Review Article: Obesity and Infertility

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ABSTRACT

Obesity is a main health problem, that affects people all over the world. According to recent articles, obese patients should be denied any therapy to aim improving ovulation rates and achieving pregnancy until their BMI is reduced. We believe that this approach does not solve the issue, but rather exacerbates the maternal and perinatal complications linked to fertility clinics. Obesity independent of polycystic ovary syndrome (PCOS) is related with anovulation, and a weight loss alone is an effective treatment for inducing ovulation in both obese women with or not PCOS. As a result, weight-loss lifestyle programs should be considered an ovulation induction therapy, with due consideration for a possible pregnancy in an obese woman.

Obesity has been linked to menstrual irregularities and infertility, Despite the fact that a critical mass of adipose tissue is needed for development female irregularities and infertility, Desp ite the fact that a critical mass of adipose tissue is needed for development female irregularities and infertility, even though body fat. In addition , regulating body fat, the protein encoded by the obese (ob) gene may have an effect on reproductive function [6]. Obesity has also been shown to have a negative influence on serum levels of inhibin B[7].

II. OBESITY

Is an excess storage of triglyceride (TG) in adipose cells? therefore, obesity is described as an extra body fat compared to lean body mass. Overweight is described by health professionals as an extra body weight that includes bone, muscle , fat, and water. Some individuals, such as bodybuilders and other athletes, may be overweight without being obese [8.9].

Obesity is more common in women than in men, which is widely acknowledged. One reason may be that women have a lower metabolic rate compare with men, even though body composition and activity levels are taken into account. Another reason why more women gain weight as they get older is the loss of the luteal phase of the menstrual cycle after menopause [10]. In later life, the disparity between men and women becomes even more pronounced.

Obesity Measurements

The measurement amount of person's body fat is not easy. Many methods have been employed; these are:
1- The most precise method of determining body fat is underwater measure, it used to assess the body's density. Individuals being submerged in water is not a realistic way to calculate density [11].
2- Dual Energy X-ray Absorptiometry (DEXA) by using X- ray[12]. This method is also not practical. There are some methods to calculate body fat;
3- Skin fold measurement with calipers has become to be widespread as an index of the body fat.
4- Height tables' weights, which have been used for years, typically list a number of suitable weights for an individual of a certain height [13].
5- (BMI) has been the medical index for determining overweight and obesity in recent years. It works by applying a mathematical formula to a person's height and weight. BMI is calculated by dividing weight in kilograms (Kg) by height in meters squared (BMI = Kg/m²). A BMI of 25 to 29.9 indicates a person is overweight. A person with BMI of 30 or higher is considered obese.
6- Waist circumference and waist to hip ratio [14].

Anatomic obesity

Health care workers are worried not only the amount of a person's fat, but also with the position of that fat within the body. Android obesity (the apple shape) indicates fat distribution in the central body, while gynoid obesity (the pear shape) means that fat distribution in the lower body (femoral and gluteal part)[15].

Fat cells

In early fetal life, connective tissue develops fat cells (adipose cells). Is excess fat accumulated by increasing the amount of cells, or by increasing the size of the single fat cells? There is a chance that the total number of fat cells has risen, which wait to be supported full of storage fat. Furthermore, an infant's total number of fat cells may be determined by infant nutritional status during the neonatal phase, as well as probably in utero. Fat cells decrease in size but not in number when a patient goes on a diet. Hypercellular obesity can be a more difficult to overcome, because a person's fat cells can continue to grow indefinitely [16].

III. CAUSES

Obesity is described as when one consumes more calories than one expends. What causes this difference in calories in and calories out varies from person to person. A variety of factors, including genetics, psychological, environmental and others can all play a role."

1- Genetic factors

Obesity appears to run in families, indicating that it has a genetic link. Families, on the other hand, share food and lifestyle patterns that can lead to obesity. It's also difficult to distinguish these from genetic influences. Despite this, research indicates that obesity is due to heredity.

2- Environmental factors

Genes do not expose individuals to obesity for their lives. Obesity is affected by the environment as well. This includes things like what a person eats and how much physical exercise he or she gets. Americans have a tendency for high-fat foods.‘ The number of calories consumed by Asians, historically speaking, haven't been that high [17].

3- Psychological factors

Eating behaviors can also be influenced by psychological factors. A lot of people eat to cope with negative feelings like boredom, frustration. The majority of overweight individuals have no additional psychological concerns than average-weight people. Even so, up to 10% of slightly obese people who attempt to lose weight on their own or via commercially available weight-loss plans have binge eating. disorder. This disorder is even more widespread in persons who are extremely obese [18].

4- Other causes of obesity

Obesity or a propensity to gain weight may be caused by a number of illnesses. Cushing's syndrome, hypothyroidism, depression, and certain neurological disorders may all contribute to overeating. In addition, certain drugs and steroids can cause weight gain [19].

Neuropeptide Y acts within the hypothalamus and stimulates feeding. Because the arcuate nucleus comprises the neuropeptide Y cell bodies. [The primary location of gonadotropin releasing hormone (GnRH) neurons] and it affects GnRH secretion, this peptide may be a link between appetite and reproductive function [20].

IV. INFERTILITY

Definition:-

Inability to conceive after first year, of regular, unprotected intercourse(coitus) and for women over 35 years old ,after six months or if one couple has known risk factors for infertility[21].

Conception is very complicated process, that depends upon several factors:-
1- Healthy sperm production by men and healthy eggs production by women.
2- Fallopian tubes that aren't blocked, enabling sperm to reach the egg.
3- The ability of sperm to fertilize egg when they meet.
4- The ability of a fertilized egg (embryo) to implant itself in the uterus of a woman.
5- A good quality embryo.

Incidence

The incidence of infertility is about 10-15 % of couples. Roughly, one-third of infertile cases attributed to male factors and another one-third to female factors for remaining caused by both partners (1/3) or is unexplained (10%). Recent medical literatures has suggested that human fertility is now under threat because of the social and environmental changes that have occurred especially in the second half of the 20th century. Female fertility begins to decline many years prior to the onset of the menopause and this decline can occur despite continued regular ovulatory cycle.

Unfortunately as a result of the significant social changes. that have been taken place over the past 50 years the average age of child bearing has increased
as women pursue a higher education, careers and postpone marriage [22].

**Aetiology**

We will classify the main factors that may affect fertility.

1- **Ovarian Factors**:

The most common cause of female infertility is oocyte development matters. 19 Many diseases can cause anovulation and infertility; these are; hypothalamic dysfunction (38%), Pituitary disease (17%), Ovarian dysfunction(45%) [23].

2- **Tubal factors**:

The major contributors to tubal diseases are pelvic inflammatory diseases(PID), appendicitis, previous tubal surgery, use of intra-uterine contraceptive device(IUD) and salpingitis [24].

3- **Uterine factors**:

These are congenital abnormalities, tuberculosis (T B) endometritis, intrauterine adhesions and submucous polyp or fibroid [25].

4- **Cervical factors**:

Congenital cervix malformations and cervix trauma can affect the cervix's ability to produce normal mucus [26]. Vaginal causes when there is purulent vaginal discharge or the presence of vaginal septum.

5- **Other factors**:

Like coital errors, anxiety, occupation and deficiency in diet (folate, zinc, antioxidants ....)[27].

V. LEPTIN

Leptin (derived from the Greek word LEPTOS, meaning thin) is a protein, discovered in 1974[27] of approximately — 16 kDa in mass, 167 amino acid, and encoded by obese "ob gene". The leptin gene is present on chromosome 7q32 in humans and is made up of three exons and two introns spanning 20 kilobases (kb) of DNA. The mouse and human ob genes have 84 percent homology [28]. This hormone has been discovered to have major effects on body weight, metabolism, and reproductive function. This discovery of leptin has led to wide research activity in the area of obesity and appetite control from which useful therapies will undoubtedly emerge [29].

**Leptin structure**

A four-alpha-helix bundle structural with a three-dimensional fold held together by a disulphide bond between Cys (96) and Cys (146) is revealed by structural analysis [30,31]. Some evidence indicates that the N-terminal region is necessary for biological and receptor binding activities, and that the C-terminal loop structure helps these functions.

This protein has previously been described as a member of the helical cytokine family. The folding pattern of leptin is similar to that of helical cytokines like Interleukin-2 [32].

Leptin is made up of four antiparallel helices, each about 5-6 turns long, with the cytokines arranged in an up-up-down-down sequence, forming a two-layer packing of the helices. Despite the fact that disulfide bonding designs are not that leptin's single disulfide bridge.

Despite the fact that the structure of leptin positions it in the long chain helical cytokine group, there are some distinguishing features of leptin that do not fit into either of the categories [33].

**Sites of secretion**

Leptin is primarily expressed by adipocytes, which match the idea that body weight is determined by the total mass of fat in the body [35]. Human plasma leptin levels are closely linked to index of body mass (BMI) and total fat, and are primarily elevated in obese individuals [36,37]. It has been postulated that, it plays a main role as achemical signal to the brain and other endocrine systems, reminding the brain of the amount of fat contained in the body, so that the brain can control energy intake and expenditure to maintain a steady body weight [38].

Epithelial cells of the stomach and in the placenta also produce small quantities of leptin [39].

**Binding protein**

Leptin secreted by adipocytes can bind to a variety of receptors in the bloodstream, including a splice variant of the receptor (Re) (see iik4) that soluble and hasn't transmembrane domain. However, only about half of total leptin is bound in lean people, and the amount of leptin in obese people is higher than in their lean equivalents [40]. Fauseknect and co-workers described binding factor in human serum with ilecular masses of "176 and 240 KDa" competitively bind leptin in human serum.

In the serum, leptin has a half-life of around 90 minutes. This 90-minute half-life in comparison to the 12-14-hour half-life in plasma may be due to variations in renal handling [41].

**Leptin receptors**

The leptin receptor belongs to the type I group 130 of cytokine receptors [42,43]. There are at least five forms of leptin receptors have been identified (Ra, Rb, Rc, Rd, & Re); a short form (Ra) lacks the intracellular signal domain, and a long form (Rb) represents the functional leptin receptor with transmembrane and cytoplasmic domain of 302 amino acid residue. May be a circulating is possible form the leptin receptor that binds the leptin [44].

The (Ra) form is the predominant form in peripheral tissue (T-lymphocyte, vascular endothelial cells, kidney, liver and lung). it was hypothesized that the high level of expression of (Ra) in the choroid plexus in humans may be transports leptin into the brain [45].

The (Rb) type of the leptin receptor has been located in many regions in brain, including the hypothalamus, in addition to peripheral tissues such as the liver, pancreas, and probably the ovaries[46]. Within the hypothalamus, (Rb) receptors are found in the regions that have been correlated with energy balance.

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control, feeding behavior, and reproduction including the arcue to nucleus and the ventromedial and paraventricular nuclei of the hypothalamus [47,48].

Both (Ra) and (Rb) kinds of leptin receptor have been confirmed in the ovaries, both types of receptors are expressed in theca cells (TC) & granulosa cells (GC) of ovarian follicles [49].

**Mechanism of action of leptin**

The Janus kinase signal transduction and translation system (JAK STAT) regulates the signaling system on the intracellular portion of the leptin receptor. The Stat-3 form of the STAT system that is assumed to carry out the signaling of intracellular [50].

1. **Brain**

   Leptin is transported intact from blood to brain by a saturable system [51]. Neuropeptide Y (NPY)-expressing neurons in the hypothalamus are leptin's targets and pro-opiomelanocortin (POMC) [52,53,54] NPY & POMC gene production are included in the regulation of body weight and reproduction. NPY gene expression is decreased by leptin (NPY increases food intake and inhibits GnRH release) [55,56,57]. Leptin feedback on paraventricular nucleus can inhibit.

   Corticotropic-releasing factor (CRF) release [58]. Thus communication exists between adipocytes (leptin), hypothalamic neuronal system (NPY, POMC, CRF) and central adrenergic pathways in the regulation of adiposity, food intake, and reproduction. This feedback loop would be disrupted if obese individuals are leptin resistant [59,60]. If the melanocortin-4 (MC4) receptor is unblocked, increasing leptin levels will stimulate it, and the response will be a deactivation of hunger; if the MC4 receptor is blocked, the animal will continue to eat and never stop feeling hungry [61].

2. **Liver**

   There was a study examined the effect of leptin on the liver tissue with leptin receptor. It was found that:-

   1. Leptin affects the secondary messenger mechanism, which is responsible for relaying insulin signals into the cell. Insulin binds to a specific receptor on the cell and leads a set of events within the cell. Phosphorylation of a tyrosine protein is the primary messenger. The rate of phosphorylation dropped significantly when leptin bound to its own receptor on the cell at the same time. This means that the usual insulin response was damped; the cell would take up glucose or amino acids much more slowly than in the absence of leptin.

   2. Insulin normally inhibits gluconeogenesis. Leptin again seems to interfere and block the inhibition somewhat [62].

3. **Ovary**

   In the granulosa (GC) and theca (TC) cells of the ovary in human, leptin antagonizes the (IGF-I) that led to increase of steroidogenesis. Leptin hasn’t effect on the synthesis of basal estradiol by (GC). IGF-I augments FSH stimulated estradiol production. Leptin has no effect on the FSH-stimulation of estradiol, but it finally eliminated the IGF-I increasing of FSH stimulated estradiol production. Leptin had a specific effect on estradiol development and had no effect on IGF-I augmentation of "FSH-stimulated progesterone that produced by (GC). In the same manner leptin totally stopped the stimulatory effect of IGF-I on LH-theca cell axis, to produce androstenedione production [63].

**IV. Leptin**

It has stimulatory effect on hCG and IL-6 secretion by human term trophoblast cells in culture. [64]

**VI. REGULATION OF LEPTIN PRODUCTION**

The near relationship between leptin, mRNA, body fat, and plasma leptin level has been demonstrated in both human and animal findings [65,66]. The circulating leptin levels increase with percent body fat, but not with visceral fat. Leptin is synthesized and secreted by a constitutive pathway, rather than being stored in the cell. Sex, age, and calorie restriction for a short period of time may be significant secondary regulators of plasma leptin [67].

**Leptin, obesity and fertility**

Many clinical studies have suggested the hypothesis that body weight is regulated by a "set point mechanism" [68]. Individuals vath equilibrium at various weights, according to this theory. It is assumed that when people reach their set point, compensatory mechanisms prevent them from shifting their weight in any direction [69].

With the cloning of the ob gene and the discovery of leptin, a potential molecular basis for variations in weight between individuals has been proposed [70,71]. In theory, weight differences may be caused by differences in leptin sensitivity and/or development. Hyperleptinemia is linked to the majority of human and rodent obesity cases, implying that leptin resistance is to blame in these cases [72,73]. However, approximately 5-10% of obese humans have relatively normal leptin levels (i.e. less than 10 ng/ml), indicating a decline in leptin RNA and/or protein synthesis. 5677" High plasma levels of leptin and/or increased levels of leptin RNA have been suggested as markers of leptin resistance in obese people [55,56,77,108]. Indeed, 90—95% of obese humans have high leptin levels. Treatment of several strains of obese rodents with leptin has confirmed that high leptin levels indicate complete or partial leptin resistance [74,75].

Obesity has been linked to mutations in the leptin gene in humans (though it is extremely rare in humans) and rodent [76,77]. Obesity may also be caused by defective regulation of the leptin gene, which results in a quantitative decrease in leptin production. Adipocyte hyperplasia occurs when leptin is completely absent [78].
If one considers leptin's effects to be mainly concerned with food intake control, elevated levels of leptin in obesity may be interpreted as a sign of leptin resistance. If the leptin signal is a representation of the amount of fat required to initiate the reproductive system, and the hyperphagia of leptin deficiency results from an attempt to increase fat stores for the fertility then the high leptin levels would expected to affect a different mechanism. It's possible that high levels of leptin have an impact on the reproductive system, which then affects the feeding system[79].

Blood leptin concentrations in obese people are generally higher, implying that they are insensitive to leptin rather than suffering from a deficiency. Mutations in ob or db gene tend to be rare cause of morbid obesity in human, but both have been identified. The effect of mutations in body weight is dramatic, as shown (Figure below) indicates the growth curve of a young girl who was discovered to have homozygous inactivating mutations in the ob gene, in comparison to normal children [80].

The growth curve for a young girl found to have homozygous vating mutations of the ob gene, contrasted to normal children.

Food intake control, body weight and energy consumption

Leptin is a central player in the long-term control of the body weight. Previous research on obese humans and non-obese found a positive association between serum leptin levels and body fat percentage, as well as a higher quantity of ob mRNA in fat from obese people than thin. It appears that as adipocytes develop larger due to triglyceride accumulation, they synthesize an increasing amount of leptin. Leptin acts as a nutritional status measure for the body[81]. The effects of leptin on body weight are mediated by hypothalamic centers that regulate feeding behavior and hunger, as well as body temperature and energy expenditure. Secreted leptin is thought to act as a signal to the central nervous system, indicating the level of body fat, stimulating sufficient food consumption and energy expenditure responses. Low levels of leptin, on the other hand, can function as a starvation signal, causing the hypothalamic-pituitary axis to respond to the nutrition [82]. The weight loss caused by leptin tends to be the product of at least two fundamental effects are combined in this effect [83].

1- Inhibition of neuropeptide Y synthesis, at least in part, reduces hunger and food intake. [Leptin decreases the content of neuropeptide Y (NPY) mRNA]. [84] In addition, leptin acts in the arcuate nucleus to reduce food intake by increasing (1-MSH [85]. Increased energy expenditure as determined by increased oxygen intake, increased the temperature, and loss of adipose tissue mass. Treatment with leptin induces lipolysis in adipose tissue but has no effect on lean tissue, in comparison to dieting, which causes both fat and lean mass loss[86].

Reproductive function

Starvation has long been considered to have a negative impact on reproductive function. For example, in females low fat is often correlated with the termination of the menstrual cycle, and starving or nutritionally deficient animals exhibit similar effects. In addition, the initiation of puberty is considered to be related to both body condition and age.

Leptin levels are low in people and animals that have low body fat, and it appears that leptin is a key regulator of reproductive function. These effects are likely due to leptin's ability to increase GnRH secretion,
and thus LH and FSH, from the anterior pituitary. One of the first evidences of the effect of leptin on reproduction dealt with puberty's onset. Prepubertal mice given leptin became thin, as expected, but they also reached reproductive maturity and started cycling much sooner than control mice. Furthermore, some people with inactivating mutations in the gene of leptin receptor are not just overweight, but they still do not reach puberty [87].

Gender differences in leptin level

Leptin levels in humans are dissimilar in men and women, leptin levels in women are much higher than in men, a disparity that can be seen in children. Women have levels that are two to three times higher than men, and this is true of both normal-weight and obese or diabetic patients [88]. These differences might be due to:

First, men and women have different body compositions. In general, women for the same body weight or BMI, have a higher proportion of fat mass [89]. Even after adjusting for BMI and fat mass, women's leptin levels were found to be significantly higher [90].

Second, men and women have different fat distributions. Obese men have more abdominal (especially visceral) fat accumulation, while obese women have more peripheral fat accumulation (especially at the level of the aithips). In vivo studies have revealed a stronger link between leptin levels and peripheral p or subcutaneous fat than with intraabdominal or visceral fat.

Other factors must play a role because variations in body composition between men and women do not fully explain differences in leptin levels. A probable candidate is steroid hormones, although the mechanism or relationship is unknown. Androgens can have a suppressive impact on men, although this has yet to be confirmed, whereas estrogen and/or progesterone may have a stimulatory effect [91].

Various studies have found a connection between leptin and progesterone, estrogen, and luteinizing hormone (LH). Leptin levels in women change during the menstrual cycle, according to long-term studies. To obtain accurate results in women, leptin levels, as like sex hormones, should always be tested at the same time of the menstrual cycle [92].

Leptin levels in the blood peak mostly during the luteal phase, when progesterone levels are at their highest, and decline during the early follicular phase. Food cravings during perimenstrual cycles may be explained by these changes in leptin levels [93].

Leptin and polycystic ovary syndrome (PCOS)

Women with "PCOS" are hyperandrogenic, which means they have visceral obesity, insulin resistance, and are mostly infertile or subfertile. The state of leptin in these women is unknown. Leptin levels in women with PCOS are higher than predicted for their BMI, implying that leptin signaling to the reproductive system is abnormal in PCOC [95]. In other studies, however, leptin levels were found to be comparable to age — and weight — in normal control women [94].

Inhibin

McCullagh suggested the presence of inhibin in 1932 [95] He discovered that a water soluble testicular extract prevented pituitary hypertrophy in rats after castration. This was later identified as inhibin, that inhibits the development of FSH by the anterior part of the pituitary gland [96].

Several fractions were found during the purification process of inhibin that stimulate pituitary FSH release, which led to the discovery of activin as a homodimer of the 13-subunits of inhibin. Another component of the inhibin purification effort inhibited FSH release, and was identified as the monomeric protein follistatin (FS) after purification and cloning. The physiological importance of (FS) remained indeterminate until its activin binding and neutralizing activity was recognized. As a result, the loop is closed and these proteins are forever joined in a regulatory triangle [97].

Tissue Localization

Dimeric inhibin appears to be formed by the ovary in females (A and B) in conjunction with the fetoplacental unit during pregnancy, and by the testis in males (only B). Folicel's granulosa cells produce inhibin-B as part of the fine regulation that lead to follicular domination in the menstrual cycle, prior to ovulation, the follicle produces inhibin-A, followed by the corpus luteum in the luteal process. Sertoli cells promote spermatogenesis in the testis by increasing local testosterone concentrations in response to FSH stimulation; they develop inhibin-B as a regulating mechanism with negative feedback on FSH at the anterior pituitary [98].

The monomeric alpha subunit is formed in the adrenal gland and brain as are the two beta subunits with dimmers to "activin", but no dimmeric inhibin has been revealed to be produced outside of the gonads [99].

Pattern of inhibin secretion:

Inhibin grows slowly but gradually during the follicular cycle, peaking at the same time as the gonadotropin surge in the midcycle.

Inhibin expression becomes regulated by LH as the follicle develops into a corpus luteum. Inhibin levels in the blood drop slightly from the midcycle peak, then rise to reach a level at the midluteal phase that is at least two times greater than the midcycle peak.” After conception, even higher circulating levels of inhibin are achieved [100].

VII. HUMAN REPRODUCTIVE INHIBIN

Endocrinology

1- Female Inhibin Secretion and Endocrinology.

Inhibin-B rises through the luteal-follicular transition and peaks in the midfollicular phase, while
inhibin-A increases through the late follicular phase, peaking in the midcycle and then the midluteal phase [101].

A number of studies have looked into the indirect negative feedback role of inhibin-A and -B in physiological situations where FSH and LH are dichotomously controlled. Increased inhibin, according to these findings, selectively inhibits FSH. Inhibin-B declines coincident, with the first detectable.

During female reproductive aging, FSH levels increase. During the perimenopause, inhibin-B declines faster than inhibin-A, coinciding with a large increase in FSH [192]. These results support the idea that inhibin-B and inhibin-A play a significant negative feedback function on FSH in humans, with FSH levels being more sensitive to early inhibin-B decreases. Researchers also studied inhibin levels in women with polycystic ovary syndrome (PCOS), a condition in which FSH is suppressed compared to LH. The levels of serum inhibin alpha-subunit, inhibin-A, and inhibin-B in PCOS women were comparable to early follicular phase levels in regular cycling women, or were higher [102].

**Clinical applications**

The availability of new generation of inhibin assays and reagents has greatly facilitated clinical and basic research into the potential applications of these molecules. The followings provide an overview into some of the clinical applications:

1- Ovarian Reserve: The quantity of inhibin-B measured in serum during the early follicular phase of the menstrual cycle (days 2-6) directly represents the number of ovarian follicles; in other words, the higher level of the inhibin B, the more ovarian follicles are present; inhibin B levels decrease as women age and ovarian follicle numbers decline[103].

2- The ability of the ovaries to develop follicles in response to hormone treatment used in IVF is also predicted by inhibin-B levels. According to research, the level of inhibin-B in the follicular phase of the menstrual cycle predicts how many oocytes will be retrieved after hormonal stimulation treatments. Furthermore, women with very low inhibin-B levels (less than 20 pg/ml) have been confirmed to have such a weak ovarian response that their in vitro fertilization (IVF) cycle must be canceled [104].

3- Inhibin has been revealed to adjust gonadal stromal cell proliferation negatively and inhibit tumor growth. Inhibin levels in the blood have also been shown to describe the size of granulosa-cell tumors, so it can be used as a marker for both primary and recurrent disease. The discovery of inhibins several years after they were first suggested and the availability of research methods have provided for a better understanding of their biological functions. In the investigation of various reproductive disorders, measuring circulating levels of activin and inhibin is proving to be of clinical interest[105].

**VIII. INHIBIN-B AND PCOS:**

There was a controversy about inhibin-B serum levels in WHO 2 and PCOS. Some studies show a typical concentration in WHO 2 and PCOS women, suggesting a normal number of healthy early "antral follicles" despite increased total follicle numbers in PCOS. Anderson and Coworkers have shown that concentrations of inhibin B and to a lesser extent inhibin A are consistently higher in PCOS than in normal follicular phase women. Inhibin-B concentration rise seven fold after FSH treatment, indicating that inhibin-B production is FSH dependent[106].

**IX. INHIBIN DURING PREGNANCY**

The placenta releases inhibin during pregnancy, which is responsible for the significant rise in maternal inhibin levels during the pregnancy. Inhibin originates in the syncytiotrophoblast, and its synthesis is stimulated by prostaglandin. Fetal adrenal cells produce inhibin, and the alpha-subunit is preferentially increased by ACTH. Inhibin levels rise to a peak at about 11 weeks of pregnancy, followed by a decline to a plateau that is maintained from 14 to 25 weeks, followed by a slow rise to the highest levels at term (4 times luteal levels)[107].

**X. INHIBIN AFTER MENOPAUSE**

The duration of the follicular stage is the most significant factor in determining period length. This menstrual cycle transition is characterized by elevated of (FSH) levels and reduced inhibin levels, but normal levels of estradiol and (LH). The decline in inhibin secretion by ovarian follicles starts early in life (around age 35), but it accelerates after age 40. Furthermore, because of the ineffectiveness of postmenopausal hormone therapy in suppressing gonadotropins due to the loss of inhibin, FSH cannot be used clinically to titrate estrogen dose [108].

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