

LABORATORY DIAGNOSTIC LINK TO FEMALE INFERTILITY

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Abstract: Female infertility is caused by many factors including nutrition, diseases, malfunction of uterus and hormonal imbalances. Among the hormones LH, FSH, Prolactin plays a major role. The other additional contributing causes like obesity, diabetes have also been discussed in this paper. rhFSH is now emerging as regimen for induction of ovulation and Hu-FSH is found to be an effective form of treatment for women with PCOS. Hyperprolactinemia is a common endocrine cause of infertility in women. Increased TSH and PRL and decreased T3 and T4 also are observed in infertile group. In laboratory diagnosis the levels of circulating LH, FSH, PRL, oestrogen, Progesterone, testosterone and thyroid profile are to be evaluated to assess the role of endocrine glands in infertility. PRL, T3, T4 and TSH are the recommended first line hormones done to evaluate infertility in women. This review articles presents research findings during the last 15 years linking reproductive hormones to female infertility depicting the role of each hormone as well as some syndromes associated with females such as PCOS, hirsutism and cancer of breast.

Keywords: Infertility, LH, FSH, PRL, PCOS.

1. INTRODUCTION

Human Infertility is a complex global health problem. It has multiple social consequences in any family life. Both male and female factors are involved in the prevalence of infertility among married couple of reproductive age. According to world Health Organization, one in every four couples in developing countries are found to be affected by infertility. The main cause cited for female infertility include damage to hormonal, fallopian tubes, cervical, uterine and certain unexplained types. Studies done in the past have focused on various factors including hormonal imbalances. This review article brings out recent concept linked to reproductive hormones as causative factors and suggesting some treatment modalities based on circulating reproductive hormone associated in female infertility.

Role of LH:

LH secretion in response to a physiologic bolus of GnRH were not significantly different in unexplained infertility patients at any phase of the cycle. LH pulse frequency and amplitude, as well as response to GnRH varied significantly across the cycle. Mean early follicular serum LH and FSH concentrations were significantly higher in unexplained infertility patients than in fertile control subjects. Metformin does indeed modulate the basal level of LH and the LH/FSH ratio, albeit indirectly, particularly in patients with Polycystic Ovarian Syndrome (PCOS). Some studies suggest that metformin does directly regulate FSH gene expression (Oride et al, 2010). Response to a physiologic dose of Gonadotropin –Releasing Hormone (GnRH) in the early follicular, late follicular, mid-luteal, and late luteal serum LH pulse frequency and pulse amplitude and LH in synergy with FSH stimulates normal follicular growth and ovulation. FSH is frequently used in Assisted Reproductive Technology (ART). Recent studies have facilitated better understanding on the complementary role of the LH to FSH in regulation of the follicle; however, role of LH in stimulation of follicle, optimal dosage of LH in stimulation and its importance in advanced aged patients has been a topic of discussion among medical fraternity (Gottumukkala et al, 2013)

Role of FSH:

Recombinant human FSH (rhFSH) demonstrates higher purity and specific activity, and is suitable for subcutaneous administration. Additionally, rhFSH has facilitated the development of additional FSH product such as FSH-carboxy terminal peptide that possess different pharmacokinetic and pharmacodynamic properties and may provide more options in the treatment of ovulatory dysfunction and infertility (Pang et al, 2005). Normogonadotropic anovulatory infertile patients have a different FSH receptor genotype than do normo-ovulatory controls. Although this characteristic is associated with increased baseline FSH serum levels, altered ovarian sensitivity to exogenous FSH during ovulation induction could not be established (Laven et al, 2003).

Women with normal ovarian reserve and the Serine/Serine FSH receptor variant had significantly higher FSH levels compared to women with Asparagine/Asparagine and Asparagine/Serine variants. FSH receptor genotyping may, thus, be interesting as an adjunct indicator of ovarian reserve for infertile women undergoing assisted reproduction, and may be helpful in the determination of the starting dosage of FSH in vitro fertilization (Falconer et al, 2005)

For infertile women above 35 years of age, Trans Vaginal Ultrasound (TVU) rather than hormonal parameters be preferred, based on some data showing a stronger association between age and TVU indices of ovarian reserve than between age and increase in basal FSH level. Thus, TVU assessment of ovarian volume and antral follicle counts is a practical and cost-effective, if not better, technique for ovarian reserve testing (Erdem et al, 2003). There was a significant inverse correlation between serum Anti Mullerian Hormone (AMH) and FSH levels in infertile women suggesting that AMH, a better predictor of ovarian reserve was found to be relatively stable throughout the cycle. Furthermore, a positive correlation between AMH and Anti Follicle Count (AFC), denotes a reduction of AMH levels in serum is the first indication of a decline in the follicular reserve (Jyoti Bala et al, 2014).

Role of Prolactin:

Infertile women with both hypothyroidism and hyperprolactinemia also responded to treatment and their PRL levels returned to normal. Measurement of Thyroid Stimulating Hormone (TSH) and PRL should be done at an early stage of infertility check up rather than straight away going for more costly tests or invasive procedures. Simple, oral hypothyroidism treatment for 3 months to 1 year can be of great benefit for conception in otherwise asymptomatic infertile women (Indu Verma et al, 2012)

Female infertility should be assessed by finding out the degree of association of thyroid hormones with hyperprolactinemia. A significantly higher mean serum PRL and TSH were observed among the infertile groups compared to the fertile controls. The mean serum T3 and T4 were significantly lower in the hyperprolactinemic infertile women compared to the fertile controls. Hyperprolactinemia with thyroid dysfunction may be a major contributory hormonal factor among infertile women and as such, estimation of PRL, T3, T4 and TSH should be included in the workup for infertile women especially those with hyperprolactinaemia (Iya Eze Bassey et al, 2015) There is a higher incidence of hyperprolactinaemia in infertile patients. There is also a greater propensity for thyroid disorders in infertile women than in the fertile ones. The incidence of hypothyroidism in the hyperprolactinaemic subjects in the study population was found to be highly significant than the normal controls (Sunita Turankar et al, 2013).

There was a significant association between abnormal menstrual patterns and anovulatory cycles, as observed on endometrial examination of infertile subjects with raised serum PRL levels. There is a greater propensity for thyroid disorder in infertile women than the fertile ones. There is also a higher prevalence of hyperprolactinemia in infertile patients (Binita Goswami et al, 2009)

2. INFERTILITY & PCOS

Women with PCOS are potentially at an increased risk of miscarriage in pregnancy as they are at an increased risk of developing Gestational Diabetes Mellitus (GDM), pregnancy-induced hypertension and pre-eclampsia. Furthermore, the neonate has a significantly higher risk of admission to a neonatal intensive care unit and a higher perinatal mortality (Hart et al, 2008) The recommended first-line treatment for ovulation induction remains the anti-estrogen Clomiphene Citrate (CC). Recommended second-line intervention, should CC fail to result in pregnancy, is either exogenous gonadotrophins or laparoscopic ovarian surgery (LOS). Based on recent data available in the literature, the routine use of this drug in ovulation induction is not recommended. Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction. Even singleton pregnancies in PCOS are associated with increased health risk for both the mother and the fetus (Tarlatis et al, 2008).

If pregnancy still eludes women with PCOS after initial pharmacologic treatments, gonadotropin therapy by itself or in conjunction with assisted reproductive therapy should be considered. These treatments come with higher expense, and increased risk, and require extensive counseling prior to implementation. Additional research is needed to better understand what risks exist for pregnant women with PCOS and for their newborns (McFarland et al, 2012). Women with PCOS undergoing *in vitro* fertilisation should be offered metformin to reduce their risk of ovarian hyperstimulation syndrome. Limited evidence suggests that metformin may be a suitable alternative to the oral contraceptive pill for treating hyperandrogenic symptoms of PCOS including hirsutism and acne. More research is required to define whether metformin has a role in improving long term health outcomes for women with PCOS, including the prevention of diabetes, cardiovascular disease and endometrial cancer (Neil P. Johnson et al 2014). Spironolactone and finasteride are used to treat symptoms of androgen excess. Treatment options for infertility include clomiphene, laparoscopic ovarian drilling, gonadotropins, and assisted reproductive technology. Recent data suggest that letrozole and metformin may play an important role in ovulation induction. Proper diagnosis and management of PCOS is essential to address patient concerns but also to prevent future metabolic, endocrine, psychiatric, and cardiovascular complications. (Susan M Sirmans et al, 2014).

Reduction of Insulin Resistance (IR) was proved to ameliorate ovulation rate in PCOS patients, but strong evidences to sustain the utility of insulin-sensitizing drugs as a therapeutic option for infertility are lacking. Future studies are needed to elucidate these aspects and to characterize the particular subtype of patients with higher probability to respond to this treatment (Susan M Sirmans et al, 2014). Chronic anovulation over a long period of time is also associated with an increased risk of endometrial hyperplasia and carcinoma, which should be seriously investigated and treated. There are androgenic symptoms that will vary from patient to patient, such as hirsutism, acne, and/or alopecia. These are troublesome presentations to the patients and require adequate treatment. Alternative medicine has been emerging as one of the commonly practiced medicines for different health problems, including PCOS (Ahmed Badawy et al, 2008).

Metformin should be considered as first-line therapy because it has the advantage to allow for normal single ovulation, for reduced early pregnancy loss, and, most importantly, lifestyle modifications and weight loss before pregnancy. Losing weight not only improves fertility but also reduces adverse pregnancy outcomes associated with obesity (Brassard M et al 2008). Laparoscopic ovarian drilling is proving equally as successful as FSH for the induction of ovulation, particularly in thin patients with high LH concentrations and it has no Ovarian Hyperstimulation syndrome (OHSS) complication. Aromatase inhibitors are presently being examined and may replace clomiphene in the future. When all else has failed, In Vitro Fertilization Pre-embryo Transfer (IVF/ET) produces excellent results. There are very few women suffering from anovulatory infertility associated with PCOS who cannot be successfully treated today (R Homburg et al, 2003).

Role of Sex Hormones:

The greater circulating levels of testosterone in obese women and smokers suggest that testosterone concentrations should be considered in the natural history of disease conditions where obesity and smoking are risk factors, including cardiovascular disease (MF Sowers et al, 2001).

Hirsutism:

Many women with PCOS experience infertility and hirsutism and often seek treatment for both concurrently. The change in hirsutism was not associated with the duration of treatment or with the presence or absence of ovulation. In infertile hirsute women with PCOS, treatment with clomiphene citrate, metformin, or both for up to six cycles does not alter hirsutism (Roth et al, 2012). Women are prone to over estimate the increased hair growth. The significantly higher levels of testosterone and dehydroepiandrosterone sulfate, higher values of free androgen index and lower levels of sex hormone binding globulin were found in females with hirsutism. Females with hirsutism complained more frequently of infertility, increased greasiness of skin, had higher body mass index, systolic and diastolic blood pressure, larger waist and hip circumference and higher waist/hip ratio (Kozloviene et al, 2005) Gynaecologists/Endocrinologists should investigate their clients for PCOS and offer appropriate treatment (Pembe AB et al, 2009).

Role of Diabetes Mellitus:

During the reproductive years, diabetes has been associated with menstrual abnormalities, such as oligomenorrhea and secondary amenorrhea. It was found that better glycemic control and prevention of diabetic complications improves these irregularities and increases fertility rates close to those that are seen in the general population. Women with persistent menstrual abnormalities despite adequate treatment need to be approached by broader evaluation, which will include the

examination of the hypothalamic-pituitary-ovarian axis and the hormonal status, presence of autoimmune thyroid disease and antiovarian autoantibodies, and hyperandrogenism (Livshits et al,2009). Women who had one or more miscarriage showed the same risk for T2 DM as women who had no miscarriage. Also, none of the other measures of low fertility were associated with increased risk for T2DM. Generally, measures of low fertility were not independently associated with a risk of T2DM in a cohort of 17 357 Dutch women (Elbers et al, 2011). It has been suggested that the GnRH pulse-generator in the hypothalamus is responsible for diabetic menstrual dysfunction. The risk of fertility and gestational problems is higher in T1DM than in the general population, but fertility in diabetic women seems to be similar to nondiabetics (Zarzycki et al, 2005).

The insulin/insulin-like growth factor (IGF) pathways and glucose metabolism act as mediators of human ovarian function and female fertility. Insulin signaling affects reproductive function and dysregulation of this pathway leads to altered puberty, ovulation and fertility. Better understanding of the normal physiology and pathophysiology of insulin, IGF, and glucose effects on human reproductive system will allow for better outcomes (Nandi et al, 2013) The stricter metabolic control exercised in the past 20 years may have helped prevent subfertility. However, although the risk of congenital malformations has decreased, it is still higher than that for the general population (Jonasson et al,2007) Pregnant Iranian women with a history of infertility and PCOS are at increased risk for developing Gestational Diabetes Mellitus (GDM). It is recommended to perform screening test for GDM in PCOS women with ART treatment, irregular menses and high serum triglycerides level in the early stage of pregnancy. Pre gestational use of metformin can be effective in reducing the occurrence of GDM (Ashrafi et al, 2014).

Role of Breast Cancer:

The combination of infertility and fertility treatment might cause harm, such as an increased risk for breast cancer Therefore, one has to consider carefully, together with the woman, the need for fertility treatment and give the lowest possible dosage for the shortest duration in order to minimize the risk (Riskin-Mashia et al, 2013) Women with non ovulatory causes treated with high-dose CC therapy may have an elevated risk for breast cancer (Orgeas CC et al, 2000). Still, there is an uncertainty regarding recommended intervals from diagnosis to conception. Preimplantation genetic diagnosis for hereditary breast cancer mutations is also becoming of increasing interest. The fertility impact of breast cancer treatment in young women is of on going concern. The effects should be universally addressed and options should be outlined with young women prior to commencement of treatment (Ronn et al,2015). Conflicting results were reported regarding the type of fertility treatment and breast cancer risk. Overall, there is no clear evidence that ovulation induction or IVF increases the risk of breast cancer. However, there may be a transient increase in the incidence of breast cancer in the first year due to earlier diagnosis. Furthermore, the risk may be increased in women with a positive family history. Future research should focus on the type of fertility treatment used and breast cancer risk. Aromatase inhibitors should be evaluated further as an alternative to standard ovulation-inducing drugs (Salhab et al, 2005).

Patients with primary infertility might represent a group at high risk for breast cancer, particularly if infertility is due to an ovulatory factor, suggesting that breast screening from the age of 35 in infertile patients who undergo treatment with fertility drugs in accordance with National Federation for Breast Cancer (FONCAM) recommendations. This might allow the identification of higher risk patients who need more closely monitored breast examinations (Meggiorini et al, 2012). Fertility preservation is an important issue for young women diagnosed with breast cancer. The most well-established options for fertility preservation in cancer patients, embryo and oocyte cryopreservation, have not been traditionally offered to breast cancer patients as E2 rise during standard stimulation protocols may not be safe for those patients. Potentially safer stimulation protocols using tamoxifen and aromatase inhibitors induce lower levels of estradiol while similar results in terms of number of oocyte and embryo obtained to standard protocols. Cryopreservation of immature oocytes and ovarian cortical tissue, both still experimental methods, are also fertility preservation options for breast cancer patients (Kenny et al, 2010).

The optimal time to address the possibility of treatment-related infertility and strategies to combat this with younger patients is prior to treatment, rather than after cancer therapy has begun, and a full knowledge of the available technologies is a prerequisite for an informed discussion. Causes of ovarian suppression and options for treatment, including consideration of pre implantation genetic diagnosis and alternative parenting approaches are also important to assist the clinician caring for young patients with cancer (Hulvat et al, 2009). When and if a breast cancer patient does not have time to undergo ovarian stimulation prior to chemotherapy, ovarian cryopreservation for future autotransplantation can be offered as the last resort. The benefit of ovarian protection by gonadotropin-releasing hormone analogues is unproven and unlikely, and thus this treatment should not be offered as the sole method of fertility preservation (Sonmezer et al, 2006).

3. CONCLUSION

This review article has extensively highlighted the pros and cons of the role of hormones and its synthetic derivatives for the diagnosis and treatment of infertility in women. The laboratory diagnosis based on the measurement of LH, FSH and Prolactin has been highlighted in details. Other factors such as PCOS, hirsutism and DM also play some part in the alteration of ovulation. Further thyroid hormone measurement and treatment to bring back hypothalamus pituitary function back to normal is also implicated to solve infertility problem. Routine investigation such as thyroid and reproductive hormone profile will aid gynaecologists to decide the appropriate treatment modalities. More clinical oriented research is required to set up a definite laboratory based diagnostic approach to treat infertility among women.

Conflict of Interest: None

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