



Biochemical Investigation of Infertility

Infertility is defined as a failure to conceive after one year of regular unprotected intercourse in women <35 years, and in women aged >35 years, after six months of unprotected intercourse. With the average age of first pregnancies now being 30 years, infertility and its investigation is becoming more common.

It should be initiated sooner in women with irregular menstrual cycles or known risk factors for infertility including endometriosis, pelvic inflammatory disease, or reproductive tract malformations.

Female infertility, male infertility or a combination of both has notably increased with an estimated 10-18% couples having trouble getting pregnant or having a successful delivery.

Causes

There are various causes of infertility which may relate to female, male, or both factors. Female causes are usually related to the woman's age, issues with ovulation or pelvic anatomy, such as endometriosis or polycystic ovarian syndrome (PCOS). Male causes include sperm defects or dysfunction.

A thorough history and examination usually focuses further diagnostic evaluations. History should focus on infertility duration, menstrual, medical, surgical and gynaecological history. Physical examination includes BMI assessment, thyroid and breast examination, signs of hyperandrogenism, vaginal or cervical abnormality, pelvic/abdominal tenderness and adnexal masses.

Diagnostic tests

NICE guidelines propose that an initial infertility evaluation of all couples consists of:

Semen analysis: Results should be

interpreted in reference to WHO values which assess; semen volume, pH, sperm concentration, total motility, vitality and morphology. If the first semen analysis is abnormal, repeat testing should be performed because of inherent variability.

Assessment of ovulatory function:

Women with regular 28-day cycles with molinimar (luteal phase) symptoms are likely to be ovulatory. In those with irregular cycles ovulation assessment should be performed. A progesterone performed 7 days prior to the onset of menses is the most easily documented.

An alternative is an over-the-counter ovulation prediction kit that measures urinary lutenising hormone (LH), which provides indirect evidence of ovulation by demonstrating a mid-cycle LH surge. Such kits have a 5-10 percent false positive/negative rate and confirmation by serum LH measurement may be required.

Non biochemical methods include endometrial biopsy, which was once considered 'gold standard' but is no longer recommended for ovulation assessment unless endometrial pathology is suspected.

Determination of ovarian reserve:

This describes reproductive potential as a function of the number and quality of oocytes. A number of screening tests are used, however no single test is highly reliable in predicting pregnancy potential thus a combination of tests is often used.

A day 3 Follicular Stimulating Hormone (FSH), with high values (>20IU/L) suggests pregnancy is unlikely with treatment using the womans' own oocytes. In women with adequate ovarian reserve sufficient production of ovarian hormones occurs from small follicles early in the menstrual cycle, to maintain FSH at a low level. A paired day 3 oestradiol (E2) is often utilised with higher values indicating advanced premature follicle recruitment that occurs in women with poor ovarian reserve. Given that high E2 levels can inhibit FSH production, measurement of both helps negate false negative results. An Antral follicle count (AFC) performed in follicular phase by ultrasound is also a good non-biomedical marker of ovarian reserve.

Anti-müllerian hormone (AMH) produced by small preantral and early antral follicles, reflects the primordial follicle pool and

About the Author

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parallels fertility; rising during puberty, peaking in the early 20s, and falling from 30 years on, to undetectable levels post menopause. AMH can be measured anytime during the menstrual cycle, although a mild decrease can occur in the luteal phase and some clinicians prefer early follicular phase testing. The oral contraceptive pill can lower AMH results so that testing may be unreliable. In general, AMH can be measured anytime during the menstrual cycle and appears to be a direct, reliable and early indicator of declining ovarian function.

AMH is useful in identifying reduced ovarian follicle pool in particular patient subgroups, including cancer patients and those with previous significant ovarian injury from radiation or surgery. Given that AMH level correlates with the number of oocytes retrieved after stimulation, it is the best biomarker for predicting poor and excessive ovarian response in patients planning IVF, though its accuracy in predicting live birth is poor and should not be used to exclude couples from IVF/ICSI.

Assessment of fallopian tube patency:

Whilst not a biochemical test, either a hysterosalpingography (HSG) or a hysterosalpingo-contrast sonography (HyCoSy) are standard of care when evaluating tubal patency, with HSG also appearing to have therapeutic effects. Diagnostic laparoscopy is reserved for suspected endometriosis or pelvic adhesions.

Further Reading

American Society of Reproductive Medicine. *Diagnostic evaluation of the infertile female: a committee opinion. Fertility and Sterility*; 103(6), 2015:e44-50.

NICE guideline. *Fertility problems: assessment and treatment: Clinical guideline*
Published: 20 February 2013, Updated 2017.
<https://www.nice.org.uk/guidance/cg156>

KEY MESSAGES

- Infertility assessment involves both female and male partners.
- Evaluation includes a comprehensive history and physical exam.
- Semen analysis, ovulatory status by history or lab testing and checking tubal patency are the 'basics'.
- Ovarian reserve is assessed with AMH, day 3 FSH and E2 levels.

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