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RESEARCH ARTICLE

ORAL OVULOGENS IN CURRENT SCENERIO

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Abstract

Objectives:- Oral ovulogens are the most commonly used intervention in a subfertile couple. A reproductive endocrinologist or infertility specialist commonly performs ovulation induction. Infertility affects up to 15% of couples in their reproductive years around the world. The overall prevalence of primary infertility in India is estimated to be between 3.9 and 16.8%, according to the World Health Organization. Infertility rates vary by state in India, ranging from 3.7 percent in Uttar Pradesh, Himachal Pradesh, and Maharashtra to 5% in Andhra Pradesh and 15% in Kashmir, and incidence differs by tribe and caste within the same region. Anovulation, polycystic ovarian syndrome (PCOS), thyroid disorders (both hyperactive and underactive thyroid glands can inhibit ovulation), and premature ovarian failure are the most common causes of infertility in females. Overall, the prevalence of anovulatory cycles ranged from 3.4 percent to 18.6 percent.Anovulatory infertility is caused by polycystic ovarian syndrome in 80 percent of patients. It's an endocrine and reproductive condition that affects 0.6-3.4 percent of infertile couples. Subclinical hypothyroidism (SCH), 0.2–4.5 percent for overt hypothyroidism (OH), 0.3–1 percent for hyperthyroidism, and 5–10 percent for thyroid autoimmunity are the most common thyroid disorders in women aged 20–45 years. Premature ovarian failure affects 1 to 5.5 percent of women. The most often used medications for ovulation induction are oral ovulogens like Clomiphene citrate, third generation aromatase inhibitors like letrozole and anastrozole, and selective oestrogen receptor modulators like tamoxifen. Trials have been undertaken in women with anovulatory PCOS to examine if clomiphene citrate and metformin benefit from one another. Metformin has been used as an adjuvant to treat polycystic ovarian syndrome for a long time (PCOS). Sitagliptin has recently been shown to improve ovarian cycles and ovulation in PCOS patients. Both have ovulation rates of 70-80% and a pregnancy rate of 20-25 percent per

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cycle. Dexamethasone is a fertility supplement that helps with raised DHEAS androgen levels and is a highly successful adjuvant to clomiphene citrate in women with PCOS.
Methods:- This systematic review comprises of articles from pubmed, cohrane, google scholar, medline.
Results:.- A total of 20 articles from 2016 to 2021 were included .Infertility causes modification at both endocrine and immune system at both cellular and tissue level.
Conclusion:- Clomiphene citrate plays an important role in mildly stimulating infertile patients because it has the property of preventing premature LH surges. Aromatase inhibitors such as letrozole and anastrozole have also had limited success in the use of IVF. Tamoxifen may be an option for clomiphene citrate in some patients who do not ovulate or become pregnant due to its beneficial effects on cervical mucus and endometrium. Recently, sitagliptin has been reported to improve the ovarian cycle and ovulation of PCOS. Dexamethasone is an additional drug for infertility and is beneficial for elevated DHEAS and androgen levels. This review describes the science behind anovulation and treatment guidelines for promoting follicle recruitment and ovulation using multiple oral ovulogens.

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Introduction:-

Infertility and its emotional burden have been known since ancient times. The World Health Organization defines infertility as a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse(1) .Primary infertility is infertility in a couple who have never had a child. Secondary infertility is failure to conceive following a previous pregnancy. Male infertility is responsible for 20–30% of infertility cases, while 20–35% are due to female infertility, and 25–40% are due to combined problems in both parts. In 10–20% of cases, no cause is found(2). Most common cause of infertility in females is anovulation, polycystic ovarian syndrome(PCOS),thyroid problems both overactive and underactive thyroid glands can prevent ovulation, premature ovarian failure .The prevalence of anovulatory cycles varied from 3.4% to 18.6% overall, with a range of 5.5% to 12.8% based on serum hormone concentrations and from 3.4% to 18.6% using urinary LH concentrations . Polycystic ovary syndrome represents 80% of anovulatory infertility cases(3). It is an endocrine and reproductive disorder with a prevalence in infertile couples about 0.6-3.4%. The prevalence of thyroid disorders in women aged 20–45 years in Europe varies between 5 and 7% for subclinical hypothyroidism (SCH), 0.2–4.5% for overt hypothyroidism (OH), 0.3–1% for hyperthyroidism and 5–10% for thyroid autoimmunity. Premature ovarian failure prevalence ranges from 1 to 5.5%. Unexplained infertility are inability to identify the subtle reproductive abnormalities, endocrine/genetic/immunological disorders, minimal/mild endometriosis, and compromised ovarian and natural fecundability that may be less than normal(4). Prognostic factors in unexplained infertility include maternal age, duration of infertility, and previous obstetric history. The prevalence of unexplained infertility ranges from 8% to 37%, of infertile couples.Since anovulation is the most common cause of infertility.According to world health organisation it is classified.

Who Classification Of Anovulation

CLASS 1-HYPOGONADOTROPIC HYPOGONADISM

Caused by any lesion affecting affecting pituitary and hypothalamus and affecting gonadotropin production.

These women have low or low-normal serum follicle-stimulating hormone (FSH) concentrations and low serum estradiol concentrations due to decreased hypothalamic secretion of gonadotropin-releasing hormone (GnRH) or pituitary unresponsiveness to GnRH.

CAUSES

-Idiopathic Hypogonadotropic Hypogonadism

-Kallmanns syndrome

-Functional hypothalamic dysfunction(excess weight loss ,anorexia nervosa,exercise ,stress,drugs,iatrogenic)

Pituitary tumor,pituitary infarct(eg sheehans syndrome)

WHO class 2: Normogonadotropic normogonadic ovarian dysfunction

It is far most commonest cause of anovulation and mostly caused by

-polycystic ovarian syndrome

These women may secrete normal amounts of gonadotropins and estrogens. However, FSH secretion during the follicular phase of the cycle is subnormal. This group includes women with polycystic ovary syndrome (PCOS). Some ovulate occasionally, especially those with oligomenorrhea.

CLASS 3-HYPERGONADOTROPIC HYPOGONADISM

The primary causes are premature ovarian failure (absence of ovarian follicles due to early menopause) and ovarian resistance (follicular form).

HYPERPROLACTEMIC ANOVULATION

These women are anovulatory because hyperprolactinemia inhibits gonadotropin and therefore estrogen secretion;
They may have regular anovulatory cycles, but most have oligomenorrhea or amenorrhea.

Chronic anovulation is probably the major cause of human infertility and is essentially associated with four distinct endocrine conditions; hyperprolactinemic anovulation, hypogonadotrophic anovulation, normogonadotrophic anovulation and hypergonadotrophic anovulation. Hyperprolactinaemia and microprolactinoma are frequent findings in young women and excessive prolactin secretion impairs ovarian function causing anovulatory subfertility. Dopaminergic treatment restores ovarian function and shrinks prolactinoma. In these patients restoration of fertility with prolactin lowering drugs does not increase the incidence of multiple pregnancies or early pregnancy loss(5). In the vast majority of hyperprolactinemic women pregnancy is safe and could be beneficial. Cabergoline is the most effective and tolerated of the antiprolactinemic drugs. Hypogonadotrophic anovulation is frequently associated with acute or chronic emotional stress and in this case the patient should be counselled. Explanation and reassurance are the first important management steps. The use of pulsatile gonadotrophin-releasing hormone is the best strategy to induce fertility. Patients with normogonadotrophic anovulation are likely to have polycystic ovary. The most cost effective profertility treatment is the administration of an anti-oestrogen such as clomiphene or tamoxifen. The second choice therapy for patients with normogonadotrophic anovulation is ovarian stimulation with human gonadotrophin preparations. Low dose modifications give pregnancy rates lower than that with the traditional high-dose step-up protocol and intensive monitoring is required, but multiple pregnancies are less frequent. No treatment is available to enable women with hypergonadotrophic anovulation to conceive. Fertility in these patients can be promoted only by an egg donation programme.

Diagnosis Of Anovulation

Diagnostic Hormonal Levels In Anovulatory Infertility

HYPOTHALAMIC:-	DECREASED FSH,LH,E2
HYPERPROLACTEMIA	**DECREASED FSH,LH,E2**
OVARIAN FAILURE/ MENOPAUSE	**INCREASED FSH,INCREASED LH, DECREASED E2**
MID CYCLE	**INCREASED FSH,LH,E2**
PCOS	**DECREASED FSH,INCREASED LH,E2**

After an initial workup to determine the cause of anovulation and going through the required lifestyle changes, the timing of ovulation induction plays a critical role in determining outcomes. Commonly, treatment is initiated in the luteal phase to minimize the consequences of flare effects, which is usually seen in the first few days of treatment. Optimal timing is determined from the diameter of preovulatory follicles, their ultrasonographic appearance, and circulating estradiol-17blevels during spontaneous or induced cycles. Premature or delayed induction is detrimental to the follicle and can lead to unfortunate outcomes and probable complications.

Treatment For Patients With Anovulation:-

DIAGNOSIS	**TREATME**
HYEPRPROLACTEMIC	Prolactin-lowering drugs; pulsatile GnRH; HMG
HYPOPROLACTEMIC	Counselling; pulsatile GnRH; HMG
NORMOGONADOTROPIC	Diet when necessary; anti-oestrogen; HMG-FSH
HYPERGONADOTROPIC	NONE

The aims of ovulation induction is to induce mono-follicular development and ovulation in anovulatory infertile women ,to overcome natural follicular selection process to increase the number of oocytes available for fertilization ,to restore normal fertility by generating normo-ovulatory cycles ,to mimic physiology and induce single dominant follicle selection and ovulation ,to augment ovulation in unexplained infertility and for controlled ovarian hyperstimulation (COH) in intrauterine insemination (IUI) and assisted reproductive treatment (ART).

Before recent advances in this field there were not many options available to overcome this affliction. Ovulation induction is known to be a pillar of infertility treatment .Ovulation induction is also widely used and benefit in cases of unexplained infertility, anovulation .

For over four decades, the first-line treatment for ovarian stimulation in unexplained infertility has been clomiphene citrate. Clomiphene is an effective and safely used oral drug, but is known to have relatively common anti-estrogenic endometrial and cervical mucus adverse effects that could decrease chances of pregnancy. In addition, there is a significant risk of multiple pregnancies with clomiphene citrate compared with natural cycles. These drawbacks are mainly a result of the extended anti-estrogenic effect of clomiphene as a result of its accumulation in

the body (clomiphene isomers have a half-life of several days up to few weeks) Because of these problems, Mitwally and Casper proposed the concept of using aromatase inhibitors as a new method of ovulation induction that could avoid many of the adverse effects of clomiphene . Over the last few years, several published studies, both controlled and non-controlled, compared clomiphene and treatment with aromatase inhibitors (AIs), either alone or in combination with gonadotropins, for ovarian stimulation for indications including unexplained infertility. These studies found AIs as effective as clomiphene in inducing ovulation, with the major advantage of absence of any anti-estrogenic adverse effects. Several other major advantages of AIs include the lower serum estrogen production per developing follicle resulting in more physiological estrogen levels around the time of ovulation and good pregnancy rates with a lower incidence of multiple pregnancy than with clomiphene .Such preliminary evidence suggested that AIs may replace clomiphene in the future because of similar efficacy with a reduced adverse effect profile. But other prospective studies concluded that letrozole and clomiphene have comparable effectiveness in ovulatory patients with unexplained infertility.

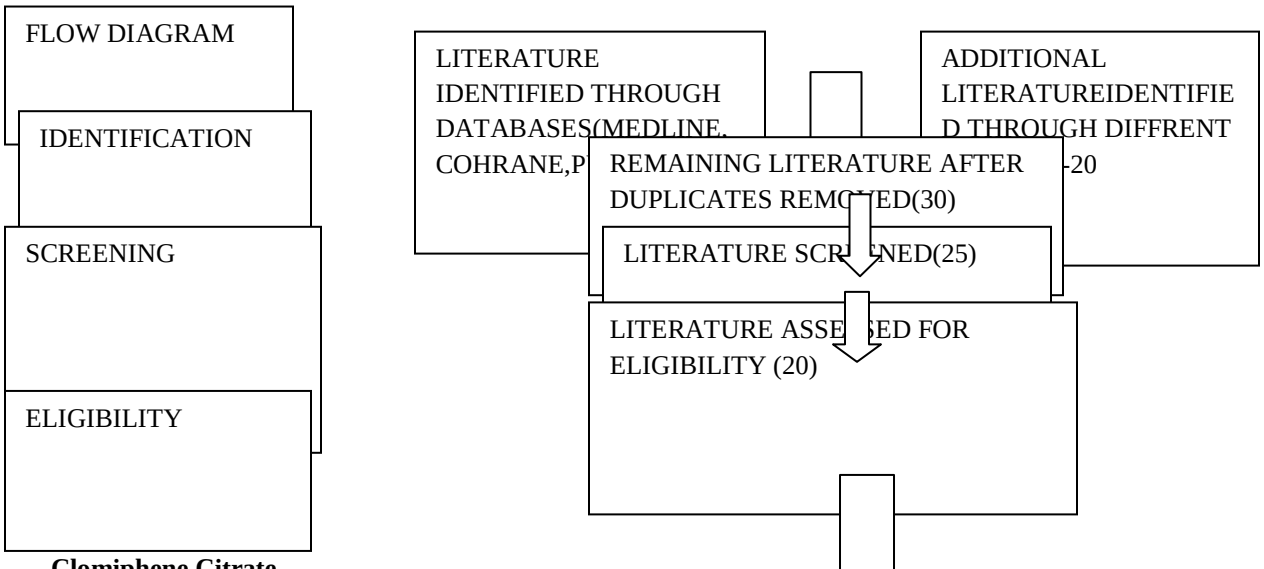
In addition to oral ovulogens drugs like metformin,sitagliptin ,dexamethasone added for more beneficial effect. Metformin is one of the longest established oral insulin sensitising agents. For decades its use was restricted to management of type 2 diabetes. However, in the past two decades, its properties as an insulin sensitising agent have been explored in relation to its applicability for women with PCOS. Recently sitagliptin, an oral drug used in T2DM, has been considered to improve the ovarian cycles and ovulation in PCOS patients (Paredes-Palma and López-Bayghen, 2014). Sitagliptin belongs to the family of dipeptidyl peptidase 4 (DPP4) inhibitors,it is expected to increase the level of growth factors such as GDF9 and BMP15 which affect the quality of oocytes and embryos in PCOS patients. on the other hand, Sitagliptin/metformin (sitaformin) has achieved more significant improvements in glycemic control than either component alone in patients with T2DM (Onge et al., 2012)(6). Addition of dexamethasone to CC enhances the number of mature follicles significantly but the ovulation and pregnancy rate is comparable to CC alone.

Materials And Methods:-

Data is collected from Cochrane,pubmed,medline,google scholar.

Results:-

A total of 50 articles from 2016-2021 were retrieved,duplicates were removed,30 articles were assessed for eligibility.Final sample of 20 articles were chosen.



Clomiphene Citrate

In situations of unexplained infertility, irregular menstrual cycles, and anovulation, ovulation induction is frequently used as the first-line treatment. The goal of ovulation induction is to increase the number of oocytes available for fertilisation by inducing mono-follicular development and ovulation in anovulatory infertile women and by

bypassing the natural follicular selection process. By producing normo-ovulatory cycles, normal fertility can be restored. To induce single dominant follicle selection and ovulation by mimicking physiology and for controlled ovarian hyperstimulation (COH) in intrauterine insemination (IUI) and assisted reproductive treatment in unexplained infertility (ART)

For more than 40 years,. Clomiphene is a selective estrogen receptor modulator (SERM)), has been the first-line treatment for patients with anovulation or oligomenorrhea. It selectively binds to estrogen receptors in the hypothalamus, ovary, endometrium, cervix and produces estrogenic and anti-estrogenic effects. It also acts as a partial estrogen agonist in the hypothalamus resulting in an estrogenic negative feedback inhibition, thus increasing gonadotropins. It increases the secretion of luteinizing hormone as well as follicle-stimulating hormone, thus increasing the production of serum levels of testosterone. It is also used as an adjuvant to alleviate pituitary suppression.

Inability of CC to induce ovulation is more likely in patients who are obese, insulin resistant and hyperandrogenic compared with those who do respond (Imani **et al.**, 1998)(7). This careful prospective study pinpointed a high free androgen index as the best predictor of non-response to CC. Although it is virtually impossible to predict who will respond to which dose of CC, if at all (Imani **et al.**, 2002)(8), body weight has been found to be an impeding factor. Overweight women respond less well (Polson **et al.**, 1989)(9) and the dose of CC needed to induce ovulation correlates with body weight (Lobo **et al.**, 1982)(10).

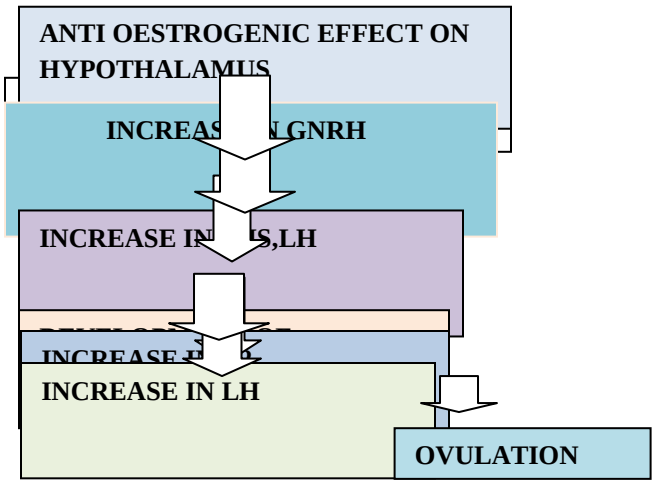
CC blocks the negative feedback mechanism which the eventually rising estradiol levels would normally invoke to reduce discharge of FSH. The continued flow of FSH encourages multiple follicle development which is relatively common. The risk of multiple gestation is therefore increased and is estimated at ~8–13% (Schenker **et al.**, 1981(11); Scialli **et al.**, 1986; Kousta **et al.**, 1997; Eijkmans **et al.**, 2003)(12). The vast majority of these are twin pregnancies, but the risk may be reduced considerably by ultrasound monitoring and withholding HCG, IUI or intercourse if more than two follicles >15 mm diameter are seen .

Clomiphene citrate is available as a 50 mg oral tablet:
Ovulation Induction: 50 mg daily (1 tablet) for five days. Treatment should start on day 5 of the menstrual cycle if there is spontaneous or induced bleeding. If the patient does not ovulate during the first cycle, the dose can be increased to 100 mg per day (two 50 mg tablets taken as a single daily dose) for five days during the second cycle. Treatment is repeatable for up to 6 cycles. A low dosage or treatment duration is explicitly recommended for patients with PCOS to prevent ovarian hyperstimulation syndrome.

Some reported adverse effects from the use of clomiphene are headache, dizziness, exacerbation of psychiatric illnesses, gynecomastia, testicular tumor, vasomotor flushing, gastrointestinal disturbance, and mastalgia. Other common adverse reactions are nausea, vomiting, ovarian enlargement, blurred vision, scintillating scotoma, abnormal uterine bleeding, pelvic pain, and hypertriglyceridemia.

Some serious reactions to the use of clomiphene are ovarian hyperstimulation, multiple pregnancies, thrombocytopenia, pancreatitis, risk of ovarian cancer after prolonged use, increased risk of malignant melanoma, severe visual disturbance, and hepatic damage.

Mechanism Of Action



In order to improve the outcome of treatment with CC, several adjuvants to CC treatment have been suggested. A correctly timed ovulation-triggering dose of HCG (5000–10000 IU) is only theoretically warranted when the reason for a non-ovulatory response is that the LH surge is delayed or absent despite the presence of a well developed follicle. Although the routine addition of HCG at mid-cycle seems to add little to the improvement of conception rates (Agarwal and Buyalos, 1995)(13), we have found it very useful, if given when an ultrasonically demonstrated leading follicle attains a diameter of 19–24 mm, for the timing of intercourse or IUI.

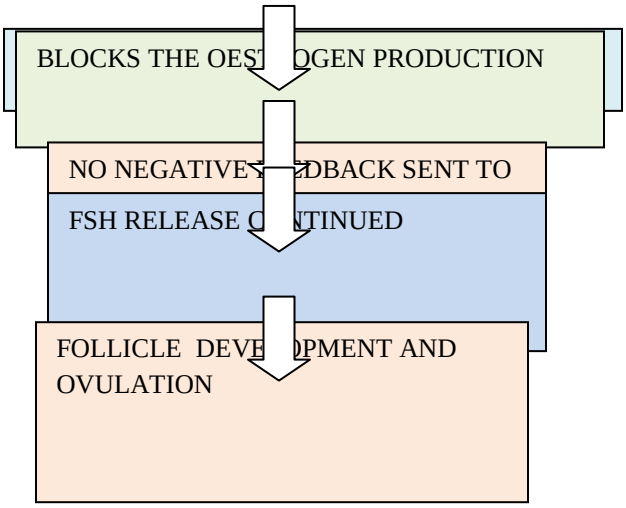
The addition of dexamethasone as an adjunct to CC therapy in a dose of 0.5 mg at bedtime is said to suppress adrenal androgen secretion and induce responsiveness to CC in previous non-responders, mostly hyperandrogenic women with PCOS and elevated concentrations of dehydroepiandrosterone sulphate (DHEAS) (Daly **et al.**, 1984)(14). However, glucocorticoid steroid therapy often induces side effects including increased appetite and weight gain, and should probably be reserved for women who have congenital adrenal hyperplasia as a cause for their anovulation.

Aromatase Inhibitors:-

Aromatase inhibitors (AIs), primarily the third-generation non-steroidal preparation known as letrozole, are another class of medication used for OI.The dose is related to body weight, age, and the indication for use in anovulation,.Aromatase inhibitors (AIs), mainly the third-generation non-steroidal preparation known as letrozole, are another class of medication used for OI. It was first approved for the treatment of estrogen-receptor-positive metastatic breast cancer in 2000, but it was later found to be helpful in patients with PCOS and those who were CC-resistant.

Aromatase is the enzyme that catalyzes a key aromatization step in the synthesis of estrogen. It converts the enone ring of androgen precursors such as testosterone, to a phenol, completing the synthesis of estrogen. As hormone positive breast and ovarian cancers require estrogen to grow, AIs are taken to either block the production of estrogen or block the action of estrogen on receptors.

Mechanism Of Action



Tamoxifen:-

Tamoxifen is a selective estrogen receptor modulator (SERM) that acts as an agonist on the estrogen receptors of the vaginal mucosa and endometrium. It is given in the dose of 20 mg from day 2 or 3 of the menstrual cycle for 5 days. If no response dose increased to maximum of 40 mg and discontinued if patient remains anovulatory despite 40 mg in two consecutive cycles. Limited evidence shows 50%–90% ovulation rates and 30%–50% pregnancy rates with Tamoxifen. Tamoxifen not the first-line treatment for OI in patients with adequate endometrium but is promising alternative to CC for ovarian stimulation in the subgroup of patients who failed to develop an adequate endometrial thickness in a previous CC induced OI cycle. This is primarily attributed to the higher score of cervical mucus and better functioning of the corpus luteum with tamoxifen. The drug has shown to increase the risk of endometrial cancer; however, it is improbable with short-term use.

MECHANISM C

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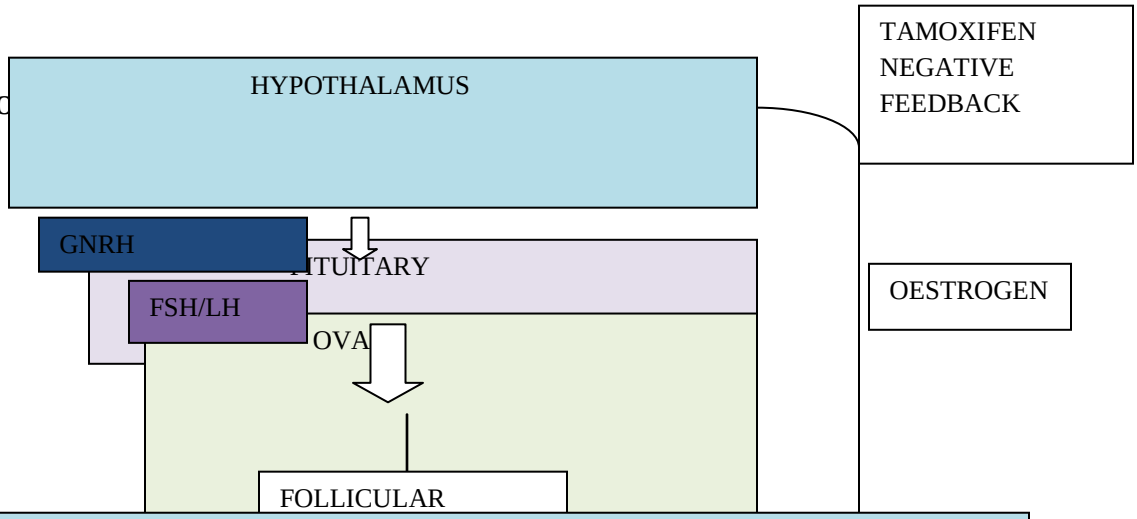

COMPARISON BETWEEN CLOMIPHENE CITRATE AND AROMATASE INHIBITERS AND TAMOXIFEN

PARAMETERS	CLOMIPHENE CITRATE	LETROZOLE/ANASTROZOLE	TAMOXIFEN
MOA	SERM	AROMATASE INHIBITERS	SERM
HALF LIFE	LONG,5-7 DAYS	SHORT,45 HOURS	9-12 HOURS
ANTI OESTROGEN EFFECTS	THIN ENDOMETRIUM AND ALTERED CERVICAL MUCOUS	THICK ENDOMETRIUM AND FAVORABLE CERVICAL MUCOUS	AGONIST ON THE OESTROGEN RECEPTOR OF THE VAGINAL MUCOSA AND ENDOMETRIUM
UTERINE BLOOD FLOW	DECREASED	INCREASED	DECREASED
OHSS RISK	HIGH	LOW	INCREASED
MULTIPLE PREGNANCY	HIGH	LOW	HIGH

Conclusion:-

Ovulatory dysfunction is a prevalent cause of infertility that is frequently referred to Reproductive endocrinologist specialists. Initiating ovulation induction medicines, on the other hand, is a reasonably straightforward treatment for female infertility that can be handled by a obstetrician . Depending on the equipment capabilities of the specific practise, a variety of approaches are available to monitor ongoing follicular development and ovulation during therapy. Further infertility evaluation, further ovulation inducing medication, or referral to a Reproductive endocrinologist specialists can be attempted in those who fail first treatment, depending on the generalist's level of comfort and expertise. Ovulation induction is a viable option for a substantial percentage of infertile women and should be recommended by a general obstetrician and gynaecologist.

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