conjunction with other markers which are considered more reliable. Secretion of FSH is largely governed by the negative feedback effect of steroid hormones, primarily oestradiol, and inhibins which are expressed in granulosa cells of growing ovarian follicles. Consequently, decreased or diminished recruitment of ovarian follicles is associated increased serum FSH measurements and high, particularly very high basal FSH reading is considered as a good marker of very low or diminished ovarian reserve [20]. However, unlike some other markers, FSH measurements do not appear to have discriminatory power for categorisation of patients to various bands of ovarian reserve. Given between-patient variability FSH measurement (CV 30%) is similar to its within-patient variability (27%), stratification of patients to various ranges of ovarian reserve does not appear to be feasible [21]. Indeed, a systematic review of

37 studies on the prediction of poor response and non-pregnancy in IVF cycle has concluded that, basal FSH is an adequate test at very high threshold levels and therefore has limited value in modern ART programs [19].

Antral Follicle Count

Basal antral follicle count estimation involves ultrasound assessment of ovaries between 2nd and 4th day of menstrual period and counting "follicles", which corresponds to antral stage of folliculogenesis [22]. The test provides direct quantitative assessment of growing follicles and is known as one of the most reliable markers of ovarian reserve. AFC measurement has been reported as having a similar sensitivity and specificity to AMH in prediction of poor and excessive ovarian response in IVF cycles [19, 23]. Given AFC measurement is available instantly and allows patients to be counseled immediately, the test eliminates the need for an additional patient visit prior to IVF cycle. However, AFC is normally performed only in the early follicular phase of the menstrual cycle, given most published data on measurement of AFC are based on studies that assessed antral follicles during this stage of the cycle [22]. Interestingly, some studies suggest that variability of AFC during menstrual cycle is small, particularly when follicles between 2 and 6 mm are counted, and therefore assessment of AFC without account for the day of menstrual cycle may be feasible.

One of the main drawbacks of AFC is that the cut off levels for size of counted follicles remains to be standardised [22]. Initially, follicles of 2–10 mm were introduced as the range for AFC and many studies were based on this cut off. Later, counting follicles of 2–6 mm was reported to provide most accurate assessment of ovarian reserve [24, 25] and therefore some newer studies are based on AFC measurements that used this criterion. Consequently, direct comparison of the outcomes of various studies on assessment of AFC requires careful analysis.

Similar to other markers of ovarian reserve (Table 4.1), AFC appears to display significant variability between measurements in same patient [26]. The study that evaluated the measurement AFC (n = 4059) in a large cohort of patient (n = 2362)

Table 4.1 Within- and—between patient variability of AFC, FSH, AMH (Gen II and DSL assays) measurement

	AFC		FSH		AHM (Gen II assay)[a]		AHM (DSL assay)	
Comparsion	Mean (SD)	CV (%)	Mean (SD)	CV (%)	Mean (SD)	CV (%)	Mean (SD)	CV (%)
Between patients	13.9 (6.3)	35	7.4 (2.2)	30	11.2	126	12.7 (12.0)	94
Within-patient		30		27		59		28
Within-sample		ND		6		3.57		4.8

Note: Data on FSH, AFC and AMH (Gen II and DSL assays) are based on population of the same centre [21, 27]

AMH measured in pmol/L, FSH in IU/L, *CV* coefficient of variation, *ND* not determined

[a]Unmodified original Gen II assay (Data collection: 17.11.2010–25.10.2011)

found that within-patient variation of AFC (CV 30%) was similar to that of between patient variation (CV 35%) suggesting that categorisation of the patients into various groups of ovarian reserve on the basis of AFC may not be as reliable as previously thought.

Anti-Müllerian Hormone

In the female, anti-Müllerian hormone (AMH), produced by granulosa cells of preantral and early antral ovarian follicles, regulates oocyte recruitment and folliculogenesis [14]. It can assess ovarian reserve and guide gonadotropin stimulation in assisted reproduction technology [28]. AMH is also used as a granulosa cell tumor marker, a tool for evaluation of ovarian reserve after chemotherapy [29], and to predict age at menopause [30, 31].

AMH immunoassays, first developed by Hudson et al. [32] in 1990, were introduced commercially by Diagnostic Systems Laboratories (DSL) and Immunotech (IOT). These assays were integrated into a second-generation AMH assay (Gen II) by Beckman-Coulter, but studies suggested that this assay exhibited clinically important, within-patient, sample variability [21, 27]. Beckman Coulter confirmed this with a field safety notice (FSN 20434-3) and withdrew the assay kits from use. Subsequently, third generation AMH assays were introduced which include: (1) modified method of Gen II ELISA by Beckman Coulter, (2) Pico AMH Ansh Labs, (3) Ultrasensitive Ansh Labs, (4) Automatic test by Roche ELECSYS and (5) automated verison of Beckman Coulter Gen II ELISA. Important to underline, all above AMH assay tests may share certain common properties due to the fact they most utilise same antibody and/or calibrated against each other. Therefore, they may have common strengths and, more worryingly, possibly same issues. Therefore, there is a clear need for an international reference standard for AMH and for robust independent evaluation of commercial assays in routine clinical samples with well-defined sample handling and processing protocols. Meanwhile, previous issues of sample instability and lack of reliable inter-assay comparability data should be taken into account in the interpretation of available research evidence and the application of AMH measurement in clinical practice.

Genetic Testing

As previously discussed both formation as well as decline of ovarian reserve is largely determined genetically and therefore extremes of poor ovarian reserve such as Premature Ovarian Insufficiency (POI) and Early menopause have genetic origin [33]. Premature ovarian insufficiency may present as a feature of certain genetic syndromes, such as galactosemia and blepharophimosis-ptosis-epicanthus produced by mutations *in FOXL2* gene that can be diagnosed by their non-ovarian phenotype. However, chromosomal abnormalities, mosaic of sex chromosome

abnormalities, premutation alleles of FMR1 and other rare mutations are associated to primary premature ovarian failure without other phenotypic features [33]. When premature ovarian insufficiency is suspected, appropriate genetic testing, including a referral to a clinical geneticist is recommended.

Patients concerned about their risk of premature ovarian insufficiency, should be referred to genetic counselling. Pre-symptomatic or carrier genetic testing will depend on family history, patient's medical history and their desire for genetic testing. The most relevant investigations are karyotyping and allele size in FMR1 gene. Analysis of repeats in *FMR1* gene is recommended as preconception or prenatal carrier screening in women with a family history of X-fragile, non-diagnosed mental retardation, developmental delay, autism or ovarian insufficiency [34]. A screening of *FMR1* in a large group (n = 2300) women found a frequency of 1.7% for premutation and 0.61% for full mutation in US [35]. These findings suggest that if women interested in preconceptional fragile X carrier screening, they should be offered the test irrespective of presence of any family history of the condition [34]. In addition, expanded carrier screening including analysis of frequent mutations in more than 100 genetics conditions can be considered in line with the recommendations of American Genetics as well as American Obstetrics and Fetal Medicine Societies [36] and supported by European Society of Human Genetics [37]. Thus, genetic testing in patients undergoing fertility preservation for ovarian ageing is determined by a family history of premature ovarian insufficiency, symptoms of genetic traits associated with premature loss of ovarian reserve and findings of assessment of ovarian reserve.

Pre-treatment Counselling

Once full assessment has taken place, patient should have an opportunity to have individualized pre-treatment counselling. This should include discussion of clinical effectiveness, cost, limitations and logistics of oocyte preservation. Patients should be provided information leaflets which is written in plain language in the format accessible to patients.

Key Message

1. Given the clinical and laboratory advances, demand for oocyte cryopreservation for both medical and social reasons is on the rise in recent times.
2. Counselling should be considered a key priority to enable women in making informed decisions regarding fertility preservation.
3. Clinicians should be aware of the importance of detailed clinical assessment.
4. Particular attention should be given to the assessment of the ovarian reserve.
5. Knowledge of the biological, hormonal and ultrasound markers of ovarian reserve and their predictive ability is vital to the assessment and counselling of women undertaking fertility/oocyte cryopreservation.

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