بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سلوي محمود عقل

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinological disorder seen in 6%–10% of women ***(Norman et al., 2007).*** It is characterized by polycystic ovaries, anovulatory cycles, and hyperandrogenism.

In nearly 20% of infertile women, PCOS is said to be the key reason behind infertility ***(Norman et al., 2007).***

PCOS is a syndrome that manifests variably from adolescence as oligomenorrhea or hirsutism or obesity and goes on to affect the reproductive performance of the female by causing anovulation. Some may even be severely affected by metabolic syndrome, diabetes mellitus, or endometrial carcinoma. It also increases the risk of ovarian and breast carcinoma ***(Atiomo et al., 2003).***

PCOS falls in WHO type II anovulation (norm-gonadotropic norm-estrogenic anovulation) and is seen in 85% of anovulatory females. Although lifestyle modification is known to improve reproductive outcomes in females with PCOS, the gold standard treatment for norm-gonadotropic oligo/amenorrheic infertility (WHO Group II) was clomiphene citrate (CC) ***(Radosh L., 2009)*** until 2018, when

ESHRE and ASRM have declared letrozole as the first-line treatment for ovulation induction (OI)(***ESHRE 2018 guidelines***).

To conclude, available data shows that letrozole is at least as effective as CC for ovulation and has comparable live birth rates. Importantly, it has definite advantages over CC. Many studies have shown letrozole to be as effective as gonadotropins, with the added advantage of low cost and lower multiple pregnancy rates. However, the quality of medical evidence supporting aromatase inhibitors for OI is inadequate, small in sample size, and inappropriate in design. Moreover, there is very limited data on potential teratogenic effects, oocyte, embryo quality, and any effect on implantation. ***(Misso et al., 2012)***

Those who fail to respond to CC are labeled as clomiphene resistant. It is common in approximately 15%–40% of women with PCOS ***(NICE, 2014).*** Major factors postulated for CC resistance include obesity, insulin resistance, (seen in nearly 50%–70% of females with PCOS), and hyperandrogenemia ***(Parsanezhad et al., 2001)***. Moreover, genetic predisposition is suggested to play a role in CC resistance ***(Overbeek et al., 2009).*** However, still, the

current data available on the causes of CC resistance are not sufficient enough to direct our treatment.

It is seen in various studies ***(Sohrevardi et al., 2016)*** that the females who initially failed to respond to CC develop better ovulation and pregnancy outcomes on treatment with insulin-sensitizing agents. This indicates that insulin resistance may be a cause of CC resistance in females with PCOS. In fact, insulin-sensitizing agents ***(Azziz et al., 2009)*** decrease the dose of ovulation-inducing agents and time for follicular maturation in females with PCOS.

As of now, there have been no concrete studies to compare the metabolic profile of females who respond to CC and those who do not. It is still an enigma as to why some women respond to clomiphene, while others do not. By identifying the various factors which affect the response of CC in patients with infertility, a lot of time can be saved by giving alternate options of treatment to these patients. This study was done with the aim to analyze various clinical, metabolic, hormonal, and ultrasound parameters that might affect the response to clomiphene.

Aim of the Work

To analyze various clinical, metabolic, hormonal, and ultrasound parameters that might affect the response to clomiphene.

Research hypothesis:

Clinical, metabolic, hormonal, and ultrasound parameters do not affect the response of women to clomiphene citrate.

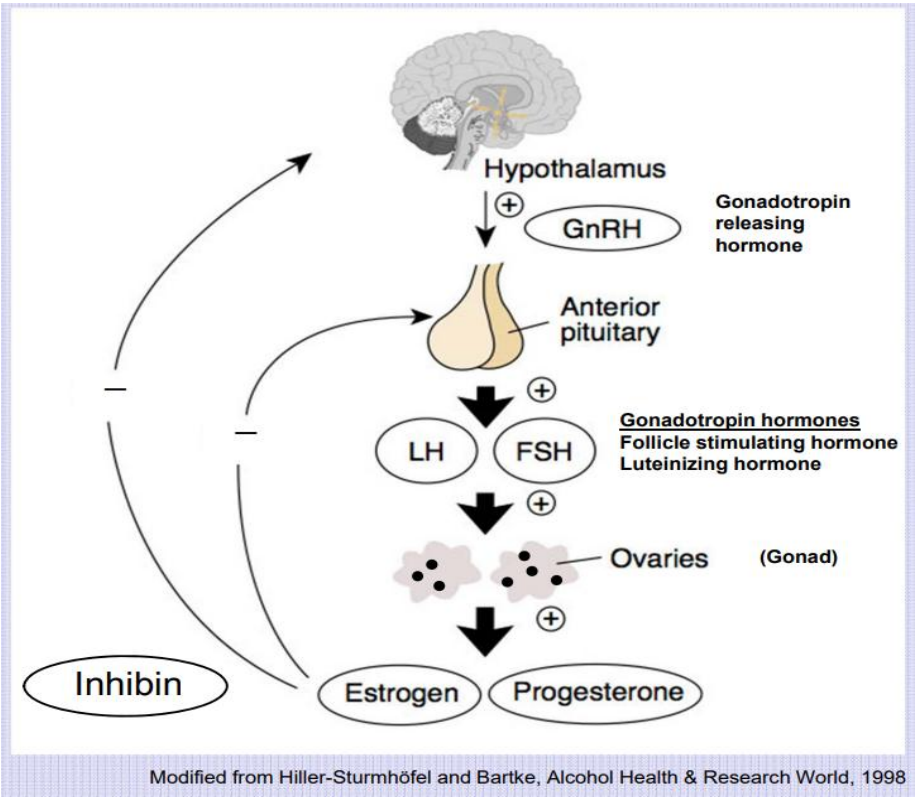
Research question:

Do clinical, metabolic, hormonal, and ultrasound parameters have an effect on the response of women to clomiphene citrate?

Polycystic Ovary Syndrome (PCOS)

PCOS is one of the most common conditions associated with chronic anovulation affecting 4–6% of reproductive-age women, although the prevalence has doubled given changes in diagnostic criteria. It is inaccurate to state that PCOS is the most common cause of anovulation. It is an association rather than a cause. Several mechanisms are recognized to contribute to the pathophysiology of anovulation in PCOS, operating at every level of the reproductive system. PCOS is a heterogeneous disorder that is best approached as a diagnosis of exclusion. When diagnosed, an approach to PCOS requires a systematic elimination of conditions that can masquerade as PCOS and thought-out management to address both overt symptoms and covert risks that are recognized as a sequel of this syndrome ***(Dumesic et al., 2015).***

I. Pathophysiology:



The hypothalamic-pituitary-gonadal (HPG) axis is primarily responsible for regulating reproductive activity and the release of ovarian hormones in animals and humans ***(Couse et al., 2003; Meethal and Atwood, 2005)***

The HPG axis is responsible for orchestrating the release of both centrally and peripherally produced ovarian hormones. Centrally produced regulatory hormones include gonadotropin-releasing hormone (GnRH) from the hypothalamus and gonadotropins from the pituitary,

specifically luteinizing hormone (LH) and follicle-stimulating hormone (FSH) ***(Meethal and Atwood, 2005***). Recently, researchers identified a central regulator of GnRH; kisspeptin was identified as a neuromodulator that modulates GnRH release and subsequently controls the activity of the gonadotropins and the HPG axis ***(Skorupskaite et al., 2014).***

The pituitary gonadotropins luteinizing hormone, and follicle-stimulating hormone regulate the ovarian production of sex steroids. According to the two-cell–two-gonadotropin theory, luteinizing hormone stimulates thecal cells to produce androgens, and follicle-stimulating hormone stimulates granulosa cells to produce estrogens from androgens. Follicle-stimulating hormone is thought to have little effect on the thecal-cell androgen production ***(N Engl J Med 2000).***

In contrast to the normal cycles, the endocrine milieu in chronic anovulatory women is a **"steady state"** in which gonadotropin and sex steroid concentration vary minimally, by comparison **(figure 1)**.

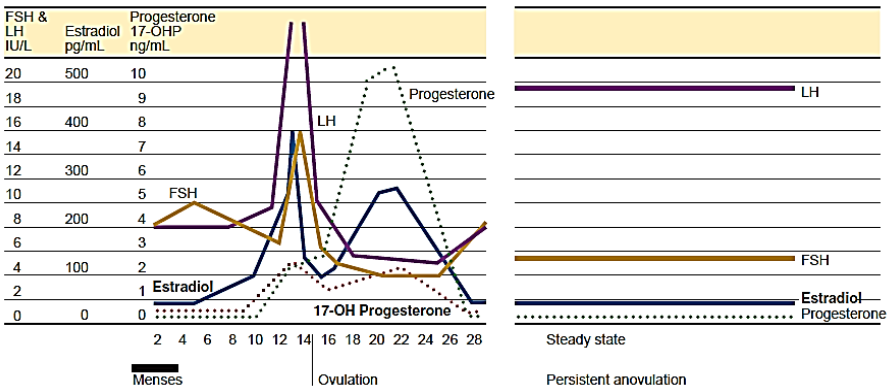


Figure (1): Cyclic pattern of hormone concentration in women with chronic anovulation ***(Sperrof and Fritz, 2020).***

Both androgen and estrogen's daily production is increased in women with PCO, which is reflected by the high level of serum of testosterone, androstenedione, dehydroepiandrostenedione (DHEA), dehydroepiandrostenedione sulfate (DHEA-S), 17α-hydroxyprogesterone (17-OHP), and estrone. A result of treatment with a long-acting GnRH agonist indicates that the increases in serum testosterone, androstenedione, and 17-OHP are derived from the ovary and are LH –dependent, whereas those in DHEA and DHEA-S derivate from the adrenal ***(Gonzalez et al .,1996).*** High levels of androstenedione are converted peripherally to a high level of estrone. In contrast, serum estradiol levels in women with PCOS fluctuate but generally remain within the range typically observed in the early follicular phase ***(Venturoli1 et al.,1988)***, reflecting continued low-level

production from limited follicular development***(Wajchenberg et al.,1988)***.

Unlike the cyclic fluctuations in the HPO hormone concentrations that occur during and are determinants of normal ovulatory menstrual cycles, an altered pattern of gonadotropin secretion, chronic hyperandrogenemia, and insulin resistance (usually, though not always, associated with obesity) all contribute, to varying degrees, to the ovarian dysfunction of PCOS ***(Dumesic et al.,2015).***

An altered pattern of GnRH release that leads to an increased LH pulse frequency (as discussed earlier) offers a unifying mechanism for both ovarian androgen excess (due to LH-mediated stimulation of androgen production by ovarian stroma) and impaired follicle development that results in chronic anovulation (due to the relatively low FSH levels that occur secondary to altered GnRH release pattern). The state of hyperandrogenism resulting from ovarian androgen excess, in turn, contributes to as well as gets further perpetuated by insulin resistance and the resultant hyperinsulinemia. A vicious cascade of events is thus created with insulin excess worsening hyperandrogenism through further ovarian androgen production and by lowering hepatic SHBG production.

Therefore, the endocrine milieu in women with PCOS reflects a chronic anovulatory state, resulting from a wide variety of causes. Currently, PCOS is viewed as a complex disorder, where numerous genetic variants and environmental factors interact, combine, and contribute to the pathophysiology ***(Azziz et al., 2009).***

Recently, the focus has been on identifying genetic variants, including those involved in regulating gonadotropin secretion and action, insulin secretion and action, weight and energy regulation, and androgen synthesis and action, which may shed light on causative mechanisms for PCOS ***(Speroff, 2020).***

Beyond the clinical stigmata of androgen excess and anovulation of PCOS, the hormonal environment sets a stage for many metabolic sequelae commonly encountered in women with PCOS, contributing to lifetime health risks in this population. The pathophysiology of PCOS is most likely multifactorial, involving endocrine, metabolic, genetic, epigenetic, and environmental factors. The section below describes how each of the factors mentioned above may be relevant to the pathogenesis of this complex disorder ***(Speroff, 2020).***

1- Genetics - many candidate genes have demonstrated some evidence of linkage or association with PCOS, but follow-up studies have often failed to replicate results on the same candidate gene in different populations. Of over 100 candidate genes examined, the table lists genes with supporting evidence from multiple reports or evidence of replication (Table 2). In the first genome-wide association and replication studies of PCOS, conducted in Chinese Han individuals, three loci were identified as significantly associated with PCOS: two loci on chromosome 2 and a third locus on chromosome 9 ***(Chen et al., 2011)***.

One of these loci, on chromosome 2p16.3, contains the gene for the LH/HCG receptor (LHCGR), a logical susceptibility gene for PCOS. Two of the three, 2p21 and 9p33.3, contained multiple SNPs that appeared to be independently associated with PCOS. The chromosome 2p21 locus contained single nucleotide polymorphisms (SNPs) in THADA, a gene that codes for a thyroid adenoma-associated protein, while the 9p33.3 locus included variants in DENND1A, a gene coding for a protein that binds endoplasmic reticulum aminopeptidase 1 (ERAP1); increased ERAP1 serum levels have been associated with PCOS

accompanied by obesity ***(Olszanecka-Glinianowicz et al., 2007).*** A subsequent study observed that several of the same variants in DENND1A and THADA associated with PCOS in the Chinese population also affected the odds of PCOS in individuals of European origin ***(Goodarzi et al., 2012).***

Table (1): Genes associated with PCOS or component traits of PCOS.

Symbol	Gene
ACVR2A	Activin A receptor type IIA
AR	Androgen receptor
DENND1A*	DENN/MADD domain-containing protein 1A
FBN3	Fibrillin-3
FEM1B	Fem-1 homolog b gene
FTO	Fat mass- and obesity-associated (BMI)
HSD17B6	17-beta-hydroxysteroid dehydrogenase type 6 (metabolic traits)
INSR	Insulin receptor
IRS1	Insulin receptor substrate 1
LHCGR*	Luteinizing hormone/choriogonadotropin receptor
MC4R	Melanocortin 4 receptor (BMI)
POMC	Proopiomelanocortin
PPARG	Peroxisome proliferator-activated receptor gamma
SHBG	Sex-hormone binding globulin
SGTA	Small glutamine-rich tetratricopeptide repeat-containing protein alpha
THADA*	Thyroid adenoma-associated

The genes in this table were selected based on supporting evidence from multiple reports or evidence of replication. * Identified by genome-wide association study. *Reproduced with permission from: Dr. Mark O Goodarzi.*

(Goodarzi et al., 2012)

2- Gonadotropin secretion and action - women with PCOS exhibit high serum LH, low-normal FSH level, and increased FSH to LH ratio, unlike normally cycling women ***(Taylor et al., 1997)***. This deviation from the norm is due to abnormal LH secretory dynamics. Increase in LH pulse frequency and pulse amplitude to a lesser extent ***(Hayes et al., 1998).***

The low FSH levels result from several factors; more3 frequent GnRH pulse, the negative feedback effects of chronically elevated estrone concentrations (derived from peripheral aromatization of increased androstenedione), and standard or modestly increased levels of inhibin B (derived from small follicles) ***(Laven et al., 2001).***

Androgens directly contribute to the abnormal gonadotropin secretory pattern in women with PCOS. Evidence from studies indicates that prenatal exposure to increased androgen concentrations may affect GnRH pulse generator programming, predisposing to an increased pulse frequency and LH secretion ***(Xita et al., 2006).*** It may be that hyperandrogenemia from any cause, arising during fetal life (maternal hyperandrogenism, classical congenital adrenal hyperplasia [CAH]) or in adulthood (obesity,

hyperinsulinemia), induces abnormalities in the feedback control of pulsatile GnRH secretion, resulting in increased LH secretion, which stimulates increased ovarian androgen production, in a self-perpetuating cycle. ***(Speroff, 2020).***

3- Insulin secretion and action - In adipose, insulin resistance increases hydrolysis of stored triglycerides elevating free fatty acid levels. Decreased glucose utilization (primarily in muscle) and increased hepatic gluconeogenesis (which insulin normally inhibits) lead to increased; blood glucose concentrations and insulin levels (in those with adequate pancreatic reserve). Elevated insulin level is a cause or contribution to hyperandrogenism in PCOS women by two important methods; further stimulation of ovarian androgen production and inhibiting SHBG synthesis. (figure 3) ***(Baillargeon., 2007).***

It is found in 50% and 75% of women with PCOS are now generally accepted as an essential risk factor for developing metabolic syndrome ***(Legro et al., 2004).***

There are several theories to explain how insulin stimulates the release of androgens. Insulin stimulates ovarian androgen production by direct and indirect