ejpmr, 2016,3(5), 247-258

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

STUDY OF PCOS AND AMH IN INFERTILE FEMALE

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Article Received on 10/03/2016 **Article Revised on 31/03/2016** **Article Accepted on 22/04/2016**

ABSTRACT

Infertility primarily refers to the biological inability of a person to contribute to conception. It is acquiring a proportion of global epidemic which affects male and female equally. Some of the most common causes of female infertility are age, polycystic ovaries, complications from being infected with sexually transmitted diseases, smoking, and being underweight or overweight. Polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory infertility in women. In PCOS, the ovary doesn't make all of the hormones it needs for an egg to fully mature. The follicles may start to grow and build up fluid but ovulation does not occur instead it remain as cysts. It is a complex, heterogeneous disorder of uncertain aetiology however the suggested causes include genetic susceptibility, obesity, elevated insulin, hormonal imbalance, life style, excess androgen, environmental factors, insulin resistance etc. Various criteria for confirmation of PCOS have been discussed in detail in this paper. Presently its diagnosis lies on symptoms and physical findings; ultrasound testing and hormonal testing. Traditionally the absolute level of LH and FSH, as well as the LH:FSH ratio, can offer significant insight into the PCOS patient. Antimüllerian hormone (AMH) also known as Müllerian Inhibiting Substance (MIS) is a new diagnostic marker of ovarian function and for diagnosis of PCOS. In female AMH is produced by the granulosa cells of the recruited follicles primarily by the pool of early-growing follicles, until they become sensitive to FSH. It is widely accepted that the reduction of AMH levels in serum is the first indication of a decline in the follicular reserve of the ovaries. AMH being more stable during the entire menstrual periods could be used as a better marker over FSH and LH for diagnosis of polycystic ovary syndrome especially where the ultra sonographic examination of the ovaries is not feasible.

KEYWORDS: Polycystic ovarian syndrome, anovulatory infertility, Antimüllerian hormone.

INTRODUCTION

Infertility primarily refers to the biological inability of a person to contribute to conception. Infertility is acquiring a proportion of global epidemic with the prevalence rate of approximately 8-12%. As per study, published at the end of 2012 by WHO. One in every four couples in developing countries had been found to be affected by infertility. According to the American Society for Reproductive Medicine, Infertility affects men and women equally. There are many causes of infertility and many times the cause of infertility goes unknown. Woman infertility also refers to the state of a woman who is unable to carry a pregnancy to full term. Some of the most common causes of female infertility are age, polycystic ovaries, complications from being infected with sexually transmitted diseases, smoking, and being underweight or overweight.

Polycystic ovary syndrome (PCOS) is a serious condition resulting in ovaries which cannot ovulate an oocyte. Polycystic ovaries are the main cause of infertility in women especially anovulatory infertility in female. Approximately 90%–95% of anovulatory women presenting to infertility clinics have PCOS. Polycystic ovary syndrome (PCOS) also called hyperandrogenic anovulation (HA)[1] or Stein-Leventhal syndrome[2] is one of the most common endocrine disorders among females. PCOS is a heterogeneous collection of signs and symptoms with varying degree of mildness and severity in affecting the reproductive, endocrine and metabolic functions.[3] Hormonal alteration is observed in FSH, LH, AMH, insulin, prolactin etc. Along with the clinical symptoms and ultrasound the biochemical study of these hormones play vital role in accurate diagnosis of PCOS. Traditionally the absolute level of LH and FSH, as well as the LH:FSH ratio, can offer significant insight into the PCOS patient.

Antimüllerian hormone (AMH) also known as Müllerian Inhibiting Substance (MIS) is a new diagnostic marker of ovarian function. Increased AMH levels correlated with PCOS severity and are associated with greater ovarian stimulation and higher clinical pregnancy rates following assisted reproductive technology.[4]

In female, Anti-Müllerian hormone (AMH) is produced by the granulosa cells of the recruited follicles until they become sensitive to FSH. Unlike the pulsative appearance of FSH and LH; AMH levels do not vary significantly during the menstrual cycle and can therefore be drawn on any day of the cycle for estimation. Along with the diagnosis of PCOS, AMH is also found significant in assessing ovarian aging and ovarian reserve.[3]

Infertility

Infertility primarily refers to the biological inability of a person to contribute to conception. World Health Organization (1991) defines infertility as failure to conceive despite one year of cohabitation and exposure to pregnancy.[5] If the couple has never conceived despite cohabitation and exposure to pregnancy (i.e. sexually active, non- contracepting, and non-lactating) for a period of one year, it is called primary infertility; primary infertility is also referred to as primary sterility.[5] Infertility is acquiring a proportion of global epidemic with the prevalence rate of approximately 8–12%.[5]

It is estimated that globally 60-80 million couples suffer from infertility every year, of which probably between 15-20 millions (25%) are in India alone [6, 7]. As per study, published at the end of 2012 by WHO, one in every four couples in developing countries had been found to be affected by infertility.[8]

Woman infertility may also refer to the state of a woman who is unable to carry a pregnancy to full term. Couples with primary infertility have never been able to conceive. While, on the other hand, secondary infertility is difficulty conceiving after already having conceived (and either carried the pregnancy to term or had a miscarriage). Generally, worldwide it is estimated that 1 in 7 couples have problems conceiving, with the incidence similar in most countries independent of the level of the country's development.[9]

Causes of infertility

According to the American Society for Reproductive Medicine, Infertility affects men and women equally.[10] There are many causes of infertility and many times the cause of infertility goes unknown. Some of the most common causes of female infertility are age, polycystic ovaries, complications from being infected with sexually transmitted diseases, smoking, and being underweight or overweight.[11]

Polycystic ovary syndrome is a serious condition resulting in ovaries which cannot ovulate an oocyte. Polycystic ovaries are the main cause of infertility in women.[12] According to The Federal Government Source for Women's Health Information, women with PCOS, the ovary doesn't make all of the hormones it needs for an egg to fully mature. The follicles may start to grow and build up fluid but ovulation does not occur. Instead, some follicles may remain as cysts. For these reasons, ovulation does not occur.[12]

Polycystic ovarian Syndrome

History

The condition was first described in 1935 by American gynecologists Irving F. Stein, Sr. and Michael L. Leventhal, from whom its original name of Stein-Leventhal syndrome is taken.[13,14]

In the 1990s, to new aspects of PCOS became apparent. First, in many instances polycystic ovaries are inherited and this could be through either the mother or father. The polycystic ovary, therefore, can be considered part of an individual's genetic makeup and remains so for life. The symptoms of PCOS however, may changes at different times of life.[15] Polycystic ovaries were later found to exist in some women with subtle endocrine disorders. The wide range and frequency of symptoms made it difficult to establish a consistent clinical picture.[16]

Polycystic ovary syndrome (PCOS) also called hyper-androgenic anovulation (HA)[1] or Stein-Leventhal syndrome.[2] Women with PCOS may have enlarged ovaries that contain small collections of fluid – called follicles- located in each ovary as seen during an ultrasound examination. It is thought to be one of the leading causes of female sub-fertility[17, 18 &19] and the most frequent endocrine problem in women of reproductive age.[20]

Epidemiology

PCOS is the most common cause of anovulatory infertility. Approximately 90 - 95% of anovulatory women presenting to infertility clinics have PCOS.[21] In addition, spontaneous abortion occurs more frequently in PCOS with incidences ranging from 42%–73%.[21,22] Its prevalence depends in part upon the diagnostic criteria used to define the disorder.[23] As an example, in a report of 827 women with World Health Organization class II Oligoovulation (euestrogenic normogonadotropic ovulatory dysfunction), 456 (55 %) were classified as having PCOS by the National Institutes of Health (NIH) 1990 criteria. In contrast, 754 (91 %) women were considered to have PCOS using the Rotterdam 2003 criteria.[24] One study in U.K concluded that the risk of PCOS development was higher in lesbian women than in heterosexuals.[25]

Criteria for confirmation of PCOS

Two definitions are commonly used

1) According to National Institute of Health (NIH)[20]

In 1990 a consensus workshop sponsored by the NIH/NICHD suggested that a person has PCOS if she has all the following

- Oligoovulation,
- Signs of androgen excess (clinical or biochemical),
- Exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism.

2) According to Rotterdam[20]

In 2003 a consensus workshop sponsored by European Society of Human Reproduction and Endocrinology (ESHRE)/American Society of Reproductive Medicine (ASRM) broadened in Rotterdam indicated PCOS to be present if any 2 out of 3 criteria are met.

- Oligoovulation &/or anovulation.
- Excess androgen activity.
- Polycystic ovaries (by gynaecologic ultrasound).

In 2006, the Androgen Excess PCOS Society suggested a tightening of the diagnostic criteria to all of.[20]

- Excess androgen activity.
- Oligoovulation/anovulation &/or polycystic ovaries.
- Exclusion of other entities that would cause excess androgen activity.

On average the normal ovary contains five follicles and is about the size of a walnut.[26] In PCOS, ovary is enlarged >9ml in volume, is smooth, sclerotic, has thickened capsular and sub-capsular follicular cysts with Artesia and hyperplastic theca and stoma.[27] Polycystic ovary contains 2-3 folds the normal number of follicles.[27] The polycystic ovary is usually the size of a hen's egg but occasionally they may be the size of an orange. The increased size of the polycystic ovary is mainly due to an increased amount of stroma and not, as may be expected, because of the extra follicles or cysts. Usually, the follicles are too small to contribute much to the ovary size.[26]

PCOS is associated with various endocrine abnormalities such as increase serum LH relative to FSH release, have long been appreciated in PCOS. Because of the pulsatile nature of their release, a single test fails to detect an increase ratio of LH: FSH and increase serum testosterone. LH is sufficient to cause anovulation. Estimation of these hormones aids in the diagnosis.[28,29]

Antral follicle count (AFC) is another measure (transvaginal ultrasonography is used to count the number of antral follicles visible in each ovary) - a low AFC indicates poor ovarian reserve. Anti Müllerian Hormone (AMH) is a newer blood test for quantifying ovarian reserve and it tends to correspond to AFC. The blood test for AMH can be carried out on any day of the cycle (FSH must be measured on cycle day 3). Repeated clinical studies have demonstrated that serum AMH levels correlate strongly to antral follicle count and are more accurate than other conventional serum markers (FSH, E2, inhibin B) in predicting preovulatory oocyte supply in response to ovulation induction.[30-35]

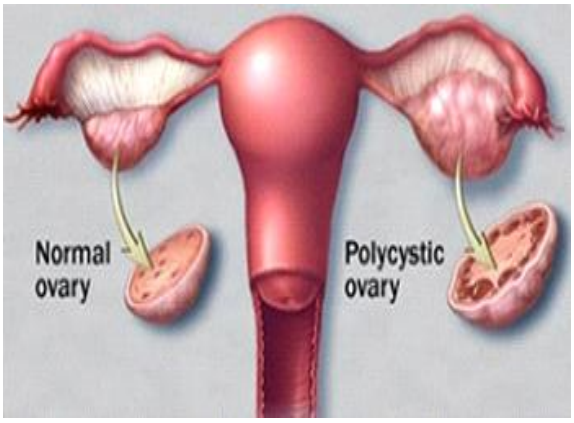

Fig. 1: Normal ovary Vs polycystic ovary

Causes of PCOS

PCOS is a complex, heterogeneous disorder of uncertain aetiology.[36,37] However there is strong evidence that it is largely a genetic disease.[3,4&5] Recent studies indicate that other factors like lifestyle and environmental factors can also be involved.[5]

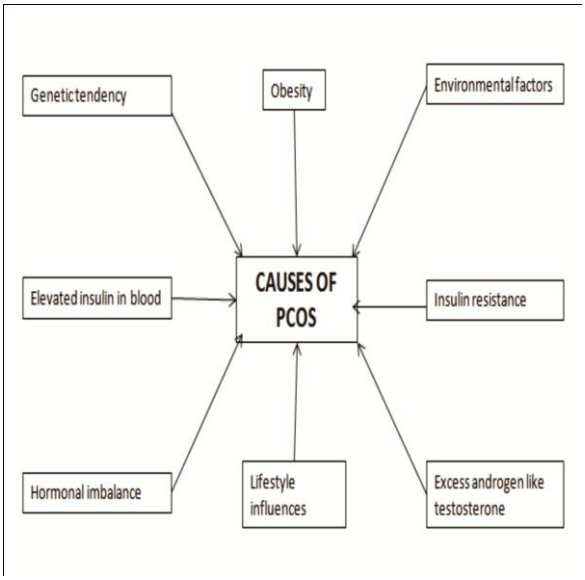

Fig. 2: The major causes of PCOS

There is also the important observation that surgical removal of a portion of the ovary, known as wedge resection, restores menses and fertility in many PCOS patients. For this reason, it has been suggested that the ovary is the origin of the abnormality [38]. Fig 2 shows the major causes of PCOS, whereas Fig 3 exhibits the suggested route of pathophysiology for PCOS. Women with PCOS have altered hormones and metabolism. 40% - 70% of women with PCOS have insulin (Lean and Obese patient) resistance. High insulin levels lead to increase androgen production and anovulation. Decreased insulin sensitivity may be due to deficiency of Glut-4, post-receptor defect in autophosphorylation of tyrosine residues on the insulin receptors.[39] Heredity, excess insulin and low grade inflammation are also suggested to be associated with PCOS.[40]

Pathogenesis

Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of male hormones (androgens), particularly testosterone by either release of excessive luteinizing hormone (LH) by the anterior pituitary gland or through high levels of insulin in the blood (hyperinsulinaemia) in women whose ovaries are sensitive to this stimulus.[41,42] Along with that reduced levels of sex-hormone binding globulin can result in increased free androgens.

Pre- antral and small antral follicles produce AMH six times the density of pre-antral follicles compared with the normal ovary in PCOS.[43] High AMH levels in PCOS also due to increased production by individual follicles.[44]

Possible role of AMH in the pathophysiology of PCOS is through its counteraction on FSH in promoting follicular growth.[45] The size of the 2-5 mm follicle pool is an independent and important contributor to the follicular arrest of PCOS.[46]

A majority of patients with PCOS have insulin resistance and/or are obese. Their elevated insulin levels contribute to cause the abnormalities seen in the hypothalamic-pituitary-ovarian axis that lead to PCOS. Hyperinsulinemia increase GnRH pulse frequency, LH over FSH dominance, increased ovarian androgen production[42], decrease follicular maturation, and insulin resistance is a common finding among patients of normal weight as well as overweight patients.[37,47]

In many cases PCOS is characterised by a complex positive feedback loop of insulin resistance and Hyperandrogenism. In most cases it cannot be determined which of those two should be regarded causative. Experimental treatment with either antiandrogens or insulin sensitizing agents improves both hyperandrogenism and insulin resistance.

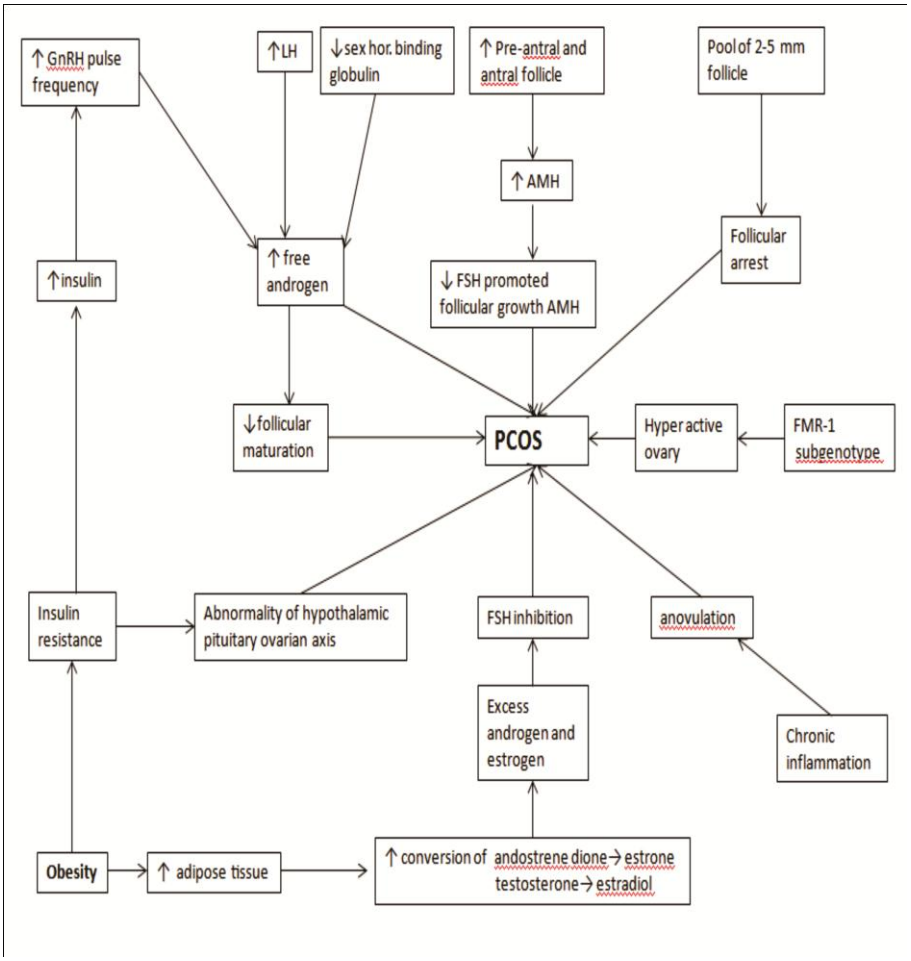

Fig. 3: The suggested route of pathophysiology for PCOS

Adipose tissue possesses aromatase, an enzyme that converts androstenedione to estrone and testosterone to estradiol. The excess of adipose tissue in obese patients creates the paradox of having both excess androgens and estrogens (which inhibits FSH via negative feedback).[48]

PCOS may be associated with chronic inflammation[42,49], with several investigators correlating inflammatory mediators with anovulation and other PCOS symptoms.[50,51]

PCOS has also been associated with a specific FMR-1(fragile X mental retardation 1) sub-genotype. The research suggests that women who have heterozygous-normal/low FMR-1 have polycystic-like symptoms of excessive follicle-activity and hyperactive ovarian function.[52]

Signs and symptoms

PCOS is a heterogeneous collection of signs and symptoms with varying degree of mildness and severity in affecting the reproductive, endocrine and metabolic functions.[54] The most common immediate symptoms are anovulation, excess androgen hormones, and insulin resistance.

Anovulation results in irregular menstruation, amenorrhea, and ovulation- related infertility. Hormone imbalance generally causes acne and hirsuitism. Insulin resistance is associated with obesity, Type 2 Diabetes, and high cholesterol level.

The symptoms and severity of the syndrome vary greatly among affected women. Common symptoms of PCOS include the following.

Menstrual disorder

PCOS mostly produce oligomenorrhea (few menstrual periods) or amenorrhea (no menstrual period), but other types of menstrual disorders may also occurs like menstrual intervals longer than 35 days; fewer than 8 menstrual cycle a year; failure to menstruate for 4 months or longer; & prolonged periods that may be scant or heavy.[20,40]

Infertility

This generally results directly from chronic anovulation (lack of ovulation).[20] PCOS causes more than 75% of cases of anovulatory infertility.[20,40]

High levels of masculinizing hormone

The most common signs are acne & hirsuitism (male pattern of hair growth), but it may produce hypermenorrhea (heavy & prolonged menstrual periods), androgenic alopecia (increase hair thinning or diffuse hair loss), or other symptoms [20, 55]. Approximately three- quarters of people with PCOS (by the diagnostic criteria of NIH/NICHD 1990) have evidence of hyperandrogenemia.[56]

Metabolic syndrome

This appears as a tendency towards central obesity & other symptoms associated with insulin resistance.[20,40] Serum insulin, insulin resistance, & homocystein levels are higher in women with PCOS.[57]

When Asian women are affected with PCOS, they are less likely to develop hirsuitism than women of other ethnic background.[58]

Hair growth and skin changes

Hair growth on the face and body and the making of grease on the skin is driven by the male hormone, testosterone. Under the influence of testosterone the hair follicle produces thicker, pigmented terminal hair at a faster rate causing hirsuitism. On the scalp however, testosterone switches hair growth off, so scalp hair thinning, or alopecia, can accompany unwanted hair growth on the body in women with PCOS. The sebaceous glands of the skin produce more sebum or skin grease in response to testosterone. One result of an excess of sebum, is that skin pores become blocked causing acne. 85% of women troubled by acne after the age of 20 have PCOS.[26] Skin changes, such as dark or thick skin markings and creases around the armpits, groin, neck, and breasts are common.

Miscarriage

Women with PCOS who also have a raised LH measurement are at an increased risk of miscarriage.[26]

The development of male characteristics is not a typical of PCOS and may indicate another problem. These changes may include thinning of hair on the head at the temples, called male pattern baldness, enlargement of the clitoris, deepening of the voice, and decrease in breast size.

PCOS and associated complications

Having polycystic ovary syndrome may make a series of conditions more likely, like Type 2 diabetes, high blood pressure, Cholesterol and lipid abnormalities, metabolic syndrome, non-alcoholic steatohepatitis, infertility, sleep apnea, depression and anxiety, abnormal uterine bleeding, cancer of uterine lining, gestational diabetes or pregnancy- induced high blood pressure especially if obesity also is a factor.[40]

Untreated polycystic ovary syndrome may be regarded as a disorder that progresses until the time of menopause. On-going studies lend support to the hypothesis that women with the syndrome are at increased risk for the development of cardiovascular disease.[59] Because the syndrome is also associated with lipid abnormalities, affected women could benefit from measures to prevent cardiovascular disease and the other sequel of longstanding hypertension and diabetes mellitus that are associated with the syndrome.

More important, the long-term effects of unopposed estrogen place women with the syndrome at considerable risk for endometrial cancer, endometrial hyperplasia and, perhaps, breast cancer.[60,61] The risk of endometrial cancer is three times higher in women with polycystic ovary syndrome than in normal women. In addition, small observational studies have suggested that chronic anovulation during the reproductive years is associated with a three to four times increased risk of breast cancer in the postmenopausal years.

Although no evidence shows that outcomes are improved, mammography and endometrial sampling to search for underlying estrogen-stimulated cancer should be considered in high-risk women with dysfunctional uterine bleeding.[62]

Early diagnoses and treatment can avoid or ease up the possible complication.

A recent study found that a questionnaire addressing the history of menstrual pattern, obesity and hirsutism can diagnose PCOS, according to a clinical prediction rule, with a sensitivity of 77.1% and specificity of 93.8%[63]

Diagnosis of PCOS

Presently practiced three ways to diagnose PCOS are based on.

- Symptoms and physical findings.
- Ultrasound testing.
- Hormonal testing.

Probably most individuals will have abnormalities in all three, some only in two, and possibly only in one. Some may argue that findings in only a single category may not constitute PCOS. The most minor of apparent problems may have significant implications for future general health and well-being.

Symptoms and physical findings

As we discussed in previous portion major sign & symptoms of PCOS includes:- oligomenorrhea/amenorrhea, high levels of masculinizing hormones (acne & hirsuitism), hair growth on face and chin, enlargement of the clitoris, deepening of the voice, decrease in breast size.

Ultrasound test

Sonography of the pelvis is warranted in virtually every potential PCOS patient. Evaluation should be performed by individuals experienced in judging ovarian and endometrial function. The finding of greater than ten (some say eight) cystic structures less than 10 mm in either ovary meets the generally established ultrasound criteria of PCOS. Often cysts of PCOS are located in a peripheral sub cortical ring leading to the reference of a "string of pearls."

Ultrasound is the imaging modality of choice and generally done on day 2-7.

The significant points to be observed in ultrasound test of PCOS patients are as follows:

1. Increase the volume of ovary
2. Polycystic ovaries are enlarged and rounder than normal with increased stromal echogenicity
3. There are numerous small cysts, less than 5mm, that line up on the periphery, in a “string-of-pearls” appearance
4. Ultra- sonographic criteria for establishing the diagnosis of PCOS are 10 or more cysts that are 2-8 mm in diameter and are peripherally arranged around an echo dense stroma.[64]

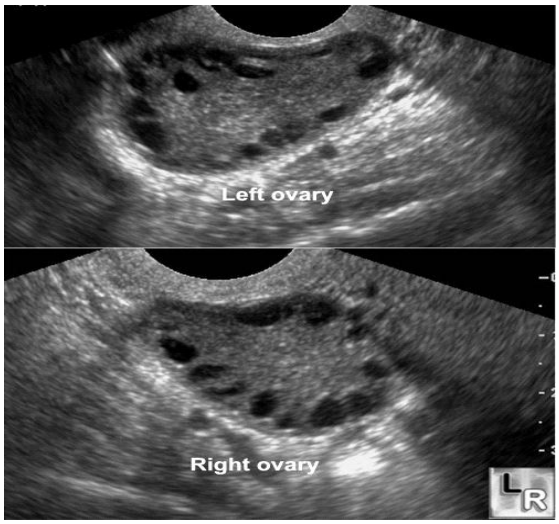

Fig. 4: Polycystic Ovarian Syndrome (Stein-Leventhal Ovaries)[64]

Hormonal assay

Major hormonal studies include estimation of AMH, FSH, and LH in serum.

Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)

FSH and LH are gonadotropins, hormones made in and released from pituitary gland that control the function of gonads, testes and ovaries, The absolute level of each, as well as the LH:FSH ratio, can offer significant insight into the PCOS patient. The ratio of LH (luteinizing hormone) to FSH (follicle stimulating hormone), when measured in international units, is greater than 1:1[65], as tested on Day 3 of the menstrual cycle. A higher LH than FSH in the early part of the menstrual cycle is a hallmark of PCOS. Clearly increased LH is related to, if not diagnostic of, PCOS. Elevation in LH is very useful in diagnostic of PCOS. The measurement of FSH will also permit the diagnosis of an occult ovarian failure where the FSH levels are particularly elevated.[5]

Women with PCOS have higher GnRH, which in turn results in an increase in LH/FSH ratio.[53.]

Antimüllerian hormone

Antimüllerian hormone (AMH) also known as Müllerian Inhibiting Substance (MIS) is a new diagnostic marker of ovarian function. The level of ANTI-MÜLLERIAN HORMONE (AMH) is increased in PCOS, and may become part of its diagnostic criteria.[38,39]

AMH levels correlate well with the ovarian antral follicle count and were the only levels that decreased longitudinally over time compared with FSH, estradiol, and inhibin-B levels. With ovarian aging, the first change

is a decrease in AMH levels, followed by a decline in inhibin-B and finally by an increase in FSH levels.

AMH levels do not vary significantly during the menstrual cycle and can therefore be drawn on any day of the cycle.

Other hormones

Insulin levels should be obtained in fasting condition and possibly after a glucose challenge. Insulin resistance may be present in advance of or without, elevated glucose level.[5]

Prolactin levels may be elevated (hyperprolactinemia) and associated with breast secretion (galactorrhea). Hyperprolactinemia regardless of PCOS, is a relatively frequent cause of infertility and usually can be easily and successfully treated.[66] Mild hyperprolactinemia has been reported in 5% to 30% of patients with PCOS.[67,68] Prolactin is generally only 50% above the upper limit of normal.[69] Thus, it is now felt that PCOS and hyperprolactinemia are independent disorders.

Standard diagnostic assessments

History taking specifically for menstrual pattern, obesity, hirsuitism, and the absence of breast development help in diagnosis of PCOS. A clinical prediction rule found that these four questions can diagnose PCOS with a sensitivity of 77.1% and a specificity of 93.8%.[70]

Gynaecologic ultrasonography, specifically looking for small ovarian follicles. These are believed to be the result of disturbed ovarian function with failed ovulation, reflected by the infrequent or absent menstruation that is typical of the condition. In a normal menstrual cycle, one egg is released from a dominant follicle- in essence, a cyst that bursts to release the egg. After ovulation, the follicle remnant is transformed into a progesterone-producing corpus luteum, which shrinks and disappears after approximately 12-14 days. In PCOS, there is a so-called "follicular arrest"; i.e., several follicles develop to a size of 5-7 mm, but not further. No single follicle reaches the preovulatory size (16 mm or more). According to the Rotterdam criteria, 12 or more small follicles should be seen in an ovary on ultrasound examination **[71].** More recent research suggests that there should be at least 25 follicles in an ovary to designate it as having polycystic ovarian morphology (PCOM) in women aged 18-35 years **[30].** The follicles may be oriented in the periphery, giving the appearance of a 'string of pearls' [31]. If a high resolution transvaginal ultrasonography machine is not available, an ovarian volume of at least 10 ml is regarded as an acceptable definition of having polycystic ovarian morphology instead of follicle count.[30]

Laparoscopic examination may reveal a thickened, smooth, pearl-white outer surface of the ovary.

Serum (blood) levels of androgens (male hormones), including androstenedione and testosterone may be elevated.**[20]** Dehydroepiandrosterone sulfate levels above 700-800 µg/dl are highly suggestive of adrenal dysfunction because DHEA-S is made exclusively by the adrenal glands.[32,33] The free testosterone level is thought to be the best measure[33,34], with ~60% of PCOS patients demonstrating supranormal levels.[15] The free androgen index (FAI) of the ratio of testosterone to sex hormone-binding globulin(SHBG) is high[20,33] and is meant to be a predictor of free testosterone, but is poor parameter for this and is no better than testosterone alone as a marker for PCOS,[35] possibly because FAI is correlated with the degree of obesity.[36]

Some other blood tests are suggestive but not diagnostic. The ratio of LH (luteinizing hormone) to FSH (follicle – stimulating hormone), when measured in international units, is elevated in women with PCOS. Common cut-offs to designate abnormally high LH/FSH ratio are 2:1or 3:1as tested on day 3 of the menstrual cycle.[33, 37] The pattern is not very sensitive and ratio of 2:1 or higher was present in less than 50% of women with PCOS in one study.[37] There are often low levels of sex hormone-binding globulin in particular among obese or overweight women.[33]

Anti-müllerian hormone (AMH) is increased in PCOS, and may become part of its diagnostic criteria.[38,39] Along with AMH the associated conditions are to be evaluated by performing fasting biochemical screen and lipid profile, oral GTT, fasting insulin level determination.[20,33]

Anti-mullelian hormone

AMH is a glycoprotein growth factor and a member of the transforming growth factor super family (TGF-B) with a molecular weight of 140kDa. AMH also known as Müllerian Inhibiting Substance (MIS) is a new diagnostic marker of ovarian function. The existence of AMH was first proposed in 1947 by Professor Alfred Jost. This hormone is made in the testes of men. However now we know that in female neonates, AMH is virtually undetectable but increases gradually until puberty and remains relatively stable thereafter and throughout the reproductive period.[72]

Source

AMH is secreted by Sertoli cells of the testes during embryogenesis of the foetal male.

In female, Anti-Müllerian hormone (AMH) is produced by the granulosa cells of the recruited follicles until they become sensitive to FSH. AMH has been identified as a regulator of the recruitment, preventing the depletion of all primordial follicle pool at once. It is primarily produced by the pool of early-growing follicles, which are believed to serve as a proxy for the number of primordial follicles in the ovary. It is widely accepted that the reduction of AMH levels in serum is the first

indication of a decline in the follicular reserve of the ovaries. AMH concentration remains stable throughout the menstrual cycle.[73]

The role of AMH in assessing ovarian aging and ovarian reserve

AMH levels decrease over time even in "fertile" women who have regular menstrual cycles. Its levels correlate well with the ovarian antral follicle count and were the only levels that decreased longitudinally over time compared with FSH, estradiol, and inhibin-B levels.[74]

With ovarian aging, the first change is a decrease in AMH levels, followed by a decline in inhibin-B and finally by an increase in FSH levels [75]. AMH levels do not vary significantly during the menstrual cycle and can therefore be drawn on any day of the cycle. This offers a great advantage of AMH over FSH and LH study to diagnose PCOS. Women who are overweight have 65% lower AMH levels than thin women, indicating that obesity may be associated with decreased ovarian reserve and/or with ovarian dysfunction.[76]

Table: 1 Factors that influence AMH levels[54]

FACTORS THAT DECREASE MIS/AMH	FACTORS THAT DONOT INFLUENCE MIS/AMH	FACTORS THAT INCREASE MIS/AMH
1) Increasing Age	1) GnRH	1) PCOS
2) Obesity	2) Day Of Menstrual Cycle	2) Increase In Number Of Antral Follicles
3) Administration of Gonadotropin	3) Birth Control Pill	3) Anovulatory Cycles
4) Administration of Chemotherapy Or Radiation	4) Pregnancy	4) Hyperinsulinemia
5) Surgical Removal of One Or Both Ovaries		

AMH levels have been found to be two to three times higher in PCOS women, making it difficult to find a threshold value for poor ovarian reserve without a significant overlap with normal values.[78]

Anti-Müllerian hormone (AMH) has been suggested as a predictor of ovarian response to ovulation induction and controlled ovarian hyper stimulation. In human ovaries, AMH is produced by granulosa cells, with the highest expression being in small antral follicles, and continues to be expressed in the growing follicles until they have reached the size and differentiation state at which they are to be selected for dominance.[78]

Many recently published studies have confirmed elevated concentrations of AMH in the blood of women with polycystic ovary syndrome (PCOS).[79–81]

As is well known, PCOS is characterized by an increase in follicle number of small antral follicles. AMH controls folliculogenesis by reducing follicle sensitivity to FSH, and leads to anovulation when secreted in excess amounts in polycystic ovary syndrome. It has been proved, however, that follicle number only added 5.3% to variance in the concentration of AMH, and raised production of hormone is an intrinsic property of granulosa cells in PCOS **[80, 82 & 83].** Age-specific AMH levels have been found to be a better predictor of oocyte yield than FSH in women aged between 34 and 42 years.**[84]**

Women with amenorrhea caused by polycystic ovarian syndrome (PCOS) unusually have high levels of AMH, as it is produced by the large number of antral follicles that are a hallmark of the disease. In contrast, women with amenorrhea due to premature ovarian insufficiency have a low AMH. Those women with amenorrhea related to hyperprolactinaemia, or other disorders of the pituitary involving reduced gonadotropins production, often have normal circulating levels of AMH.[85]

AMH levels are the better reflectors of antral follicle count as compare to FSH and LH. In PCOS there is increase in number of follicles, therefore AMH is better indicative for diagnosis of PCOS. FSH and LH levels have drawback over AMH levels as their values vary with every cycle and day of menstrual cycle.

CONCLUSION

The prevalence of infertility is significantly high world-wide. Amongst the female infertility PCOS is an important cause and which must be correctly diagnosed for the effective treatment. Oocyte number and quality decline with age; however, fertility varies significantly even among women of the same age. Serum anti-Müllerian hormone (AMH), is one of the hormone biomarker of follicle number has become known in recent years.[86]

AMH being more stable during the entire menstrual periods could be used as a better marker over FSH and LH for diagnosis of polycystic ovary syndrome especially where the ultra sonographic examination of the ovaries is not feasible. AMH levels represent the most sensitive marker for the inevitable decline in the number of primordial follicles related to aging which is also an important cause of female infertility. A number of studies suggested great correlation of AMH levels with the ovarian follicle reserve and so its level help the clinician to predict the success of assisted reproductive techniques like IVF. Finally, the recently revealed relation between AMH and metabolic syndrome will be a future research target linking AMH with a series of biochemical analytes of carbohydrates, fats etc.

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