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Section 1 Patient selection and preparation

Chapter 1

# Pre-treatment hormone assessment to optimize IVF outcomes

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## Introduction

There is considerable debate and substantial individual variation in clinical practice regarding what hormones should be assessed in all patients prior to commencing in vitro fertilization (IVF) treatment. While it would appear logical to measure multiple hormones such as gonadotropins (luteinizing hormone [LH]; follicle stimulating hormone [FSH]), steroids (testosterone, 17 hydroxy-progesterone), prolactin, and thyroid function (thyroid stimulating hormone [TSH]; thyroxine [FT4]) in all women with suspected anovulation (irregular menstrual cycle), the utility of such an extensive hormone analysis in the average ovular patient about to commence IVF for male or tubal factor infertility is less certain. In today's environment of escalating medical costs it is imperative that we only order tests that have potential clinical value. Furthermore, abnormal test results can produce anxiety in the patient, an undesirable outcome at a time when the patient is already under considerable psychological distress. The focus of this chapter is to explore the evidence behind which hormone tests should be a mandatory prerequisite for all women about to undergo their first cycle of IVF treatment.

## Hormone assessments of ovarian reserve

It is well known that the response to controlled ovarian hyperstimulation (COH) during IVF treatment is highly variable, even among women of similar age. This undoubtedly reflects the wide variation in ovarian reserve between different women, which is primarily determined by the size of the primordial follicular pool. Unfortunately history and examination have a very poor sensitivity in predicting ovarian responsiveness to COH. Therefore performing hormone assessments of ovarian reserve before commencing a first cycle of IVF treatment may be useful. Firstly, these tests may allow for a more accurate prediction of a woman's anticipated response to COH, allowing for tailoring of the starting dose of gonadotropin stimulation. Secondly, since it is well recognized that low ovarian reserve has a significant negative influence on the chances of pregnancy during IVF treatment, hormone assessment of ovarian reserve can give couples better information on the likely benefits/success of treatment beyond maternal-age prognostic assessment.

The traditional hormones used for assessment of ovarian reserve include early follicular phase FSH/estradiol, serum inhibin B, and anti-mullerian hormone (AMH) [1]. A recent review of over 2000 cycles of IVF from 20 individual studies has concluded that AMH is a

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better marker for predicting ovarian response to COH than patient age, day 3 FSH, estradiol and inhibin B [2]. All of the available data show a strong positive correlation between basal serum AMH levels and the number of retrieved oocytes in women undergoing ovarian stimulation [2]. This observation is not surprising since AMH is produced by the granulosa cells of the small antral follicles, with several studies reporting an excellent correlation between serum AMH levels and ultrasound-assessed antral follicle counts. It is these small antral follicles (2–10 mm) that are recruited as mature oocytes in response to gonadotropin stimulation during IVF treatment. Not only is AMH a more accurate measure of ovarian response to COH, its concentration in serum does not fluctuate significantly during the menstrual cycle, unlike other hormonal assessments of ovarian reserve (FSH, inhibin B, and estradiol) [2]. This makes it a more practical measure of ovarian reserve since it can be sampled at any time that the patient attends clinic, unlike FSH, estradiol, and inhibin B that are only accurate if taken in the early follicular phase of the menstrual cycle [1].

While serum AMH appears to be an excellent marker of quantitative ovarian reserve, it appears to have very limited usefulness as a marker of oocyte quality. Serum AMH levels do not predict embryo morphology or the rate of embryo aneuploidy [2]. Furthermore, recent data from studies of natural conception show no correlation between serum AMH and rates of miscarriage or genetic abnormality in the foetus [3, 4]. Similar studies have also failed to find a correlation between FSH levels and embryo aneuploidy [5]. Therefore, hormone assessments of ovarian reserve should not be used to judge oocyte quality, but only to predict qualitative ovarian reserve.

It may be useful to correctly predict the occurrence of a poor response as this may avoid treatment in women destined not to respond to COH, thus reducing the financial and emotional costs associated with cancelled cycles. Traditionally a day 3 FSH exceeding 15 IU/l has been seen as a very poor prognostic sign and has been used by many clinics to exclude patients from IVF treatment [1]. Several authors have investigated the utility of AMH in the prediction of poor response to FSH. The reported sensitivity and specificity for predicting poor response are in the range 44–97% and 41–100% respectively, depending on the "cut off" serum AMH value used in the individual study [2]. In our own clinic we have reported that a serum AMH of less than 14 pmol/l (1.96 ng/ml) has a sensitivity and specificity of 73% for predicting a poor response (≤ four oocytes) to ovarian stimulation [6]. If serum AMH measurements suggest low ovarian reserve, it has been our practice to double the starting dose of gonadotropin stimulation from 150 to 300 IU/day in young women in their first cycle of IVF treatment. While this approach would be expected to increase the oocyte yield, no randomized control trial has yet been conducted to confirm this benefit. A small retrospective observational study has reported that increasing the starting dose of gonadotropin stimulation in young patients with predicted poor response did not result in a significant improvement in oocyte yield or pregnancy rates, but also reassuringly did not produce any dangerous levels of ovarian hyperstimulation [7]. Therefore, the clinical utility of predicting poor ovarian reserve using serum AMH may only be in helping prepare patients for a poor oocyte response in their first cycle of IVF treatment.

Serum AMH levels in women with polycystic ovarian syndrome (PCOS) are on average two to three times higher than their age matched ovulatory peers, with serum AMH having a relatively high sensitivity and specificity (92% and 67% respectively) for diagnosing the presence of polycystic ovaries on scan [2]. Since PCOS or polycystic ovaries are a very significant risk factor for the development of ovarian hyperstimulation syndrome (OHSS), serum AMH is highly likely to predict the occurrence of OHSS during IVF treatment. Our

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group was the first to report this association between high serum AMH and the development of OHSS [8]. Since then, four prospective studies have been published on the topic, each reporting a relevant value for AMH for the prediction of hyper-response and OHSS [2]. The results of these publications suggest that once serum AMH exceeds approximately 30 pmol/l (4.2 ng/ml), or is in the top quartile of serum AMH results for their age, the patient is at considerable risk of OHSS. Unfortunately no randomized controlled trial has analyzed if reducing the starting dose of gonadotropin stimulation does reduce the incidence of OHSS, while still maintaining good pregnancy rates. It was standard practice in our unit to reduce the starting dose of gonadotropin stimulation from 150 IU/day to 100–125 IU/day in young patients (< 36 years of age) if the serum AMH was greater than 30 pmol/l. However, it became evident that the optimal "therapeutic window" in these PCOS patients is quite narrow, with 150 IU FSH producing an excessive response, while 100–112 IU FSH often producing an inadequate response. Therefore it has now become our standard practice to place all young women with high AMH (> 30 pmol/l) on a starting dose of 125 IU of FSH in a gonadotropin-releasing hormone (GnRH) antagonist cycle of IVF. The use of a GnRH antagonist has been shown to half the risk of hospitalization with severe OHSS, while also giving the treating doctor the opportunity to use a GnRH agonist trigger to further minimize the severity of OHSS if an exaggerated response to stimulation is still observed despite the reduction in starting dose of gonadotropin stimulation [9].

The vast majority of studies suggest that serum AMH has a very poor performance for predicting pregnancy outcome during a stimulated cycle of IVF [2]. Only one prospective study has reported a fall in pregnancy rates derived from both fresh and subsequent frozen embryo transfers once the serum AMH concentration dropped below 7.8 pmol/l (1.1 ng/ml) [10]. A retrospective study has reported a similar significant reduction in cumulative pregnancies (fresh plus frozen embryo transfers) once the serum AMH fell below 14 pmol/l [6]. These observations are a consequence of the relationship between AMH and quantitative response to COH. Women with higher AMH produce a greater number of oocytes during IVF treatment, with a resulting greater number of good quality embryos available for cryopreservation. However, extreme caution should be shown when using AMH to exclude women from IVF treatment based on predicted poor reserve since there have been documented cases of live-birth pregnancy in women with undetectable levels of serum AMH.

## Assessment of thyroid dysfunction

There are several logical reasons for testing thyroid function in all women presenting for IVF treatment. Firstly, undiagnosed hypothyroidism is relatively common in the infertile population, affecting 5–6% of women with idiopathic or anovulatory infertility and 2% of women with tubal or male factor infertility [11]. Hyperthyroidism is significantly less common, affecting between 0.1 and 1% of women in the reproductive age group [12]. The treatment of women with previously undiagnosed hypothyroidism with thyroxine replacement can itself result in natural conception, removing the need for IVF treatment. Furthermore, undiagnosed hypothyroidism may adversely affect the IVF cycle as it has been linked with failed oocyte fertilization despite the use of good quality sperm [13]. Finally, untreated hypothyroidism may lead to pregnancy complications such as miscarriage, growth restriction, and pre-term delivery, plus a possible reduction in the neuropsychomotor development of the child conceived by fertility treatment [12]. It has been suggested that thyroid function is best assessed in infertile

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women with both a TSH and FT4 test, since isolated hypo-FT4 (normal TSH) has been reported in up to 2% of pregnancies and may still interfere with the child's neurological development [12].

Compared to natural conception, IVF treatment itself may exacerbate hypothyroidism since the supra-physiological levels of estradiol seen during COH will result in an increase in production of thyroxine-binding globulin, thereby reducing the concentration of biologically active free thyroxine hormone. It would therefore appear prudent to order a screening TSH and FT4 test on all women before commencing IVF treatment [12].

## Miscellaneous hormone assessment

Two previous studies have analyzed the utility of measuring hormones such as prolactin, LH, FSH, estradiol, progesterone, testosterone, DHEAS (dehydroepiandrosterone sulfate), 17 hydroxy-progesterone, and androstenedione in ovulatory women prior to IVF treatment [14,15].While a mild elevation in prolactin levels was more commonly observed in women about to commence IVF treatment than a fertile reference population, there was no significant difference in hormone levels between those women who became pregnant during the IVF cycle and those who did not. The minor increase in serum prolactin seen in these ovulatory women probably reflects an anxiety related "stress" response common in infertile patients. Furthermore, another study has shown that treatment of minor elevations in prolactin

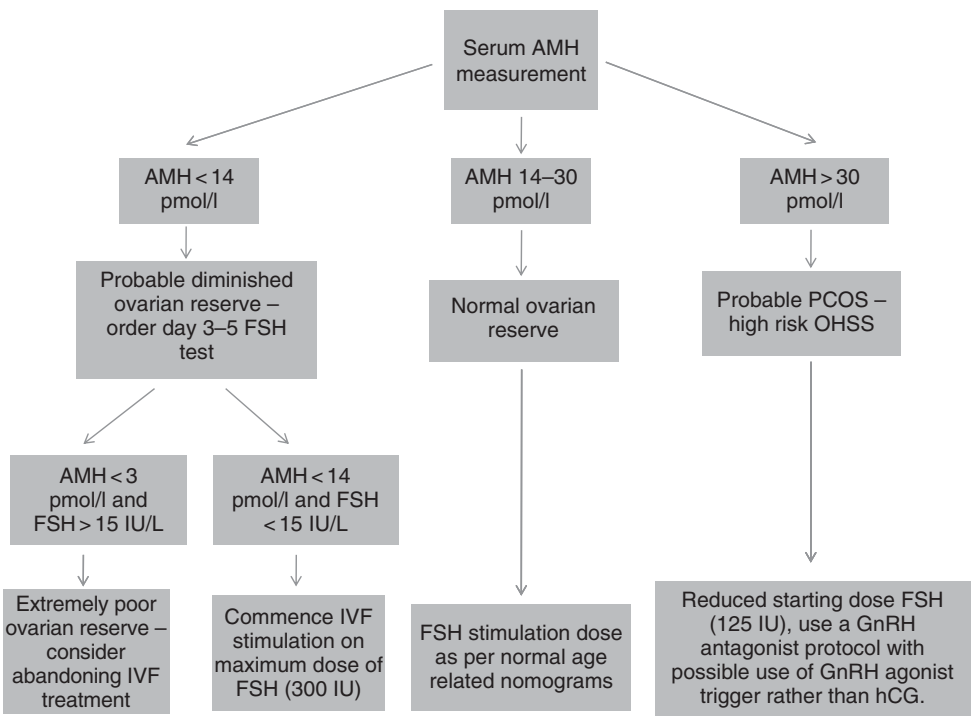


**Figure 1.1** Use of serum anti-mullerian hormone (AMH) to tailor controlled ovarian hyperstimulation treatment in patients undergoing their first cycle of IVF.

The serum AMH measurement thresholds depicted are for the Immunotech AMH assay platform. Conversion units: 1 ng/ml AMH = 7.14 pmol/l.

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using dopamine agonist therapy before IVF actually worsens embryology outcomes [16], thereby providing no justification for the routine assessment of prolactin or any of these other reproductive steroids/gonadotropins prior to IVF treatment in ovulatory women.

## Conclusion

The literature would suggest that measurement of serum AMH and TSH/FT4 should be a mandatory part of the infertility "work-up" in any woman undergoing IVF treatment for the first time. Serum AMH allows for the best assessment of likely ovarian response to COH, with the added advantage of being able to be sampled at any time in the menstrual cycle. For those women with low AMH, an additional day 3–5 FSH assessment may be appropriate as it may identify those women with a very poor chance of successful pregnancy (FSH > 15 IU/L). Serum AMH measurements can be used to predict patients response to COH in their first cycle of IVF and individualize their treatment regime, as outlined in Figure 1.1. Patients identified as having abnormal thyroid function should have this corrected before commencing IVF treatment so as optimize IVF embryology and pregnancy outcomes.

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