Short Letrozole Therapy Versus Extended (Long) Letrozole Therapy For Induction Of Ovulation In Women With Polycystic Ovary Syndrome

Thesis

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List Of Contents

List of Tables

List Of Figures

POLYCYSTIC OVARY SYNDROME

Introduction:

Polycystic ovary syndrome (PCOS) is a heterogeneous syndrome and is considering the most common endocrine disorder in women at reproductive age ***(Azziz et al., 2019).***

Polycystic ovary syndrome (PCOS) was first described in 1935 by ***Stein and Levanthal (1935)*** in the American Journal of Obstetrics and Gynecology. Yet, it remains a syndrome that is confusing to many patients and practitioners in terms of its presentation, work-up, and management. There is a spectrum of presenting complaints and physical findings as well as overlap with other disorders, such as the metabolic syndrome.

Definitions:

Polycystic ovarian syndrome (PCOS) is a common endocrinopathy represented by oligoovulation or anovulation, signs of androgen excess and multiple small ovarian cysts. These signs and symptoms vary widely between women and individuals over time. Women with this endocrine disorder also have higher rates of dyslipidemia and insulin resistance which increase longterm health risks.

Incidence:

PCOS is the most common endocrine disorder of reproductive aged women and affects approximately 4% to12% in general population studies ***(Lauritsen et al., 2014).*** PCOS is associated with 75% of all anovulatory disorders causing infertility, with 90% of women with oligomenorrhea, more than 90% with hirsutism and more than 80% with persistent acne ***(Bozdag et al.,2016).***

Although symptoms of androgen excess may vary among ethnicities, PCOS appears to affect all races and nationalities equally.

Recognition of the syndrome affords the health provider an opportunity for not only reducing the emotional impact of manifestations such as acne, hirsutism, alopecia, and infertility, increased IGT, GDM and DM2 risks, independent of obesity in PCOS patients ***(Ng, N. Y. H et al., 2019)*** (DM2 was four times higher in a recent Danish registry study and was diagnosed four years earlier in PCOS,(***Rubin et al., 2017***) also the affected women have the potential of subsequent strokes and myocardial infarction as identified by Two systematic reviews ***(de Groot et al., 2011); (Heida et al., 2016)*** and eight observational studies to address risk of CVD in women with PCOS.

Diagnostic criteria of PCOS:

PCOS Defined by **ESHRE / ASRM (Rotterdam) 2003** as a syndrome includes two out of the following:

1.Oligo- or anovulation.

2.Clinical and / or biochemical signs of hyperandrogenism

3.Polycystic ovaries by ultra sound (presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (10 cm^3; calculated using the formula 0.5 x length x width x thickness). The transvaginal approach should be used ***(sujata et al., 2018).***

With exclusion of other conditions with similar signs such as androgen- secreting tumors or Cushing's syndrome and thyroid dysfunction and hyperprolactinemia.

Different categories in the clinical presentations of PCOS have been distinguished according to the Rotterdam criteria ***(Wijeyaratne et al., 2011)***. They include (i) ―classic PCOS‖ characterized by the presence or absence of ovarian cysts with excessive androgen secretion and irregular menstrual periods, (ii) ―ovulatory PCOS‖ characterized by the presence of increased androgen secretion and multiple cysts, and (iii) ―non-androgenic PCOS‖ associated with irregular menstruation and multiple cysts ***(Wijeyaratne et al., 2011)***.

Theories of etiology and pathogenesis of PCOS

The underlying cause of PCOS is unknown **(Franik et al., 2012).** However, a genetic basis that is both multifactorial and polygenic is suspected, as there is a well documented aggregation of the syndrome within families **(Barber et al., 2019).**

Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of male hormones (androgens), particularly testosterone, either through the release of excessive luteinizing hormone (LH) by the anterior pituitary gland or through high levels of insulin in the blood (hyperinsulinemia) in women whose ovaries are sensitive to this stimulus **(Fatima et al., 2018).**

A majority of patients with PCOS have insulin resistance and/or are obese. Their elevated insulin levels contribute to or cause the abnormalities seen in the hypothalamic-pituitary-ovarian axis that lead to PCOS, **(Zheng et al., 2017).**

Insulin resistance is a key pathophysiological abnormality in women with PCOS and the longer the interval between menstrual bleeds the greater is the degree of insulin resistance **(Jeanes et al.,2017).**

PCOS is also likely to have a genetic predisposition. An increased prevalence has been noted between affected individuals and their sisters (32- to 66%) and mothers (24 to 52 %) **(Ajmal et al., 2019)**.

Some have suggested an autosomal dominant inheritance with expression in both females and male. For example, first- degree male relatives of women with PCOS have been shown to have significantly higher circulating dehydroepiandrosterone sulphate (DHEAS) levels than control males **(Goodarzi et al.,2015).**

Clinical and in vitro studies of human ovarian theca cells have suggested dysregulation of the CYP 11 a gene in patients with PCOS. This gene encodes the cholesterol side-chain cleavage enzyme, the enzyme that performs the rate- limiting step in steroid biosynthesis. 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 (which are responsible for hirsutism and virilization) and estrogens (which inhibits FSH via negative feedback) **(West et al., 2020).**

Hyperinsulinemia increases GnRH pulse frequency, LH over FSH dominance, increased ovarian androgen production, decreased follicular maturation, and decreased sex hormone binding globulins (SHBG) binding; all these steps contribute to the development of PCOS. Insulin resistance is a common finding among patients of normal weight as well as those overweight patients **(Hamed,et al., 2010)**.

PCOS may be associated with chronic inflammatory reaction, with several investigators correlating inflammatory mediators with anovulation and other PCOS symptoms (**Chen et al., 2017).**

Abnormal estrogen clearance metabolism**:** The clearance and metabolism of estrogen can be impaired by pathologic conditions such as thyroid or hepatic disease. It is for this reason; a careful history and physical examination are important elements in the different diagnosis of anovulation. Both hyperthyroidism and hypothyroidism can cause persistent anovulation by altering not only metabolic clearance but also peripheral conversion rates among the various steroids **(Kowalczyk et al., 2017)**.

Consequences of polycystic ovaries Short term consequences

1.Irregular menses

In women with PCOS, menstrual dysfunction may range from amenorrhea to oligomenorrhea to episodic menometrorrhagia with associated iron-deficiency anemia. In most cases, amenorrhea and oligomenorrhea result from anovulation. Namely, without ovulation and endogenous progesterone production from the corpus luteum, a normal menstrual period is not triggered.

Alternatively, amenorrhea can stem from elevated androgen levels. Specifically, androgens can counteract estrogen to produce an atrophic endometrium. Thus, with markedly elevated androgen levels, amenorrhea and a thin endometrial stripe can be seen

In contrast to amenorrhea, women with PCOS may have heavy and unpredictable bleeding. In these cases, progesterone is absent due to anovulation, and chronic estrogen exposure results. This produces constant

mitogenic stimulation of the endometrium. The instability of the thickened endometrium leads to unpredictable bleeding. Characteristically, oligomenorrhea (fewer than 8 menstrual periods in 1 year) or amenorrhea (absence of menses for 3 or more consecutive months) with PCOS begins with menarche.

Those with PCOS fail to establish monthly ovulatory menstrual cycles by mid-adolescence, and they often continue to have irregularity. However, approximately 50 % of *all* post-menarchal girls have irregular periods for up to 2 to 4 years because of hypothalamic-pituitary-ovarian axis immaturity. Thus, due to the frequency of both irregular cycles and acne in unaffected adolescents, some advocate delaying the diagnosis of PCOS until after age 18 ***(Shayya et al., 2011).*** Also, 25% to 45% of women who have PCOS continue to have regular menses, yet exhibit other signs of androgen excess and infertility ***(Azziz et al., 2019).***

Last, some evidence suggests that PCOS patients with prior irregular cycle intervals may develop regular cycle patterns as they age. A decreasing antral follicle cohort as women enter their 30s and 40s may lead to a concurrent decrease in androgen production ***(Meri-Maija ollila et al., 2020).***

2.Hyperandrogenism

Hyperandrogenism is typically manifested by hirsutism, acne, and/or androgenic alopecia. In contrast, signs of virilization such as increased muscle mass, deepening of voice and clitromegaly are not typical of PCOS. Approximately three fourths of patients with PCOS have an evidence of hyperandrogenism **(Huang et al., 2010).**

- **Hirsutism:**

In females, hirsutism is defined as the presence of coarse, dark terminal hairs in a male pattern. PCOS accounts for 70 to 80% of cases of hirsutism. Elevated androgen levels play a major role in determining the type and distribution of hair **(Wu C et al., 2017).**

Within a hair follicle, testosterone is converted by 5 - reductase enzyme into the more effective form dihydrotestosterone (DHT) and both convert short, soft vellus hair into terminal hair. This conversion occurs in hairs in androgen sensitive areas which are upper lip, chin, sideburns, chest and linea Alba of the lower abdomen **(Hawryluk, 2009).**

- **Acne:**

Ace vulgaris is a frequent clinical finding in adolescents. However, acne that is particularly persistent or of late onset should suggest PCOS **(Azziz et al., 2019).**

The prevalence of acne in women with PCOS is unknown, although, one study found that pathogenesis of acne involves four factors, which include: blockage of the follicular opening by hyperkeratosis, sebum overproduction, proliferation of commensally propionibacterium' acne, and inflammation **(Purdy et al., 2006)**.

Androgen excess is involved in the above factors and treatment by lowering androgen levels reducing the development of acne **(Guan et al., 2020)**.

- **Alopecia:**

Androgenic alopecia is a less common finding in women with PCOS. Hair loss progresses slowly and is characterized either by diffuse

thinning at the crown with preservation of the frontal hairline or by temporal recession **(Liepa et al., 2008)**.

Its pathogenesis involves an excess of 5α reductase activity in the hair follicle leading to a rise in HDT levels, also there is an increased expression of androgen receptors in these individuals **(Roth et al., 2012)**.

3.Infertility and pregnancy complication

Infertility is a frequent complaint in women with PCOS and results from anovulation. Women with PCOS are more likely to be obese and overweight and obesity is related with impaired ovarian response, and negatively affects the outcomes of fertility management **(Dan Zhang et al., 2010).**

Women with PCOS who become pregnant are known to experience an increase rate (30 to 50%) of early pregnancy loss compared with a baseline rate of approximately 15% in the general population **(Lavazzo et al., 2010).**

The etiology is unclear, but several studies suggested that insulin resistance is related to miscarriage in these women, so they found that taking insulin-lowering drugs as metformin during pregnancy reducing the incidence of miscarriage rate in women conceiving while taking metformin **(Bidhendi Yarandi et al., 2019).**

Several pregnancy and neonatal complications in women with PCOS also increase to two to three folds as gestational diabetes mellitus, pregnancy induced hypertension, preterm labor, and perinatal mortality **(Palomba et al., 2010).**

In addition, many women with PCOS require ovulation induction medications or in vitro fertilization with resultant increase in maternal and neonatal complications **(Fauser et al., 2012).**

4.Obesity

Obesity is also associated with polycystic ovary syndrome (PCOS) **(West et al., 2020).**

Obesity occurs in 30-75% of women with PCOS **(Zeng et al., 2020).** increased body mass index (BMI) is associated with anovulatory infertility with poorer outcomes following fertility treatment and poorer fertilization rates **(Shilpi- Pandey et al., 2010).**

5.Abnormal lipid level/Glucose intolerance

The classic atherogenic lipoprotein profile seen in PCOS is characterized by elevated low-density lipoprotein (LDL), Triglyceride level, and total cholesterol: high-density lipoprotein (HDL) ratios, and by decreased HDL levels **(Wang et al., 2019).**

Women with PCOS are at increased risk for impaired glucose tolerance (IGT) and type 2 diabetes mellitus (DM), the prevalence of IGT is approximately 30% **(Kelsey et al., 2007).**

6.Metabolic disturbance (syndrome)

This syndrome is characterized by insulin resistance, obesity, atherogenic dyslipidemia and hypertension. The syndrome is associated with an increased risk of cardiovascular disease and type II DM **(Kazemi Jaliseh et al., 2017).**

Clinical manifestations of MetS such as dyslipidemia develop from insulin resistance through increased secretion of non-esterified fatty

acids, and increased synthesis of TGs while hypertension develops through endothelial damage and reduced nitric oxide bioavailability **(S.S. Lim et al., 2019)**. In addition, hyperglycemia develops from insulin resistance through compensatory hyperinsulinemia and pancreatic beta cell exhaustion**(S.S. Lim et al., 2019)** .

Long term consequences

- **Type II diabetes mellitus**

There is little doubt that the prevalence of impaired glucose tolerance and diabetes mellitus is increased substantially in women with polycystic ovary syndrome **(Kazemi Jaliseh et al., 2017)**.

Conversion rates of glucose tolerance from normal to abnormal are accelerated in polycystic ovary syndrome , and up to 10% of women with this disorder develop diabetes during the third or fourth decade **(Saha et al., 2010).**

- **Cardiovascular diseases**

PCOS shares several endocrine features with the metabolic syndrome, although definitive evidence for an increased incidence of CVD in women with PCOS is lacking. However many studies suggest that women with PCOS should have CVD factors identified and treated ***(*Wild et al., 2010*)***

Women with chronic anovul ation and hyperandrogenism have been observed to have increase risk for coronary heart disease, especially in relation to lipids, blood pressure, DM, clotting factors and insulin resistance **(Torres Fernandez et al., 2018)**

Altered vascular and endothelial function in young women with polycystic ovary syndrome is well documented, and increased death rates from cardiovascular disease have been shown in women with menstrual irregularity (possibly with polycystic ovary syndrome) **(Osibogun et al., 2020)**.

- **Endometrial neoplasia:**

The effects of the unopposed and uninterrupted estrogen increase the risk for endometrial neoplasia in these patients for 3 folds **(Fearnley et al., 2010).**

Spectrum of clinical presentations:

1- Menstrual dysfunction

A common feature of PCOS is irregular and unpredictable uterine bleeding. Commonly, bleeding episodes are infrequent occurring less than six times per year. The occurrence of oligomenorrhea may be explained by PCOS in approximately 85 % to 90 % of women, whereas 30 % to 40 % amenorrheic patients have been reported to have the disorder **(Goodman et al., 2015)**.

2-Androgen excess

The most distinctive clinical expression of PCOS is excessive hair growth which occurs in approximately 80 % of patients **(Delitala et al., 2017).**

The face and chin are commonly involved along with the tendency to a male pattern of hair distribution. Prolonged exposure to high circulating

androgens may paradoxically induce loss of hair as manifested by temporal balding **(Kelly et al., 2016)**.

3.Infertility

A significant number of patients have infertility as a presenting feature of PCOS. Anovulation is the primary defect responsible for the failure to achieve pregnancy in this disorder, presenting with amenorrhea, oligomenorrhea or with irregular bleeding **(Bani Mohammad et al., 2017).**

4.Android obesity

It has been noted that obese women with body mass index (BMI)> 25 kg/m2 exhibit an increased rate of hirsutism, cycle disturbance and infertility **(Barber et al., 2019),**and have more abnormal oral glucose tolerance test (OGTT) than with PCOS patients **(Goodman et al., 2015).**

PCOS, if indicated by history, a specific general physical examination is performed, with particular relevance to stigmata of hyperandrogenism, thyroid dysfunction or other endocrine and systemic conditions **(Gorthia et al., 2012)**.

Investigations:

To diagnose PCOS, we need special investigation, the aim of which is to confirm the diagnosis suspected from the clinical data and to assess the relative contribution of both the ovary and adrenal to the disease process. These investigations are laboratory, imaging and laparoscopic.

Laboratory investigations:

a-Thyroid stimulating Hormone and Prolactin:

Thyroid disease may frequently lead to menstrual dysfunction. Thus, a serum thyroid stimulating hormone level is typically measured during evaluation.

Similarly, hyperprolactinemia is a well-known cause of menstrual irregularities and occasionally amenorrhea. Elevated prolactin levels lead to anovulation through inhibition of GnRH pulsatile secretion.

b-Testosterone:

Tumors of the ovary or adrenal are a rare but serious cause of androgen excess. Various ovarian neoplasms, both benign and malignant, may produce testosterone and lead to virilization. Diagnostically, serum testosterone levels can aid ovarian tumor exclusion. Free testosterone levels are more sensitive than total testosterone levels as an indicator of hyperandrogenism. Although improving, however, current free testosterone assays lack a uniform laboratory standard ***(Faix, 2013).*** For this reason, total testosterone levels remain the best approach for identifying a possible tumor. Threshold values > 200 ng/dL of total testosterone warrant evaluation for an ovarian lesion **.** Pelvic sonography is the preferred method to exclude an ovarian neoplasm in a female with very high androgen levels. Alternatively, CT or MRI may also be used**(Bozkurt et al., 2020).**

c-Dehydroepiandrosterone Sulfate (DHEAS):

This hormone is essentially produced exclusively by the adrenal gland. Therefore, serum DHEAS levels > 700 µg/dL are highly suggestive of an adrenal neoplasm, and adrenal imaging with abdominal CT or MRI is warranted.

d-Gonadotropins:

During evaluation of amenorrhea, FSH, LH, and estradiol levels are typically measured to exclude premature ovarian failure (POF) and hypogonadotropic hypogonadism. Although LH levels classically measure at least two fold higher than FSH levels, this is not found in all women with PCOS. Specifically, one third of women with PCOS have circulating LH levels in the normal range, a finding more common in obese patients ***(Burt Solorzano et al., 2012).*** Moreover, serum LH levels are affected by sample timing within a menstrual cycle, use of oral contraceptive pills, and BMI.

e-17 alpha Hydroxyprogesterone:

The term congenital adrenal hyperplasia (CAH) describes autosomal recessive disorders that result from complete or partial deficiency of an enzyme 21-hydroxylase or less frequently 11- hydroxylase. As a result of these defects, precursors are shunted into pathways leading to androgen production. Thus, depending on the enzyme affected, symptoms of CAH vary, It may present in the neonate with ambiguous genitalia and life-threatening hypotension. Alternatively, symptoms may be milder and delayed until adolescence or adulthood.

In this late-onset form of CAH, the enzyme deficiency leads to a relative cortisol deficiency. In response, adrenocorticotropic hormone (ACTH) levels are increased to normalize cortisol production. Consequent to this accommodation, adrenal gland hyperplasia and elevated androgen levels develop. Therefore, symptoms of late-onset CAH reflect accumulation of precursor C19 steroid hormones. These precursors are converted to dehydroepiandrosterone, androstenedione, and testosterone. Thus, signs of hyperandrogenism predominate. With

late-onset CAH, the most commonly affected enzyme is 21-hydroxylase, and deficiency leads to accumulation of its substrate, 17-hydroxyprogesterone. Serum values are drawn in the morning from a fasting patient. Threshold values of 17-hydroxyprogesterone that measure> 200 ng/dL should prompt an ACTH stimulation test.

f-Anti-Müllerian Hormone:

The classic polycystic ovary contains 2 to 3 fold more growing preantral and antral follicles than normal ovaries **(Jarrett et al.,2020).** Within the granulosa cells of these developing follicles, the dimeric glycoprotein antimüllerian hormone (AMH) is produced, and serum AMH levels correlate closely with the number of antral follicles. Not surprisingly, AMH levels are 2 to 3 fold higher in women with PCOS compared with non-affected age-matched controls **(Cui et al., 2014).** For this reason, some view AMH as a potentially useful diagnostic marker for PCOS **(Teede et al., 2019)**. That said, data regarding this marker in both PCOS and controls are incomplete and require further investigation before it can be adopted as a formal diagnostic criterion ***(Dewailly et al., 2014).***

g-Cortisol:

Cushing disease term is reserved for cases stemming from increased adrenocorticotropin hormone (ACTH) secretion by a pituitary tumor. Cushing syndrome shares many symptoms with PCOS such as menstrual dysfunction, signs of androgen excess, truncal obesity, dyslipidemia, and glucose intolerance. Classically, moon facies and purple abdominal striae

are also noted. Cushing syndrome is rare, and routine screening in all women with oligomenorrhea is not indicated. However, in those with classic Cushing findings, proximal muscle weakness, and easy bruising, screening is strongly considered ***(Pivonell et al.,2017).***

h-Measurements of Insulin Resistance and Dyslipidemia:

Many women with PCOS have insulin resistance and compensatory hyperinsulinemia. Although the consensus meeting in Rotterdam suggested that tests of insulin resistance are *not* required to diagnose or treat PCOS, these tests are often used to evaluate glucose metabolism and impaired insulin secretion in these women ***(The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).***

The gold standard for evaluating insulin resistance is hyperinsulinemic euglycemic clamp. Unfortunately, this test requires an intravenous line and frequent sampling so it is time intensive and not practical in a clinical setting.

A 2-hr GTT is frequently used to exclude impaired glucose tolerance (IGT) and type II DM. This test is particularly important in obese PCOS patients who are at higher risk for both. According to several organizations, women with PCOS should undergo such screening ***(American Diabetes Association, 2014).*** Their recommendations vary from all women or only specific PCOS subgroups. The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group promotes evaluation in the following circumstances: hyperandrogenism with anovulation, acanthosis nigricans, obesity (BMI > 30 kg/m^2), and family history of DM or gestational DM. Women with PCOS may demonstrate a worsening of IGT over time, with a reported conversion rate of approximately 2% per year to type II DM. This demonstrates the

importance of periodic assessment of glucose tolerance with a 2-hr GTT in women with PCOS ***(Stovall et al., 2011).*** The AE-PCOS Society recommends that those with normal glucose tolerance be rescreened at least once every 2 years or more frequently if additional risks exist. Those with impaired glucose tolerance are tested annually. These same organizations counsel against use of a fasting glucose level and note that a surrogate HbA1c level can be considered.

In addition to assessment of insulin resistance, a fasting lipid profile is used to evaluate dyslipidemia.

Imaging investigations:

Ultrasonography:

Sonographic criteria for polycystic ovaries from the 2003 Rotterdam conference include 12 small follicles (2-9 mm in diameter) or an increased ovarian volume (> 10ml) or both. Often there is an increase in the amount of stroma relative to the number of follicles. Only one ovary with these finding sufficient to define PCOS **(Sylvia Kiconco et al., 2020).**

In contrast, other findings are not valuable diagnostically, for example, the typical "black pearl necklace" appearance and the perceived increase in the stromal echogenicity. Moreover, a polycystic ovary should not be confused with a multicystic ovary, which is normal size, contains six or more follicles without peripheral displacement and lacks an increase in central stromal volume **(Marrinan, 2011)**.

Color Doppler Ultrasonography:

Aleem and predanic, (1996), determined the blood flow characteristics of ovarian and uterine arteries in patients with

endocrinologically and clinically confirmed PCOS. Their results showed that polycystic ovaries had typical vascular pattern, increased stromal vascularities, a positive correlation between increased blood velocities and a tend toward lower resistance index and pulsatility index values.

Laparoscopic investigation:

The typical laparoscopic finding of PCOS is bilateral enlargement of the ovaries (size of the ovary is greater than one half of the diameter of the fundus of the uterus), with smooth glistening surface, unbroken by the usual wrinkles, and thick white capsule. Sometimes the ovaries are of normal size or even unilateral enlargement is present. Multiple small cysts are seen giving the ovary a blue mottled appearance due to the numerous follicles just below the surface with absent corpora lutea. Laparoscopy provides an important tool for ovarian biopsy confirming the diagnosis and may indeed re-establish regular menses with possibilities of adhesions **(Azziz , 2018)**.

TREATMENT OF PCO

In women with infertility secondary to anovulation, PCOS is the most common cause and accounts for 80 to 90% of cases. So treatment of the condition is of both medical and social importance **(Fauser et al.,, 2012).**

The goals of treatment are:

1-To reduce the production and levels of circulating androgens.

2-To protect the endometrium against the effects of unopposed estrogens.

3-To support the life style changes to achieve normal body weight.

4-To lower the risk of cardiovascular disease.

5-To avoid the effects of hyperinsulinemia on increasing the risk of cardiovascular diseases and diabetes mellitus.

Induction of ovulation to achieve pregnancy.

***General measures**

I- Weight loss:

Benefit of weight loss:

Available data suggest that as little as 5%-10% weight loss can improve fertility, with improvement of endocrine parameters, such as decrease in free testosterone, lower fasting insulin levels and increased frequency of ovulation. In addition, weight loss returns the normal menstrual cycles **(Teede et al.,2010)**. Weight loss can be achieved by

lifestyle modification, dietary restriction, physical activity and pharmacotherapy with varied results **(Willoughby et al., 2018).**

II - Stoppage of cigarette smoking:

A number of studies have suggested that in some way cigarette smoking may stimulate adrenal androgens. Furthermore, in premenopausal hirsute women androstenedione levels were significantly higher amongst smokers than in women who did not smoke **(Moran et al., 2011).**

III - Acupuncture:

Lim, 2010, concluded that acupuncture is a safe and effective treatment for PCOS, and may have a role in:Impacting on beta-endorphin production, which may affect gonadotropin- releasing hormone (GnRH) secretion **(Johansson et al., 2013).**

- A regulatory effect on follicle stimulation hormone (FSH), luteinizing hormone (LH) and androgens **(Feng et al., 2012).**
- Regulating steroid hormone/peptide receptors **(Feng et al., 2012).**
- Modulating the activity of the sympathetic nervous system and improving blood flow to the ovaries **(Davis et al., 2019)**.
- Down regulating the expressions of serum levels of testosterone and oestradiol **(Zeng et al., 2020).**
- Controlling hyperglycemia by increasing insulin sensitivity and decreasing blood glucose and insulin levels **(Lim et al.,2010)**
- Reducing stress and anxiety.
- Strengthening the body to prevent miscarriages.

Stener-Victorin, 2010, found no truly randomized controlled trials (RCTs) of acupuncture for PCOS and, while it found non-randomized

studies that suggested acupuncture was associated with a low adverse events rate and no increased risk of multiple pregnancies, the reviewers concluded that properly designed RCTs are needed before a conclusive statement can be drawn to support the use of acupuncture in the management of PCOS.

Medical therapy:

1.Antiestrogens

- ***Clomiphene citrate (CC):***

For over 40 years, the first-line therapy for ovulation induction (OI) has been clomiphene citrate (CC) **(Jones et al., 2018).**

Its inherent properties such as low price, oral route of administration and high ovulation success rate (60-90%) make it an attractive therapy. However, the pregnancy rate is disappointing **(Gadalla et al., 2018)**.

Sub-optimal pregnancy rates with CC have been attributed to peripheral anti-estrogenic effects, mainly on the endometrium and the cervical mucus **(Bedawy et al., 2009)**.

The endometrium is believed to be one of the most important targets for the antiestrogenic effect of CC and may explain a large part of its low pregnancy rate and high miscarriage rate. Successful implantation requires a receptive endometrium with synchronous development of glands and stroma **(Johal et al., 2019)**.

With CC, the endometrium is demonstrated by a reduction in glandular density and an increase in the number of vacuolated cells **(Gadalla et al., 2018)**. CC will be discussed in details in the next chapter.

- ***Tamoxifen:***

Other antiestrogens such as tamoxifen and cyclofenil have been used in ovulation induction in PCOS, and although they have fewer side effects on cervical mucus than CC, the pregnancy rate is no better; therefore these drugs are much less used for ovulation induction than CC **(He D et al., 2011)**.

- ***Aromatase inhibitors (AIs):***

The third generation aromatase inhibitors agents commercially available include two nonsteroidal preparations, anastrazole and letrozole and a steroidal agent, exemestane **(D.V. et L., 2018)**.

Letrozole has a short half life (around 2 days) and it clears rapidly from the body. It inhibits the aromatase enzyme by competitively binding to the haeme of the cytochrome p 450 subunit of the enzyme, resulting in a blockage of androgens conversion into estrogens with subsequent increase in intraovarian androgens. Letrozole can be administered early in the follicular phase to induce ovulation by releasing the hypothalamus and pituitary from estrogen negative feedback on GnRH and gonadotrophin secretion, leading to an increase in gonadotrophin production which would stimulate ovarian follicular development, but unlike CC, it does not lead to estrogen receptor depletion so, no adverse effects on either endometrium nor cervical mucus **(Amer et al., 2017)**.

2.Insulin sensitizing agents

The recognition of an association between PCOS and hyperinsulinemia has led to the use of insulin-sensitizing agents in ovulation induction. Metformin, the most widely studied agent used in PCOS, is a biguanide insulin- sensitizing agent that acts by inhibiting

hepatic glucose production and increasing peripheral glucose uptake **(Sharma et al., 2019)**.

It does not stimulate secretion of insulin or cause hypoglycemia. Arandomaized controlled trial **(Ambreen Fatima et al., 2018)** comparing CC and metformin, both alone and in combination, found that metformin alone increased the odds of ovulation compared with placebo but did not result in a statistically significant difference in pregnancy rates. When CC and metformin were compared with CC alone, both ovulation and pregnancy rates were statisetically increased. Also, some studies have shown that continuing metformin in pregnancy may decrease the spontaneous abortion rate **(Zang et al., 2016)**.

(Siebert et al., 2006), examined 6 trials in which metformin was randomized with either placebo or CC in clomiphene-resistant patients and found an overall statistically significant improvement in ovulation with combination therapy. Further, another study also suggested that women with PCOS who are older and have obesity may benefit from the additional use of metformin **(Sam et al., 2017)**.

Patients on metformin often experience unpleasant side effects of nausea, bloating, cramps, and diarrhea, and they should be counseled to start with 250 mg to 500 mg per oral daily and increase as tolerated to the optimal daily dose of 500 mg to 750 mg 3 times daily with food. Metformin can also be dosed 850 mg per oral twice daily or a long-acting formulation can be used to improve compliance.

3.Gonadotrophins:

Use of intramuscular gonadotropins began in the 1960s. These preparations, from the purified urine of postmenopausal women, contained both FSH and LH. Over the last decade, recombinant human

FSH has been the main preparation, and it can be self-administered subcutaneously **(Balen ,2013)**.

Gonadotrophins are inactive orally, must be given parentally, the heavy protein content of the urinary preparation require intramuscular injections. A more purified urinary preparation of FSH became available by removing most of the LH in the urinary product. This product still requires intramuscular injection. A more highly purified preparation is available that can be administered subcutaneously. Recombinant FSH is now produced in Chinese hamster ovary cells transfected with the human FSH subunit genes and could be injected subcutaneously **(Ferreira Leão ET AL., 2015)**.

Injectable gonadotropins are very expensive and require frequent monitoring, with serum estradiol and ultrasound assessments to minimize the risks of excessive follicular growth and development. Because of the high number of antral follicles in women with PCOS, it is not uncommon that treatment is cancelled to minimize the occurrence of multiple pregnancies and also of ovarian hyperstimulation syndrome **(Tannys et al., 2010)**.

Pregnancy rates with gonadotropins are 20% to 25% per cycle. Drawbacks to gonadotropin treatment are requirements for intensive monitoring, cost, multiple pregnancy, and ovarian hyperstimulation. Gonadotropins should be administered by physicians with specific training in reproductive medicine and with ready access to ultrasound monitoring and rapid hormone testing **(Balen, 2013)**.

4-Gonadotrophin – releasing hormone agonist (Gn RH – a):

The theory underlying the use of Gn RH –as adjunctive therapy in ovulation induction is straight forwards; convert normogonadotropic

anovulation into hypogonadotropic hypogonadal state by the process of pituitary Gn RH receptor down – regulation and desensitization **(Kasum et al., 2016)**.

Treatment with Gn RH- a for 6-8 weeks prior to the initiation of pulsatile Gn RH therapy has the effect of lowering both intraovarian androgens and LH and increasing the ovulatory rate to approximately 30 % **(Kasum et al., 2016).**

Gn RH – a therapy should be initiated any time from the mid to late luteal phase (cycle day 21 to 28) until the early follicular phase (cycle day 1 to 3), but initiation at the midluteal phase may lead to a more prompt suppression of ovarian estrogen production **(Weiss et al. 2019)**.

Also, GnRH agonist can be used in triggering of ovulation instead of HCG and this use has been suggested as a measure to prevent ovarian hyperstimulation syndrome (OHSS) **(Youssef et a/l., 2014).**

Combination of GnRH agonist and GnRH antagonist prevent ovarian hyperstimulation syndrome, safer and at the same time efficacious way to perform IVF **(Iliodromitis et al., 2013)**

5-Gonadotrophin – releasing hormone antagonist:

Gonadotrophin-releasing hormone (GnRH) antagonists can be used to prevent a luteinizing hormone (LH) surge during controlled ovarian hyperstimulation (COH) without the hypo-estrogenic side-effects, flare-up, or long down-regulation period associated with agonists **(Abuzeid et al., 2011).** The antagonists directly and rapidly inhibit gonadotropin release within several hours through competitive binding to pituitary GnRH receptors. This property allows their use at any time during the follicular phase **(Al-Inany et al., 2016)**. Several different regimes have

been described including multiple-dose fixed (0.25 mg daily from day six to seven of stimulation) **(AL-Inany et al., 2016)**, multiple- dose flexible (0.25 mg daily when leading follicle is 14 to 15 mm) **(Bakas et al., 2011),** and single-dose (single administration of 3 mg on day 7 to 8 of stimulation) protocols, with or without the addition of an oral contraceptive pill. Further, women receiving antagonists have been shown to have a lower incidence of ovarian hyperstimulation syndrome (OHSS) **(Pundir et al., 2012).**

Complications of ovulation induction therapy:

Multiple pregnancy and ovarian hyperstimulation syndrome are the most serious complications to be avoided in ovulation induction treatment. Multiple pregnancies, even twins, is undesirable because of the increased risk of perinatal mortality and morbidity **(Kawwas et al., 2018).**

Furthermore, in severe cases, ovarian hyperstimulation syndrome can lead to ascites and pleural and sometimes pericardial effusions, with symptoms of abdominal discomfort, nausea, vomiting, and difficulty in breathing, haemoconcentration and coagulopathy. Deaths have occurred as a consequence, usually as a result of thromboembolism **(Gorthi et al., 2012).**

Although there have been concerns regarding cancer risk and infertility **(Lundberg et al., 2019),** the only consistent association observed is an increased risk of endometrial cancer for women with PCOS with prolonged amenorrhea **(Louise et al., 2013).**

In the early 1990s, a link was suggested between fertility drugs and ovarian cancer; current evidence does not indicate an increased risk of

ovarian cancer with 12 months or less of clomifene citrate treatment (**Van Leeuwen et. al, 2011).**

Surgical induction of ovulation

Diet and exercise followed by CC should be used for nonsurgical ovulation induction. For CC-resistant PCOS women, metformin may be included in a stepwise approach before a surgical approach. LOD with electrocautery is superior to laser drilling and gonadotropin therapy**(Goss et al., 2014)**.

Clomiphene citrate (CC) is the first-line treatment for ovulation induction for infertile women with PCOS. In CC-resistant women, a particular surgical interference has been proposed as an alternative treatment **(Debras et al., 2019)**.

The response of ovary to injury may be destruction of ovarian androgen- producing tissue and reduce the peripheral conversion of androgens to estrogens (one of the many disturbances of endocrine physiology that occur in women with polycystic ovarian syndrome). The endocrine changes following the surgery are thought to restore the hormonal environment to normal by correcting disturbances of the ovarian-pituitary feedback mechanism. Thus, both local and systemic effects are thought to promote follicular recruitment, maturation and subsequent ovulation (**Farquhar et al., 2012).**

Wedge resection:

Surgical ovarian wedge resection was the first established treatment for women with anovulatory polycystic ovary syndrome (PCOS) **(Stien, 1939)** but was largely abandoned both due to the risk of postsurgical

adhesions and the introduction of medical ovulation induction **(Hashim, 2015)**.

Wedge resection involves removing one- half to three- quarters of the ovary and then sewing the ovary closed. It is believed that removing some of the ovarian tissue will reduce androgen production, which can reduce the symptoms that women experiences and may even help restore regular ovulation **(Sawin, 2011)**.

Studies have been inconsistent in the effectiveness of the procedure, ranging from 6% to 95% of patients resuming a normal menstrual cycle and 10% to 90% of women achieving a pregnancy. The reason for this range is uncertain. However, it is accepted that around 30% of women end up with pelvic adhesions or scarring after the procedure, which all experts agree is bad for fertility **(T.K. Al-Hussaini et al., 2017)**.

Laparoscopic ovarian drilling (LOD):

Laparoscopic ovarian drilling (LOD) introduced by **Gjonnaess (1984)**.

LOD produces overall spontaneous ovulation and pregnancy rates of 30 to 90% and 13 to 88%, respectively, with effects lasting six to nine months **(Farquhar et al., 2012)**

Laparoscopic ovarian surgery is a second-line therapy in clomiphene citrate resistant (CCR) PCOS women, which is equally effective to three to six treatment cycles of gonadotrophin ovulation induction in terms of fertility outcome but with a lower risk of multiple pregnancies and less direct costs. Second-look laparoscopic adhesiolysis performed 3 months following LOS in CCR PCOS women has no benefit in terms of

pregnancy or miscarriage rates per patient over 6-month follow-up **(Micheal et al., 2012).**

However, women with PCOS who are treated with medical ovulation induction, with drugs such as gonadotropins, often have an overproduction of follicles which may result in ovarian hyperstimulation syndrome and multiple pregnancies. Moreover, gonadotropins, though effective, are costly and time- consuming and their use requires intensive monitoring. Surgical therapy with laparoscopic ovarian drilling (LOD) may avoid or reduce the need for medical ovulation induction, or may facilitate its usefulness **(Farquhar et al., 2012).**

A variety of surgical techniques have been used since the 1930s, such as classical ovarian wedge resection, monopolar and bipolar coagulation, laser vaporization and ovarian biopsies. For several years now, a modified technique of LOD has been used. The technique is based on the classical monopolar electrocoagulation LOD. Drilling itself is performed with the help of a monopolar hook electrode. The modified technique was introduced based on the rationale that the superficial but more extensive 'drilling' would lead to a more extensive destruction of the ovarian capsule, making it more permeable, and would thereby lead to an improved outcome **(Johansson et al., 2013)**.

LETROZOLE

About 10 years ago, researchers decided to attempt development of an oral ovulation treatment that would be free of the antiestrogenic side effects associated with CC **(Mitwally, 2011).** AIs were first used in ovulation induction in 2001**(Mitwally , 2001a).**

Mechanism of action of Aromatase Inhibitors:

Aromatase:

Aromatase (cytochrome P-450 [CYP]) catalyzes the rate-limiting step (conversion of steroidal C-19 androgens to C-18 estrogens) in estrogen biosynthesis **(Thomas et al., 2017).** Aromatization is the final step in steroid biosynthesis; and, therefore, aromatase is an attractive target for selective inhibition **(Gibson et al., 2009).**

Aromatase is expressed primarily in the ovary and also in central and peripheral tissues, fat, muscle, liver, and breast. With increasing age, as ovarian estrogen production declines, the contribution of peripheral production of estrogens increases, and in postmenopausal women, peripheral aromatization of androstenedione produced by the adrenal gland becomes the main source of endogenous estrogens **.**

Of note, normal and malignant breast tissue contributes to the peripheral synthesis of estrogens. The presence of intracellular aromatase activity could explain why estrogen concentrations are 10–20 times higher in peripheral tissue than blood in postmenopausal but not pre-menopausal women. Moreover, estrogen concentrations are higher in tumors than in surrounding non-malignant tissue **(Dixon et al., 2008).**

Recent research has increased understanding of how aromatase is regulated by tissue-specific promoters and how genetic variation may affect the pathophysiology of estrogen-dependent disease ***(Bulun et al., 2005).***

Aromatase inhibitors:

The search for potent and selective inhibitors of aromatase started with the first-generation inhibitor aminoglutethimide. However, aminoglutethimide lacked selectivity for aromatase and inhibited biosynthesis of cortisol, aldosterone, and thyroid hormone as well as aromatase; moreover, aminoglutethimide was also found to induce hepatic enzymes ***(Santen and Harvey, 1999).***

Second-generation AIs included the nonsteroidal inhibitor fadrozole and the steroidal inhibitor formestane (4-hydroxyandrostenedione). Fadrozole was superior to aminoglutethimide in terms of potency, selectivity, and safety, but its selectivity was not complete and clinical trials suggested that it was no more effective than tamoxifen. To improve on fadrozole, Novartis synthesized a series of new compounds. Structure-activity relationship studies were then performed to identify the most potent AIs from a series of benzyl-azole derivatives of fadrozole **(Simone Brixius-Anderko et al., 2019).**

The third-generation AIs Letrozole (Femara1) was the result of this structure-activity approach to drug design and achieved the research goal of creating a highly potent and totally selective AIs. These compounds were also used to design pioneering molecular modeling techniques used to map the active site of aromatase. Other third generation AIs developed during this period was the nonsteroidal agents vorozole (since

discontinued) and anastrozole and the steroidal agent exemestane ***(Anat Biegon et al., 2020).***

Pharmacodynamics and Pharmacokinetics of Letrozole:

Potency:

The chemical structure of Letrozole (4,40-[(1H-1,2,4-triazol- 1-yl) methylene] bis-benzonitrile) is compared with other AIs ***(Hallman et al., 2019).***

The nitrogen-containing structures like the imidazoles and the triazoles bind to the iron in the heme moiety of CYP-450, whereas the cyanobenzyl moiety present in the nonsteroidal AIs such as Letrozole partially mimics the steroid backbone of the enzyme's natural substrate androstenedione. Furthermore, the triazole compound letrozole was found to be superior to other derivatives of fadrozole in terms of in vivo inhibition of aromatase. Letrozole is a highly potent inhibitor of aromatase in vitro, in vivo in animals, and in humans. The relative potencies of letrozole, anastrozole, and fadrozole were determined in a variety of model cellular endocrine and tumor systems containingaromatase (hamster ovarian tissue fragments, adipose tissue fibroblasts from normal human breast, the MCF-7Ca human breast cancer cell line transfected with the human aromatase gene, and the JEG-3 human choriocarcinoma cell line) **(Pistelli et al., 2018).**

The degree of aromatase inhibition can be determined in vivo by measuring uterine weight after treatment with a standard dose of androstenedione in immature female rats. Using this assay, it was found that the in vivo potency of letrozole is more than four orders of

magnitude greater than aminoglutethimide (50% effective dose [ED_{50}], 1–3 lg/kg vs. 30 mg/kg, respectively) **(Pistelli et al., 2018)**

It has also been shown that neo-adjuvant letrozole profoundly inhibits in situ aromatase activity and reduces endogenous estrogens within the breast in postmenopausal women with large primary breast cancers **(Beslija et al., 2019).**

In postmenopausal women, letrozole achieves significantly greater plasma estrogen suppression of estrogens and greater inhibition of in vivo aromatization than anastrozole. In the study, levels of aromatase were detectable in 11 of 12 patients during treatment with anastrozole (mean percentage inhibition in the whole group, 97.3%) but in none of the 12 patients during treatment with letrozole ([99.1% suppression in all patients) ***(Geisler et al., 2002).***

Suppression of estrone and estrone sulfate was found to be significantly greater during treatment with letrozole compared with anastrozole (P = 0.019 and 0.0037, respectively). Another study conducted in 54 postmenopausal women with invasive breast cancer showed that more complete inhibition of aromatase was achieved with 2.5 mg of letrozole than

1 mg of anastrozole, resulting in significantly greater suppression of estradiol (P<0.0001), the most bioactive estrogen ***(Dixon et al., 2008).***

Selectivity of Letrozole:

Letrozole is highly selective for aromatase and unlike first and second-generation AIs does not significantly affect cortisol, aldosterone, or thyroxine. In vitro studies showed that letrozole was more than three orders of magnitude more selective than aminoglutethimide in its effects

on progesterone and corticosterone production and more than 300-fold more selective against aldosterone than fadrozol. In vivo adrenocorticotrophic hormone (ACTH) stimulation tests in rats showed that letrozole had no significant effect on either aldosterone or corticosterone levels, even at a dose 1,000 times greater than that required for inhibition of aromatase ***(Haynes et al., 2003).***

The selectivity of letrozole has been demonstrated in clinical studies in postmenopausal women. These studies showed that letrozole has no effect on the plasma levels of 17a-OH progesterone, thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), or androstenedione and does not affect normal urine electrolyte excretion or thyroid function ***(López et al., 2016).***

Pharmacokinetics of Letrozole:

Clinical pharmacokinetic studies of letrozole have been conducted in healthy volunteers and in patients with breast cancer. Following oral administration, letrozole is rapidly and completely absorbed (mean absolute bioavailability of 99.9%) and extensively distributed to tissues. It has a large apparent volume of distribution at steady state (1.87 l/kg [range, 1.47–3.24]), and approximately 60% is bound to plasma proteins, mainly to albumin (55%). The terminal half-life ($T^1/_2$) of letrozole is 42 h. The terminal $T^1/_2$ was observed to be longer and area under the curve (AUC) greater in patients with breast cancer than in healthy volunteers, possibly due to reduction in metabolic clearance ***(Pfister et al., 2001).***

The major route of elimination of letrozole is metabolism by CYP-450 isoenzymes (CYP 3A4 and CYP 2A6) into an inactive carbinol metabolite. Systemic exposure to metabolites is, therefore, low. Steady-state concentrations of letrozole are reached after 2–6 weeks and

maintained for long periods with no evidence of drug accumulation. In marked contrast to the first-generation AI aminoglutethimide, no significant drug interactions have been reported for letrozole; however, when combined with tamoxifen, letrozole plasma concentrations are reduced by between 35% and 40% ***(Ruhstaller et al., 2019).***

Age does not have an effect on the pharmacokinetics of letrozole. Exposure to letrozole, measured by AUC, is increased in renally impaired subjects but remains in the range seen in subjects without impaired function. However, hepatic impairment can markedly increase the $T^1/_2$of letrozole, and caution is required in such patients. Differences in pharmacokinetics, including uptake rates, elimination $T^1/_2$, and metabolism and clearance exist between AIs and have been reviewed by ***(Lønning ,2004).***

USE OF LETROZOLE IN TREATMENT OF PCOS

Induction of ovulation with AIs

Central mechanism of action of AIs:

Administration of an AI in the early part of the menstrual cycle would be possible to block estrogen-negative feedback, without depletion of ERs as occurs with CC. Both circulating estrogen (produced mainly by the ovarian follicles and peripheral conversion of androgens in fat and other tissues) and locally produced estrogen in the brain exert negative feedback on gonadotrophin release **(Palomba, 2015).**

Inhibition of aromatization will block estrogen production from all sources and release the hypothalamic/pituitary axis from estrogenic negative feedback. The resultant increase in gonadotrophin secretion will stimulate growth of ovarian follicles. Withdrawal of estrogen centrally also stimulate synthesis of FSH by a direct action on the gonadotropes. The selective nonsteroidal AIs have a relatively short half-life (45 h), compared with CC, and would be ideal for this purpose because they are eliminated from the body rapidly **(Franik et al., 2018).**

Because AIs do not deplete ERs, as does CC, normal central feedback mechanisms remain intact. As the dominant follicle grows and estrogen levels rise, normal negative feedback occurs centrally, resulting in suppression of FSH and atresia of the smaller growing follicles. A single dominant follicle, and monoovulation, should occur in most cases. In women with PCOS, relative oversuppression of FSH may be the result of excessive androgen produced from the ovary being converted to estrogen by aromatization in the brain. The AIs suppress estrogen production in both the ovaries and brain. In the case of PCOS, therefore,

AIs should result in a robust increase in FSH release and subsequent follicle stimulation and ovulation. The actual FSH release is likely to be blunted by the high levels of circulating inhibin found in PCOS patients that would not be altered by aromatase inhibition. In addition, as pointed out above, aromatase inhibition does not antagonize ERs in the brain, and the initiation of follicle growth accompanied by increasing concentrations of both estradiol and inhibin results in a normal negative feedback loop that limits FSH response, thereby avoiding the risk of high multiple ovulation and ovarian hyperstimulation syndrome (OHSS) **(Mai et al., 2017)**.

Peripheral mechanism of action:

A second hypothesis that may add to the mechanism of action of the AIs in ovarian stimulation involves an increased follicular sensitivity to FSH. This could result from temporary accumulation of intraovarian androgens because conversion of androgen substrate to estrogen is blocked by aromatase inhibition. Androgens promote follicular growth and estrogen biosynthesis indirectly by amplifying FSH effects **(Kang et al., 2018)**.

It is likely that women with PCOS already have a relative aromatase deficiency in the ovary, leading to increased intraovarian androgens **(Zeng et al., 2020)** that lead to the development of multiple small follicles responsible for the polycystic morphology of the ovaries. The androgens, may also increase FSH receptors making these PCOS ovaries exquisitely sensitive to an increase in FSH through either exogenous administration of gonadotrophins (hence the high risk of OHSS) or endogenous increases in FSH as a result of decreased central estrogen feedback induced by aromatase inhibition.

Another part of the peripheral hypothesis involves estrogen receptors (ERs) in the endometrium. It is possible that aromatase inhibition, with suppression of estrogen concentrations in the circulation and peripheral target tissues, results in up-regulation of ERs in the endometrium, leading to rapid endometrial growth once estrogen secretion is restored **(Hussein, Z et al., 2017)**.

This could increase endometrial sensitivity to estrogen resulting in more rapid proliferation of endometrial epithelium and stroma and improved blood flow to the uterus and endometrium **(Li Wang et al., 2019)**.

As a result, normal endometrial development and thickness should occur by the time of follicular maturation, even in the face of the observed lower-than- normal estradiol concentrations in AI-treated cycles.

Indications for AIs in induction of ovulation:

To summarize, the AI when used alone should result in a predictable response with the development of one or two mature follicles and a significantly reduced risk for OHSS and multiple gestation. To achieve multiple ovulations, the addition of FSH to the AIs is likely necessary.

Clinical studies of AIs for ovulation induction:

Induction of ovulation after CC failure:

Eckmann and Kockler (**2009),** concluded that AIs were an effective alternative to CC, particularly in cases with recurrent CC failure. However, it is important to point out that in cases of CC resistance (failure to ovulate) due to severe insulin resistance or the use of CC for inappropriate indications (*e.g.* hypothalamic amenorrhea or ovarian

failure), the use of an AI is also unlikely to be successful. The correction of insulin resistance with an insulin sensitizer is the logical approach in patients with insulin resistance. Alternative treatments should be considered for other problems such as exogenous gonadotrophin injection in patients with hypo gonadotropic hypogonadism and oocyte donation for cases with ovarian failure.

In a study of CC-resistant women with PCOS, letrozole induction of ovulation was associated with an ovulation rate of 54.6% and pregnancy rate of 25% **(Elnashar et al., 2006).**

AIs plus gonadotrophins:

Mitwally and Casper (2004), and others found a significant reduction in the FSH dose required (from 45 to 55%) when combined with an AI to achieve optimum controlled ovarian stimulation (COH), without adverse antiestrogenic effects.

Improving ovarian response to FSH stimulation in poor responders:

Although letrozole has been used in several studies of poor responders to super ovulation, its use has usually been combined with gonadotrophin injection, resulting in a shorter stimulation duration and lower dosage of gonadotrophin **(Shi, S et al., 2020)**.

A randomized trial of letrozole compared with gonadotrophins would be of interest. This group of patients will not produce a large cohort of oocytes whatever stimulation regime is used, and if letrozole is able to induce development of a similar number of follicles as gonadotrophins, as suggested by a retrospective analysis**(Ege, S et al., 2020)**, the costs of treating this group of patients could be substantially reduced.

Optimal dose of AIs for repeated administration:

The optimal dose of each AI is not yet clear. **(Badawy et al., 2007)**, in a randomized study comparing 2.5 and 5.0 mg of letrozole in women with unexplained infertility suggested that the higher dose might be associated with more follicles developing. Similarly, a study using 7.5 mg letrozole from cycle d 3 to 7 showed, for the first time, a thinning of the endometrium similar to CC **(A S Elhoussieny et al., 2020)**.

Based on current data, it is likely that the optimal dose of letrozole for a 5- days course of treatment is between 2.5 and 5.0 mg, with higher doses resulting in persistence of aromatase inhibition and estrogen levels too low for normal endometrial development by the time of ovulation. Also data published on a single 20-mg dose of letrozole given on cycle day 3 **(Mitwally, 2005)**. This single dose administration seemed to be as effective as 5 days administration and may be an option to improve patient compliance.

Another regimen for aromatase inhibitor administration is a step-up protocol as described by **(Mitwally et al. 2008)**. In this protocol, letrozole was given in an escalating dose from 2.5mg on day 3, up to 10mg on day 6. This protocol seems to be associated with 2 or more follicles in many patients and may be a novel approach to mild stimulation for intrauterine insemination (IUI) cycles. They have more recently used an ‘‘extended dose’’ protocol with success in women with PCOS resistant to ovulation after receiving 5 days of letrozole treatment. This protocol involves continuing letrozole for up to 7 to 10 days if, after the usual 5 days treatment, no growing follicle(s) (12mm or more) are seen on ultrasound. They believe this protocol mimics the extended use of low dose FSH

injections for several days to induce single follicle development in PCOS patients.

Adverse effects and concerns about using AIs for induction of ovulation:

AIs are generally well tolerated. The most common adverse effects are hot flushes, GI disturbances (nausea and vomiting), and leg cramps. In clinical trials involving postmenopausal women with breast cancer who were taking an AI, very few withdrew because of drug-related adverse effects **(Mitwally, 2008)**.

Those women took an AI on a daily basis over several months. Fewer adverse effects would be expected among usually healthy younger women administered a short course (a few days) for ovarian stimulation. Mild gastrointestinal disturbances account for most of the adverse events, although these have seldom limited therapy **(Winer et al., 2002)**.

Other adverse effects are asthenia, hot flashes, headache, and back pain**(Sing Ranger, 2005)**.

Safety concerns:

The main safety concerns are with regard to possible teratogenic effects of letrozole. As a result of the short half-life of the drug, administration in the early follicular phase should result in clearance of letrozole before implantation takes place. Nevertheless, care should be taken in all cases of ovulation induction with aromatase inhibitors to ensure that the patient is not pregnant before administration. A blood beta human chorionic gonadotropin level is recommended to be ascertained before using letrozole in premenstrual women **(Casper et al., 2018)**.

Pregnancy outcome with AIs:

Pregnancies conceived after use of letrozole were associated with rates of miscarriage and ectopic pregnancy that were comparable to rates associated with all other pregnancies, including spontaneous conceptions **(Donghong , 2011)** .

Letrozole use was associated with a significantly lower multiple gestation rate than use of CC **(Behnoud et al., 2019)**.

Teratogenic effects of letrozole happen if administered unintentionally during pregnancy **(T. Tatsumi et al., 2017**).

Nakajo (2010), concluded that the use of letrozole for ovulation induction does not appear to increase the risk of congenital malformations and does not affect birth weight .

RESULTS

This study was conducted on forty patients attending the obstetrics and gynecology Department in Benha University Hospitals as a Prospective randomized comparative study.

Table (1) General characteristics in both groups

		Short protocol(n= 20)	Long protocol(n= 20)	P value
Age (years)	Mean ±SD	29 ±4	31 ±3	0.221
	Range	22 - 35	25 – 35	
Weight (kg)	Mean ±SD	67 ±11	65 ±11	0.575
	Range	47 - 88	47- 88	
Height (cm)	Mean ±SD	157 ±9.3	158 ±10.6	0.637
	Range	140 - 170	140 - 180	

Independent t-test was used

There were no statistically significant differences between both groups regarding the age, weight, and height of patients. P values were 0.221, 0.575, and 0.637, respectively.

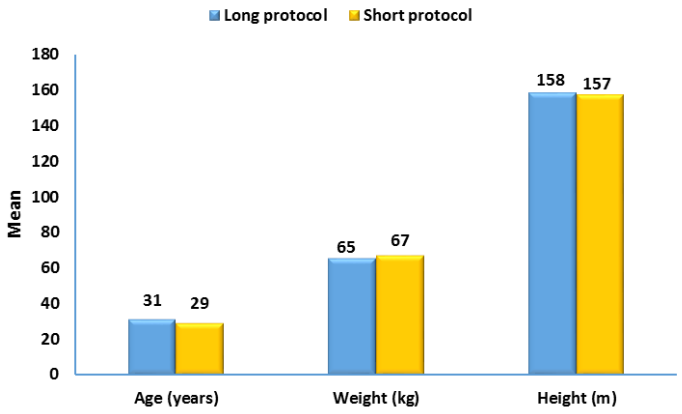

Figure (1) General characteristics in both groups

Table (2) Type of infertility in both groups

		Shortprotocol(n= 20)	Long protocol (n = 20)	P value
Typeof infertility	1ry n (%)	7 (35.0)	9 (45)	0.519
	2ry n (%)	13 (65)	11 (55.0)	

Chi-square test was used

Type of infertility showed a non-statistically significant difference between both groups. P-value was 0.519

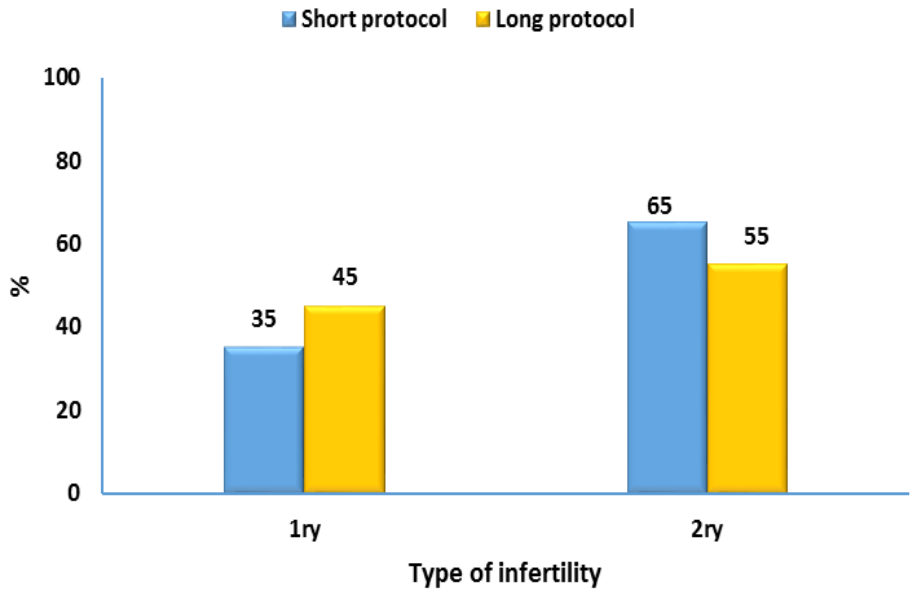

Figure (2) Type of infertility in both groups

Table (3) Infertility duration in both groups

		Short protocol(n = 20)	Long protocol(n= 20)	P value
Infertility duration (years)	Mean ±SD	4 ±1	3 ±1	0.675
	Range	2 – 5	2 - 5	

Independent t-test was used

Infertility duration showed a non-statistically significant difference between both groups. P-value was 0.675

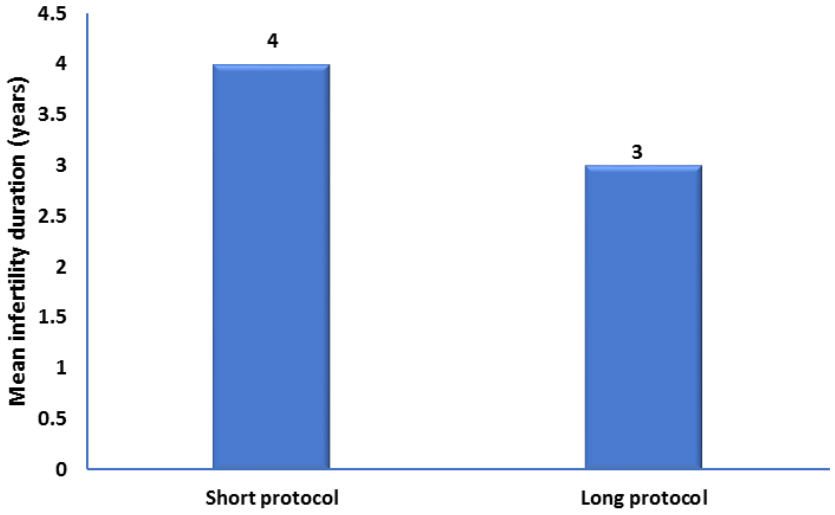

Figure (3) Infertility duration in both groups

Table (4) Previous induction & its types in both groups

			Short protocol (n = 20)	Long protocol (n = 20)	P value
Previous induction	n (%)		16 (80.0)	16 (80.0)	1.0
Type of previous induction	Tablet	n (%)	2 (12.5)	5 (31.3)	0.394
	Tablet & injection	n (%)	14 (87.5)	11 (68.8)	

Fisher's exact test was used

Previous induction and its types showed non-statistically significant differences between both groups. P values were 1.0 and 0.394, respectively.

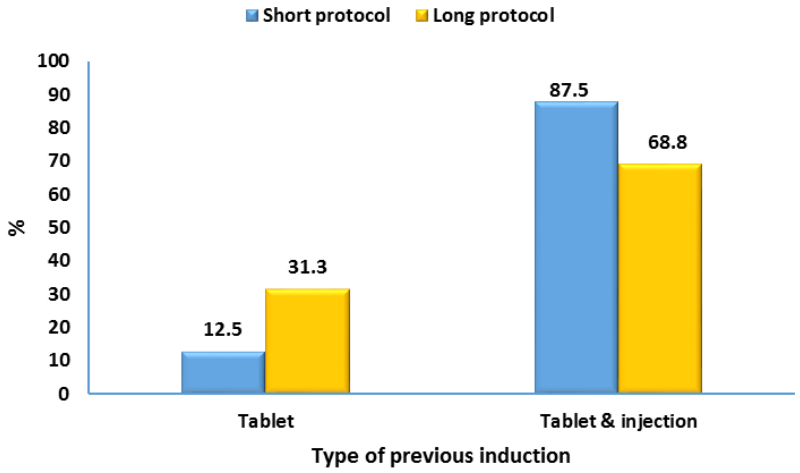

Figure (4) Type of previous induction in both groups

Table (5) Number of cycles in both groups

			Short protocol (n = 20)	Long protocol(n= 20)	P value
Number of cycles	One	n (%)	11 (55.0)	9 (45.0)	0.844
	Two	n (%)	5 (25.0)	6 (30.0)	
	Three	n (%)	4 (20.0)	5 (25.0)	

Fisher's exact test was used

The number of cycles showed a non-statistically significant difference between both groups. P-value was 0.844

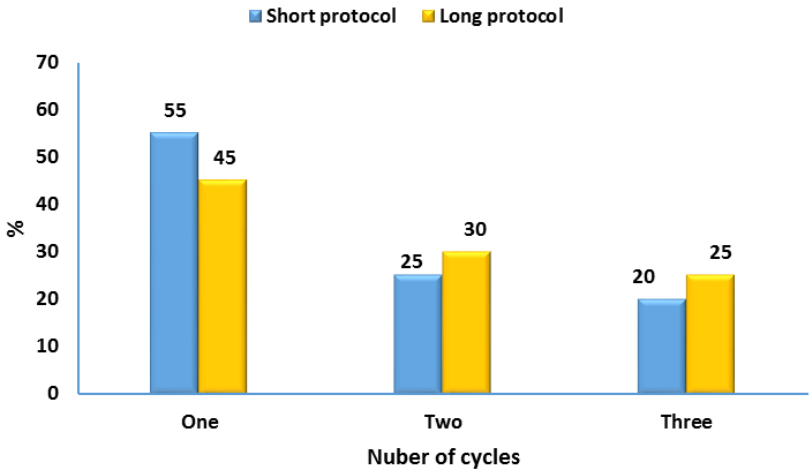

Figure (5) Number of cycles in both groups

Table (6) Ultrasound criteria of PCOs in both groups

		Short protocol(n = 20)	Long protocol (n = 20)	P value
US criteria of PCOs	n (%)	15 (75.0)	13 (65.0)	0.490

Chi-square test was used

Ultrasound criteria of PCOs showed a non-statistically significant difference between both groups. P-value was 0.490

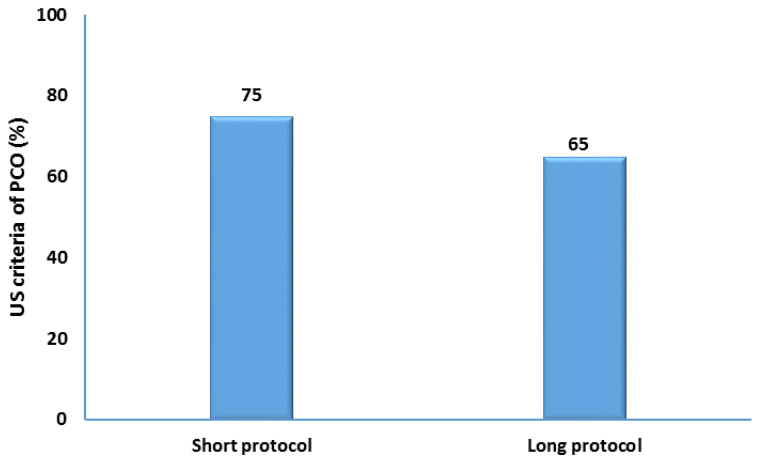

Figure (6) Ultrasound criteria of PCOs in both groups

Table (7) Hyperandrogenism in both groups

		Short protocol(n = 20)	Longprotocol (n= 20)	P value
Hyperandrogenism	n (%)	12 (60.0)	10 (50.0)	0.525

Chi-square test was used

Hyperandrogenism showed a non-statistically significant difference between both groups. P-value was 0.525

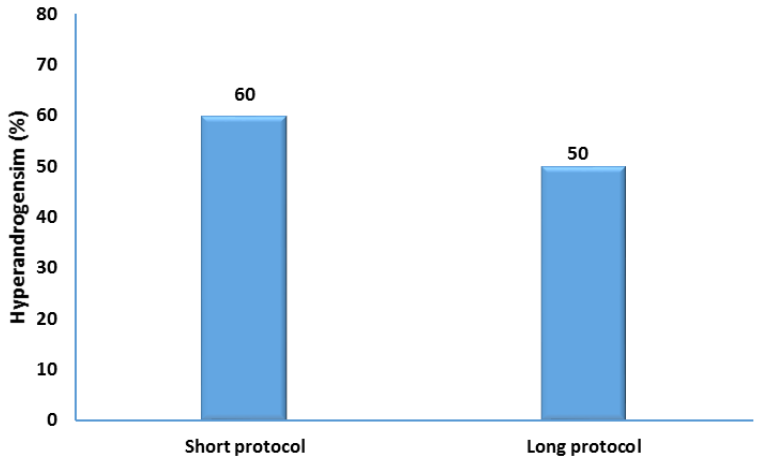

Figure (7) Hyperandrogenism in both groups

Table (8) Oligo-ovulation in both groups

		Short protocol (n = 20)	Long protocol (n = 20)	P value
Ovulation	Anovulation	9 (45.0)	7 (35.0)	0.519
	Oligo-ovulation	11 (55.0)	13 (65.0)	

Chi-square test was used

Ovulation status showed a non-statistically significant difference between both groups. P-value was 1.0

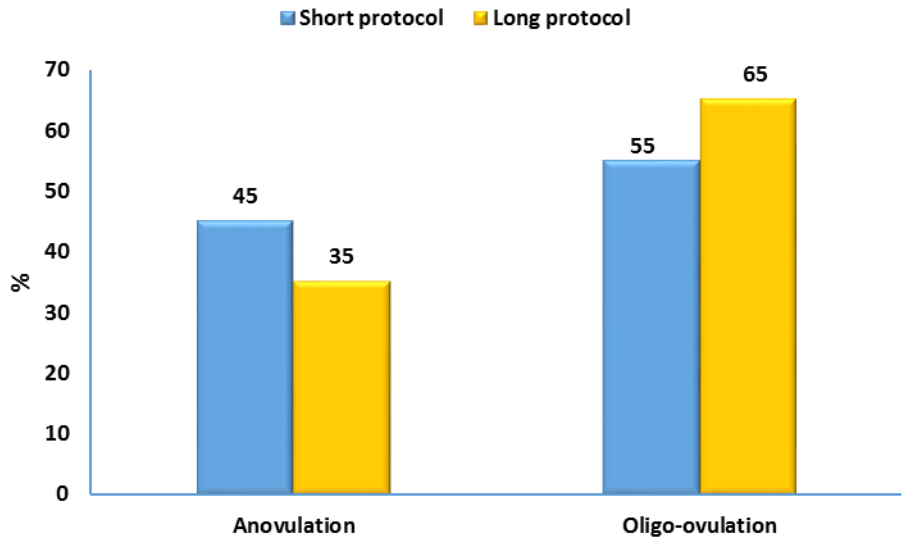

Figure (8) Ovulation in both groups

Table (9) Levels of FSH, LH, and testosterone in both groups

		Short protocol (n = 20)	**Long protocol (n = 20)**	**P value**
FSH	Mean ±SD	5.7 ±1.7	6.4 ±2.1	0.257
	Range	3.5 – 9	3.4 – 9.5	
LH	Mean ±SD	10.6 ±4.4	11.1 ±4	0.667
	Range	4.5 – 19	6 - 19	
Testosterone (nmol/l)	Mean ±SD	2.7 ±0.7	2.7 ±0.7	0.946
	Range	1.5 – 3.8	1.5 – 3.7	

Independent t-test was used

Levels of FSH, LH, and testosterone showed non-statistically significant differences between both groups. P values were 0.257, 0.667, and 0.946, respectively.

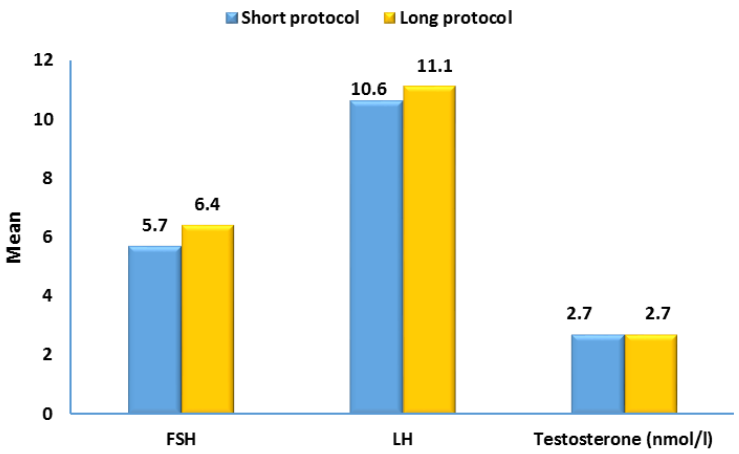

Figure (9) Levels of FSH, LH, and testosterone in both groups

Table (10) Total number of follicles in both groups

		Short protocol (n = 20)	Long protocol (n = 20)	P value
Total N of follicles	Mean ±SD	3 ±1	4 ±1	<0.001
	Range	2 - 3	3 -5	

Independent t-test was used

The mean total number of follicles was precycle of ovulation induction significantly higher in the long protocol group (4) than the short protocol group (3). P-value was <0.001.

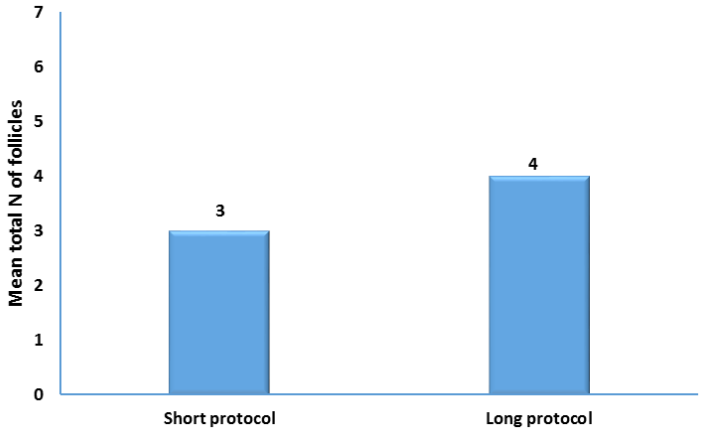

Figure (10) Total number of follicles in both groups

Table (11) Dominant follicle size in both groups

		Short protocol (n = 20)	Long protocol (n = 20)	P value
Dominant follicle size (mm)	Mean ±SD	17 ±4	18 ±4	0.476
	Range	12 – 25	12 - 25	

Independent t-test was used

Mean dominant follicle size was larger in the long protocol group (18 mm) than the short protocol group (17 mm), with no statistical significance. P-value was 0.476.

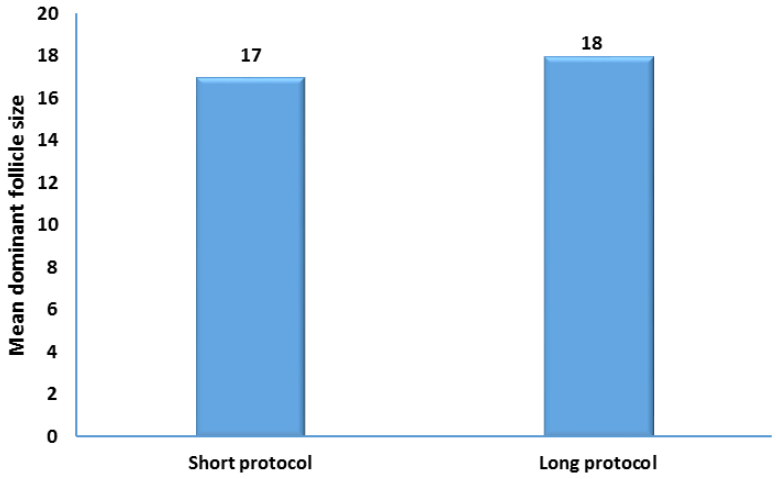

Figure (11) Dominant follicle size in both groups

Table (12) Dominant follicle size categories in both groups

			Short protocol (n = 20)	Long protocol (n = 20)	P value
Dominant follicle size	<14	n (%)	8 (40.0)	6 (30.0)	0.766
	14 to 17	n (%)	2 (10.0)	3 (15.0)	
	≥ 18	n (%)	10 (50.0)	11 (55.0)	

Chi-square test was used

Follicle size <14 mm was higher in short protocol (40.0%) than long protocol (30.0%), follicle size of 14 to 17mm was higher in long protocol (15.0%) than short protocol (10.0%), and follicle size of ≥ 18 mm was higher in long protocol (55.0%) than short protocol (50.0%), with no statistical significance (P value = 0.766)

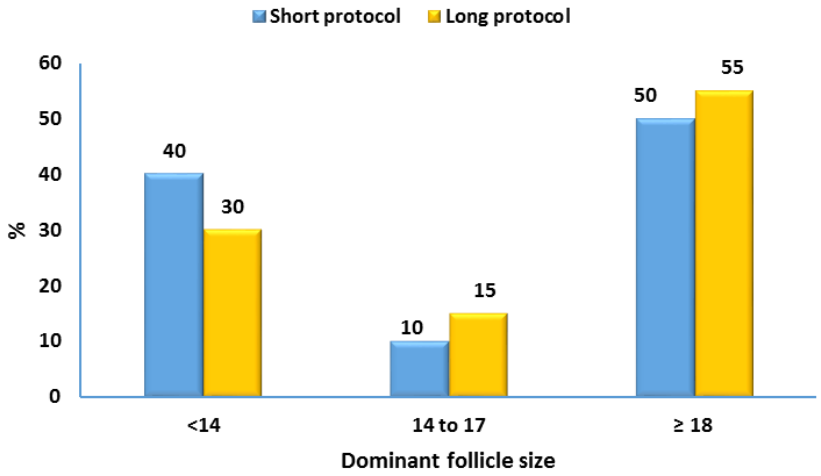

Figure (12) Dominant follicle size categories in both groups

Table (13) Endometrial thickness at the time of HCG administration size in both groups

		Short protocol (n = 20)	**Long protocol (n = 20)**	**P value**
Endometrial thickness at time of HCG (mm)	Mean ±SD	8 ±2	8 ±2	0.713
	Range	5 - 11	5 – 11	

Independent t-test was used

Endometrial thickness at the time of HCG administration showed a non-statistically significant difference between both groups. P-value was 0.713

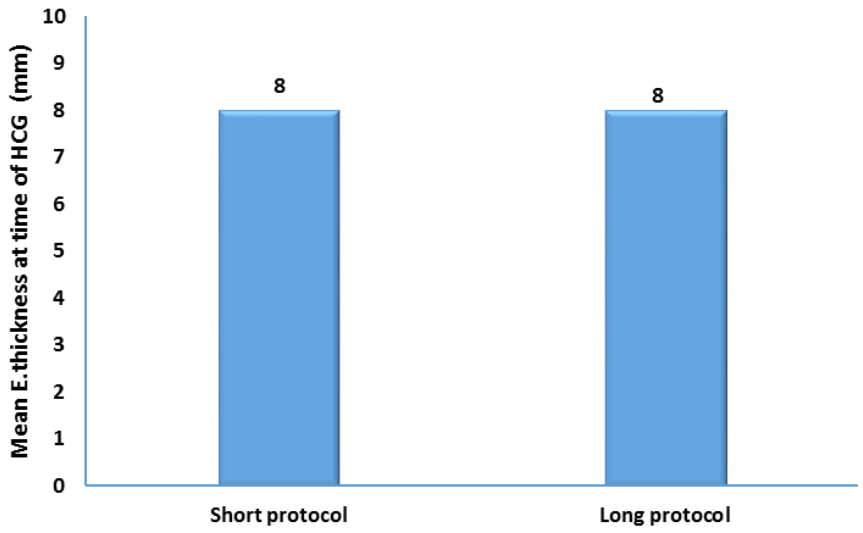

Figure (13) Endometrial thickness at time of HCG administration size in both groups

Table (14) Occurrence of ovulation in both groups

		Short protocol(n = 20)	Long protocol(n= 20)	P value
Ovulation occurrence	n (%)	12 (60.0)	13 (65.0)	0.744

Chi-square test was used

Ovulation occurrence was higher in the long protocol group (65.0%) than the short protocol group (60.0%), with no statistical significance. P-value was 0.744

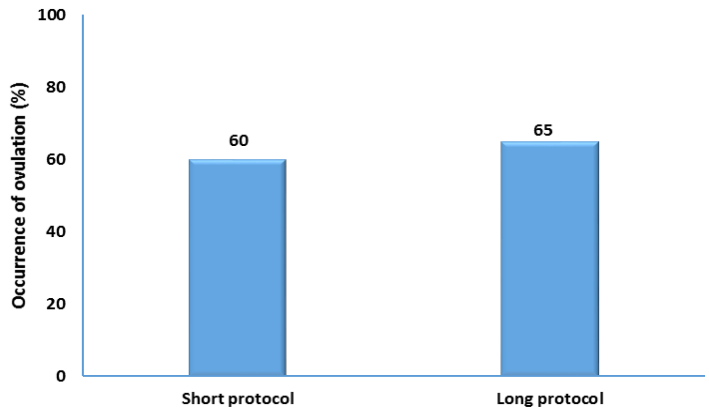

Figure (14) Occurrence of ovulation in both groups

Table (15) Occurrence of pregnancy & miscarriage in both groups

		Short protocol(n= 20)	Long protocol (n = 20)	P value
Occurrence of pregnancy	n (%)	3 (15.0)	5 (25.0)	0.695
Miscarriage*	n (%)	0 (0.0)	1 (20.0)	-

Fisher's exact test was used

The occurrence of pregnancy was higher in the long protocol group (25.0%) than the short protocol group (15.0%), with no statistical significance. P-value was 0.695

* Percentage was calculated based on total pregnancies

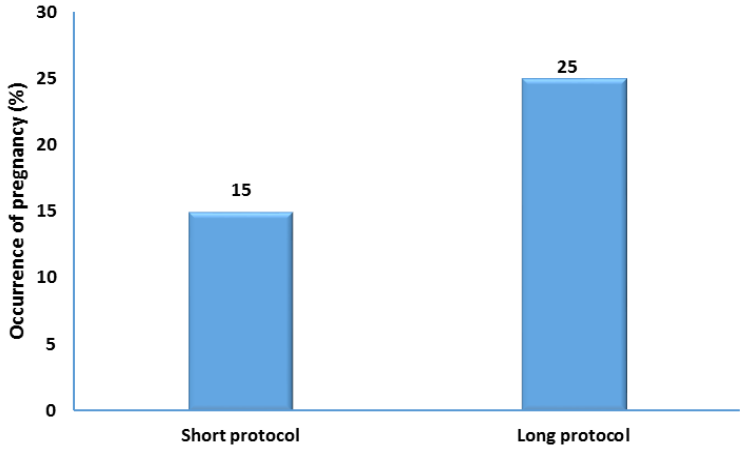

Figure (15) Occurrence of pregnancy in both groups

STATISTICAL METHODS

Data management and statistical analysis were done using SPSS vs.25. (IBM, Armonk, New York, United States). Before analysis, the normality of numerical data was assessed using the Shapiro-Wilk test and data visualization methods. Numerical data were summarized as means and standard deviations. Categorical data were summarized as numbers and percentages. Comparisons between both groups were done using independent t-test for numerical data. Categorical data were compared using Chi-square or Fisher's exact test if appropriate. All P values were two-sided. P values less than 0.05 were considered significant.

DISCUSSION

PCOS is a common endocrine disorder, It is associated with chronic anovulation, and causes infertility in 4%–6% of women in the reproductive age group.Despite the wide acceptance of clomiphene citrate as afirst-line drug for ovulation induction in women with PCOS, a signifcant proportion of women do not respond to this treatment ***(Atay et al.,2006).***

Various managements were proposed for infertile women with PCOS ***(Zeng et al., 2016; Zhou et al., 2017; Wang et al., 2017).*** However, the optimal management option has not been addressed satisfied. Although multiple treatments including weight reduction, clomiphene citrate, metformin, gonadotropins, and ovary cauterization have been reported to treat such condition, the efficacy still has insufficient evidence to support ***(Rouzi et al., 2006; Jirege et al., 2010).***

Previous study had suggested that letrozole, a third-generation aromatase inhibitor, can be used for ovulation induction, and it is associated with a higher chance of uncomplicated pregnancy and a lower risk of multiple pregnancy than clomiphene citrate ***(Ekerhovd ,2009).***

There have been several mechanisms proposed for AI success. It was put forward that it would be possible to block estrogenic negative feedback, without depletion of estrogen receptors by administration of an AI in the early part of the menstrual cycle. Inhibition of aromatization would block estrogen production from all sources and would release the hypothalamic-pituitary axis from estrogenic negative feedback**(Rajan et**

al., 2017). The resultant increase in gonadotropin secretion would stimulate growth of ovarian follicles. Withdrawal of estrogen centrally also increases activins, which are produced by a wide variety of tissues, including the pituitary gland **(Roberts et al.,1989)**, and stimulate synthesis of FSH **(Badawy et al., 2009)**.Because AIs do not deplete estrogen receptors, normal central feedback mechanisms remain intact. As the dominant follicle grows and estrogen levels rise, normal negative feedback occurs centrally, resulting in suppression of FSH and atresia of the smaller growing follicles. A single dominant follicle, and mono-ovulation, should occur in most cases. This might be of advantage in cases of PCOS, thereby avoiding the risk of ovarian hyperstimulation syndrome. Nonetheless, this monofollicular growth might come at the cost of lower ovulation and pregnancy rates. Therefore, letrozole could be used in conjunction with FSH injections to increase the number of preovulatory follicles that develop and improve the outcome of treatment. Addition of FSH, however, will remarkably increase the cost of therapy and recommence the risk of ovarian hyperstimulation syndrome. In the present study, we tested a novel protocol of extended letrozole therapy to keep the in vivo production of FSH continuous for a longer duration. This allowed a greater cohort of small follicles, recruited in the early part of the cycle, to reach maturity (R18 mm). Pregnancy rate was significantly greater in the extended letrozole group. The rationale behind using this extended regimen was based on our understanding of the physiology of follicular growth. Decremented follicular-phase FSH levels (referred to as the FSH window) appear to be crucial for selection of a single dominant follicle from the recruited cohort **(Welt et al., 1997).** As FSH levels fall, all but the dominant follicle (with its increased sensitivity to FSH) lose the stimulus to further development and become atretic (**Ramezanzadeh**

et al., 2011). The concept of extending the FSH window by administering exogenous FSH or extending the duration of letrozole therapy in the midfollicular phase would maintain FSH levels above the threshold, allowing multifollicular development to occur. There were no extra costs for the extended therapy, because we used the same ten tablets over 10 days rather than 5 days. This new 10-day letrozole protocol proved to be more effective than the standard 5-day protocol, with more mature follicles and more pregnancies. The extended therapy caused no increase in the number of twin pregnancies than usual or in ovarian hyperstimulation syndrome(**Franik et al., 2018)**.

The present study was carried out at Benha University Hospital out-patient clinic of obstetric &gynecology to compare between short(5mg daily for 5 days) vs. extended course (2.5mg daily for 10 days) of letrozole therapy for ovulation induction in women with polycystic ovary syndrome.

This prospective comparative study included 40 infertile women who were diagnosed as having PCOS. The included women in this study were divided into two groups. Group I was induced to ovulate by short course. Group II was induced to ovulate by extended course.

In the present study, the results were as following:

- Age distribution among group I (short letrozole group) was 22y to 35y (29 ± 4) and among group II (long letrozole group) was 25y to 35y (31 ± 3).

- Number of Oligo-ovulating patients was greater in the long letrozole group compared to short letrozole group (65% vs 55%). respectively.

- Number of patients with Hyper-androgenism among groupI (short letrozole) was 60% and group II (long letrozole)was 60%.

- Percentage of patients with positive US data was 75% in short letrozole group and 75% in long letrozole group.

- The mean value ± SD for total number of follicles after stimulation was significantly greater in the long letrozole group (4 ± 1) vs. (3 ±1) in short letrozole group; P=<0.001).

This result come in agree with the result of study done by EL-Aziz et al.,(2019)that was done to evaluate the efficacy -on fertility outcome- by short term letrozole versus extended letrozole regimen in clomiphene citrate resistant PCOS women ,conducted on 60 women with clomiphene resistant PCOS, Group 1 (30 patients) received short letrozole regimen, group 2 (30 patients) received long letrozole regimen

Their results -in this point –were that the total number of follicles during stimulation was significantly greater in the long letrozole group (4+/- .91vs 6.48+/- .68)

This result also come in agree with the result of study done by ***Yadav, P et al.,(2018)***that was done to evaluate the efficacy -on fertility outcome- by short term letrozole versus extended letrozole regimen in clomiphene citrate resistant PCOS women ,conducted on 105 women with clomiphene resistant PCOS, Group 1 (55 patients) received short letrozole regimen, group 2 (50 patients) received long letrozole regimen

Their results -in this point –were that the total number of follicles during stimulation was significantly greater in the long letrozole group (6.8+/-.3 vs 3.5+/- .5)

These results were consistent to the study conducted by **Badawy and Alaa Mosbah** in which the pregnancy rate was 12.4% and the miscarriage rate was 18.4 % in the short letrozole group while it was 17.4% and 17.9% in the long letrozole group respectively

These results also come agree with the results of study done by ***Badawy A. et al., (2009)*** that was done to evaluate the outcome of long letrozole therapy for induction of ovulation in patients with clomiphene-resistant polycystic ovary syndrome (PCOS) on 218 patients with clomiphene- resistant PCOS and patients were randomly allocated to treatment with either long letrozole therapy (n = 108) or short letrozole therapy (n = 110). Their results in this point were the total numbers of follicles during stimulation was significantly greater in the long letrozole group (6.7 +/- 0.3 vs. 3.9 +/- 0.4).

Another study was done by ***Ramezanzadeh et al., (2010)*** to compare the effects of either a 5 or 7.5 mg daily dose of Letrozole in PCOS women undergoing ovulation induction. Sixty-seven PCOS patients with infertility were randomly divided into two groups and treated with either 5 mg/day (30 patients, group 1) or 7.5 mg/day (37 patients, group 2) Letrozole, for 5 days starting from day 3 of the menstrual cycle. The result showed no significant difference in the number of intermediate (0.83 ± 0.75 vs 0.62 ± 0.76) and mature follicles (1.13 ± 1.11 vs 1.22 ± 1.03) on days 12–14 between group 1 and 2, respectively.

- In the present study, the mean size (mm) of biggest follicles was greater (18 ± 4) in the long letrozole group when compared to short letrozole group (17± 4), without statistical differences (P=0.476).

- In the present study, the number of patients with follicles measuring ≥18 mm and between 14-17mm was greater in the long letrozole group (P=0.766). These results came in comparable with the results of ***Badawy A. et al., (2009)*** and ***El-Aziz. Et al., (2019).***

- In the present study, The mean of endometrial thickness at the time of hCG administration ± SD in group I was 8 ± 2 mm and 8 ± 2 among group II. There was no significant difference in the endometrial thickness at the time of hCG administration between the two groups (P=0.713).

That came agree with ***Badawy A. et al., (2009)*** and ***Ramezanzadeh et al.,(2010)***and ***El-Aziz et al., (2019).***

- In the present study, percentage of ovulation occured after treatment , group II (long letrozole group) was greater than Group I (short letrozole group) (65% vs 60% , respectively).

This result come in agree with ***El-Aziz et al.,(2019)*** The number of ovulating patients was greater in the long letrozole group (63.3% vs.56.7%), but without statistical differences.

This result also come in agree with ***Badawy A. et al., (2009)*** The number of ovulating patients was greater in the long letrozole group (65.7% vs. 61.8%), but without statistical differences.

This came in contrast with ***Ramezanzadeh et al., (2010)*** (Ovulation occurred in 90 and 89.2% of patients in group 1 and 2).

-The present study showed that pregnancy occurred in 3 out of 20 patients in the short letrozole group (15%) and in 5 out of 20 patients (25%) in the long letrozole group. pregnancies was in favor of long group and P-value was 0.695(not significant)

These results not comparable with ***Badawy A. et al., (2009)*** as their study showed that pregnancy occurred in 28 of 225 cycles in the short group (12.4%) and 38 of 219 cycles (17.4%) in the long letrozole group, and the difference was statistically significant.

In contrast to these result, ***Ramezanzadeh et al., (2010)*** showed that the pregnancy rate was 25.8%in group 1 and 21.2% in group 2 without significant difference.

Depending on results of the present study, we conclude that inspite of the non statistically significant difference between both regimens the long letrozole therapy (2.5mg for 10 days) can produce more and bigger mature follicles and better endometrial thickness and subsequently more pregnancies than the short letrozole therapy (5mg for 5 days) and so, the long letrozole therapy (2.5 mg for 10 days) should take the superiority of ovulation induction in PCOS patients.

SUMMARY & CONCLUSION

Approximately 8-12% of women in general population have PCOS syndrome but it is the cause in about 30% of women with infertility.

Clomiphene citrate (**CC**) is the most commonly used oral agent for ovulation induction in this group, but there are some drawbacks with the use of it as it causes long lasting estrogen receptor depletion which have an adverse effect on the cervical mucus and endometrium in 15– 50% of patients causing higher incidence of miscarriage. In addition to increased risk of multiple pregnancies and ovarian hyper stimulation syndrome (OHSS), also, clomiphene resistance occurs in 15–20% of patients and is not predictable before beginning the treatment.

Recently, the new aromatase inhibitor, letrozole has been used for induction of ovulation. Letrozole reversibly inhibits the enzyme responsible for estrogen biosynthesis. By decreasing the estrogen levels in the body, it may release the hypothalamus and/or pituitary from the negative feed back of estrogen on the release of gonadotropins. This will result in an increase in end. However, Letrozole may have another peripheral mechanism of action directly in the ovaries. Letrozole is eliminated from the body in a few days after last administration (in contrast to CC which may last up to few months). Also, it does not have a direct antiestrogen action by itself as in CC. So there should be no unwanted peripheral antiestrogen effects on the endometrium, and the cervix. Letrozole (Femara®, Novartis) is available in 2.5 & 5 mg tablets. It is an approved drug that was developed to inhibit the estrogen production in postmenopausal women with breast cancer. Therefore, it has been tested and tolerated very well when administered continuously

for several months.ogenous FSH and LH, which stimulate the development of ovarian follicles.

Letrozole is associated with thicker endometrium favorable cervical mucous and better uterine blood flow

The present study was done to compare the efficacy of Short course (5mg daily for 5 days) Vs extended course (2.5mg daily for 10 days) of letrozole therapy for ovulation induction in women with polycystic ovary syndrome.

The study included 40 patients who are attending Benha Hospital and previously diagnosed as having polycystic ovary syndrome. Patients were divided randomly into 2 treatment groups, short letrozole therapy group (20 patients) and long letrozole therapy group (20 patients).

Patients of short letrozole therapy group received 5mg of letrozole daily starting from day 1 menstrual bleeding for 5 days. Patients of long letrozole therapy group received 2.5mg of letrozole daily starting from day 1 of menstrual bleeding for 10 days.

All patients of both groups monitored by trans-vaginal ultrasound for the mean follicular volume and thickness of the endometrium on day 10 of the cycles.

hCG injection (5,000 IU IM) given when at least one follicle measured ≥ 18mm. Patients advised for intercourse 24- 36h after HCG injection.

Serum hCG determined 2 weeks after hCG injection in the absence of menstruation for diagnosis of pregnancy followed by trans- vaginal ultrasound for demonstration of the gestational sac.

The study results showed that total number of follicles during stimulation was significantly greater in the long letrozole group (4 ± 1) vs. (3 ± 1; p=<0.001) in short letrozole group. The mean of biggest follicles size (mm) was greater (18± 4) in the long letrozole group when compared to short letrozole group (17± 4), without statistical differences (p=0.476). The number of patients with follicles measuring >18 mm was greater (55%) in the long letrozole group without statistical significance (p=0.766). The mean of endometrial thickness at the time of HCG administration was (8± 2) in the long letrozole group similar to short letrozole group (8 ± 2) without significant difference (p=0.713). The pregnancy was greater (25%) in the long letrozole group when compared to short letrozole group (15%), with no statistical differences (p=0.695).

CONCLUSION

The long letrozole therapy (2.5mg for 10 days) can produce more mature follicles and subsequently more pregnancies than the short letrozole therapy (5mg for 5 days).

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مقدمة

تمثل متلازمة المبيض المتعدد الكيسات حوالي ٨٠ ٪ من النساء المصابات بالعقم. هناك عوامل مختلفة تؤثر على وظيفة المبيض وتتأثر الخصوبة سلبًا بسبب زيادة الوزن لدى الفرد ودرجة فرط الأندروجينية وارتفاع تركيز الدم منالهرمون المنشط للجسم الابيض . متلازمة المبيض المتعدد الكيسات هي السبب الأكثر شيوعًا لقلة الطمث وانقطاعه ، مما يؤثر على حوالي ٤-٨٪ من النساء في جميع أنحاء العالم في سنواتهن الخصبة.

تعد متلازمة المبيض المتعدد الكيسات واحدة من أكثر أسباب العقم الإباضي شيوعًا ، حيث تصيب ٨-١٣٪ من النساء في سن الإنجاب. إنه إلى حد بعيد السبب الأكثر شيوعًا للعقم المفرط الإندروجين ، وقد تم وصفه قبل أكثر من نصف قرن ، ولا يزال السبب الأساسي لهذا الاضطراب غير مؤكد. تعود الأعراض الكلاسيكية للمرض إلى زيادة إنتاج أندروجين المبيض والإباضة المزمنة. هناك العديد من المعايير السريرية والمخبرية مثل السمنة ، قلة الطمث ، الشعرانية وحب الشباب. أيضا ، قد يكون هناك زيادة هرمون اللوتين لهرمون المنشط للجسم الابيض بالنسبه لهرمون المنشط لتكوين الحويصلات ، وكذلك انخفاض معدل التبويض.

اروماتيز هو بروتين السيتوكروم و P-450الذي يحتوي على مركب إنزيم (منتج الجين CYP19) الذي يحفز خطوة الحد من معدل في إنتاج هرمون الاستروجين وهو تحويل هرمون أندروستينيديون وهرمون التستوستيرون عبر ثلاث خطوات هيدروكسي إلى استرون

نشاط أروماتيز موجود في العديد من الأنسجة مثل المبيضين والأنسجة الدهنية والعضلات والكبد وأنسجة الثدي وأورام الثدي الخبيثة. في النساء قبل انقطاع الطمث ، يتم إنتاج الإستروجين في المقام الأول في المبيضين ، الجسم الأصفر ، والمشيمة ، على الرغم من أن كمية صغيرة ولكنها مهمة من الإستروجين يمكن أن تنتجها الأعضاء غير النانوية ، مثل الكبد والقلب والجلد والدماغ .

تم اقتراح مثبطات أروماتيز كعلاج بديل لعلاج عقار كلوميفين سيتراتحيث أن التناقض بين الإباضة ومعدل الحمل معكلوميفين سيتراتيعزى إلى عمله المضاد للإستروجين ونضوب مستقبلات الإستروجين. تثبيط إنزيم أروماتيز يقلل من أرومة الأندروجينات إلى هرمون الاستروجين الذي بدوره يحرر المحور تحت الغدة النخامية من ردود الفعل السلبية للإستروجين. هناك تقارير عن معدلات حمل جيدة مع انخفاض حالات الحمل المتعدد

مثبطات الأروماتيز هي فئة أحدث من الأدوية التي تم إدخالها لتحريض الإباضة في عام ٢٠٠١ على مدى السنوات العشر الماضية ، تم جمع بيانات من العديد من التجارب السريرية ، وهناك أدلة على أن ليتروزول قد يكون فعالًا مثل كلوميفين سيترات، لكن بيانات النتائج تختلف. تشبه مثبطات الأروماتيز مثلكلوميفين سيتراتحيث يتم اخذه عن طريق الفم ، ولكن نظرًا لقصر فترة نصف العمر للتخلص منه حوالي ٤٨ ساعة ، فان اثاره الجانبيه أقل على الأنسجة المستهدفة للإستروجين مثل بطانة الرحم وعنق الرحم مقارنةً بكلوميفين سيترات

انواع مثبطات الاروماتيز :تمنع كل العناصر الفعاله بقوه تخليق هرمون الاستروجين وقد تنقسم الي مثبطات ستيرويديه (من النوع الاول) ومن النوع الثاني من النوع غير الستيرويديه ،تتفاعل انزيمات الاروماتيز

النوع الثاني من مثبطات الاروماتيز الغير ستيرويديه تقوم بوظيفتها من خلال ربطها بمتلازمه انزيم السيتوكروم P-450

ف حين ان مثبطات الاروماتيز الستيرويديه ترتبط تساهميا وبلارجعه فيه بالانزيمات الاستيرويديه

يعد كل من الانسترازول والليتروزول من الجيل الثالث للمثبطات الاروماتيزيه ومتاحين للاستخدام السريري لعلاج سرطان الثدي بعد انقطاع الطمث، وهما عباره عن مثبطات اروماتيزميه قابلا للانعكاس والتنافس ، وهما شديد الفعاليه و الانتقائيه

علي الرغم من ان العلاجات المتعدده بما فيها عقار كلوميفين سترات والجونادوتروبين وحفر المبيض بالمنظار وخفض الوزن والميتفورمين قد تم الابلاغ عنها لعلاج مثل هذه الحالات ،لاتزال الفعاليه لاتملك ادله كافيه لدعمها

لاتزال الجرعه المثلي ومده اعطاء الليتروزول للتخثر عند مرضى متلازمه تكيس المبايض غير واضحه

الهدف من الدراسه:

هو تقييم فعالية العلاج باليتروزول قصير المدى (٥ ملغ يوميًا لمدة ٥ أيام) مقابل دورة ممتدة منه (طويل المدى) (٢,٥ ملغ يوميًا لمدة ١٠ أيام) من علاج ليتروزول لتحريض الإباضة عند النساء المصابات بمتلازمة المبيض المتعدد الكيسات

الهدف من العمل:

في هذه الدراسه تم تقييم فعالية العلاج باليتروزول قصير المدى (٥ ملغ يوميًا لمدة ٥ أيام) مقابل دورة ممتدة منه (طويل المدى)(٢,٥ ملغ يوميًا لمدة ١٠ أيام) من علاج ليتروزول لتحريض الإباضة عند النساء المصابات بمتلازمة المبيض المتعدد الكيسات

المواضيع وطرق

- ✓ تم إجراء هذه الدراسة على (٤٠) مريضه بقسم التوليد وأمراض النساء في مستشفيات جامعة بنها كدراسة مقارنة عشوائية مستقبلية
- ✓ تم اعتماد بروتوكول الدراسة من قبل اللجنة الأخلاقية لمستشفيات جامعة بنها بجامعة بنها.
- ✓ تم الحصول على تركيز مكتوب مستنير من جميع المرضى المشاركين في هذه الدراسة بعد شرح تدابير الدراسة بالتفصيل.

حجم العينة:

حساب حجم العينة ، باستخدام حزمة الكمبيوتر StatCalc 3.02 (برنامج Acastat، Leesburg، VA).

تم تشخيص جميع المرضى على أنهم يعانون من التبويض بسبب متلازمة المبيض المتعدد الكيسات. يعتمد تشخيص متلازمة تكيس المبايض على إجماع عام ٢٠٠٣ المنقح على معايير التشخيص والمخاطر الصحية طويلة الأجل المتعلقة بمتلازمة تكيس المبايض.

تم تخصيص المرضى بشكل عشوائي باستخدام جدول عشوائي تم إنشاؤه بواسطة الكمبيوتر في مجموعتين للعلاج

- **المجموعة الأولى**: مجموعة العلاج باليتروزول القصيرة (المرضى).
- **المجموعة الثانية**: مجموعة العلاج طويلة ليتروزول (المرضى).

معايير الاشتمال:

١-العمر: ١٨-٣٥ سنة.

٢- العقم ≤ ٢ سنة

٣- تشخيص متلازمة تكيس المبايض وفقًا لمعايير روتردام.

٤-غير مدمنة أو مدمنة على أي مادة.

٥- متزوجة

معايير الاستبعاد:

١- تاريخ جراحة الحوض

٢ - النساء المصابات بعقم سببه غير الإباضة.

٣- عامل ذكري هو سبب العقم.

٤. مدمنة على الكحول.

لجميع المرضى المشاركين ما يلي:

I- **التاريخ الكامل**:

- ✓ التاريخ الشخصي
- ✓ تاريخ المرض الحالي
- ✓ تاريخ الحيض
- ✓ التاريخ الجنسي
- ✓ تاريخ الماضي
- ✓ تاريخ العائلة

الفحص الثاني الكامل:

- الفحص العام
- فحص البطن
- فحص الحوض

III-**التحاليل والفحوصات** :

عام: (صورة دم كامله ، تحليل البول ، سكر الدم العشوائي)

خاص :البرولاكتين وهرمون منشط للجسم الاصفر وهرمون منشط لتكوين الحويصلات

أساليب الدراسه:

اعطاء المرضى من مجموعة العلاج باليتروزول القصير (المرضى) على ٥ ملغ من اليتروزول (حبتان من اليتروزول ٢,٥ ملغ ، شركة ساندوس ، أستراليا) يوميًا ابتداءً من اليوم الأول من تلقائية عفوية (أو المستحثة بالبروجسترون ، باستخدام علامة استروجينميدروكسي

بروجيسترون ، علامة تبويب واحدة يوميا لمدة ٥ أيام) نزيف الحيض لمدة ٥ أيام (ما يصل إلى ٣ دورات)

اعطاء المرضى الذين يعانون من مجموعة طويلة من العلاج باليتروزول على ٢,٥ ملغ من اليتروزول (علامة واحدة من اليتروزول ٢,٥ ملغ ، شركةساندوس للمستحضرات الصيدلانية ، أستراليا) يوميًا بدءًا من اليوم الأول من نزيف الحيض التلقائي (أو المستحث بالبروجسترون) لمدة ١٠ أيام (ما يصل إلى ٣ دورات.)

سيتم رصد جميع المرضى من كلتا المجموعتين عن طريق الموجات فوق الصوتية عبر المهبل لمعرفة الحجم الجريبي وسماكة بطانة الرحم في اليوم ١٠ من الدورات .

تم إعطاء حقن هرمون الحمل ٥٠٠٠(وحدة دولية فعالة) عند قياس بصيلة واحدة على الأقل 18 ملم .

تم نصح المرضى بالجماع ٢٤-٣٦ ساعة بعد حقن هرمون الحمل

تم تحديد نسبه هرمون الحمل بعد أسبوعين من حقن الهرمون في حالة عدم وجود الحيض لتشخيص الحمل يليه الموجات فوق الصوتية عبر المهبل لإظهار كيس الحمل .

كانت مقاييس النتائج االاولية هي عدد من بصيلات النمو والناضجة

كانت مقاييس النتائج الثانوية هي حدوث الحمل والإجهاض.

وقد اظهرت النتائج ان متوسط عدد بصيلات النمو ف النساء اللاتي استخدمن علاج ليتروزول قصير المدي كان ٣ ومتوسط عدد بصيلات النمو الناضجه كان ١٧ والنساء اللاتي استخدمن علاج ليتروزول طويل المدي كان ٤،ومتوسط عدد البصيلات النمو الناضجه كان ١٨ .

عدد الحالات التي قد حدث معها الحمل في علاج ليتروزول قصير المدي كان ٣ وذلك بنسبه ١٥% وعدد الحالات التي قد حدث معها الحمل في علاج ليتروزول طويل المدي كان ٥ بنسبه ٢٥%.

عدد الحالات التي قد حدث لها اجهاض كانت صفر ف علاج ليتروزول قصير المدي وكانت واحد في علاج ليتروزول طويل المدي.

الاستنتاج :

استخدام ليتروزول بجرعه ٢,٥ مللغ لمده ١٠ ايام ينتج عدد اكبر وانضج من بصيلات النمو وبالتالي عدد حالات حمل اكثر بالنسبه لعلاج ليتروزول بجرعه ٥ مللغ لمده ٥ ايام.