

Impact of Obesity in Male and Female Infertility

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Abstract

Obesity has negative effects on the fertility of males and females. In females the obesity can induce hormonal imbalances for example adipokines (leptin, adiponectin, resistin, visfatin, omentin, chemerin) on reproductive axis, irregularities in menstrual cycle, reduce conception rate and complications in pregnancy. The adverse effect is insulin resistance and insulin excess that is associated with PCOS (polycystic ovary syndrome)-irregular periods. In males the obesity affects HPG gland that in turn disturb the endocrine regulation of reproductive function with high level of estrogen and low level of testosterone, progesterone, and SHBG (sex-hormone binding globulin). DNA damage of sperm, high scrotal temperature because of highly fatty scrotum area, low production of sperms and decreased motility of sperm are all the effects of obesity in males that cause infertility. The aim of the review article is to thoroughly cover the effect of obesity on reproductive functions, hormonal concentrations & fertility potential in females & males.

Keywords; Infertility, Adipokines, Menstrual cycle, PCOS, SHBG

I. Introduction

Obesity is a metabolic disease that happens because of environmental, hereditary & nutritional factors and it is basically an excessive accumulation of adipose tissue. If body mass index crosses 35kg/m² then it is called morbid obesity while obesity is articulated as BMI (body mass index) over 30kg/m². The incapability to conceive in spite of engaging for one year in unprotected consistent sexual contact is called infertility defined by WHO (World Health Organization). The married couples that are affected by infertility are nearly thirteen to fifteen percent. The outbreak of obesity and the disorders induced by obesity are increasing and because of this problem we are facing the emergency of worldwide public health (Kumar & Singh, 2015).

Current evaluations demonstrate that with some exceptions the alleviated incidence of obesity is recognized worldwide. With the novel Asian BMI, the criteria are higher as compared to the current record including three hundred and thirteen million obese people in which over one billion are adults as estimated by the International Obesity Task Force (Sengupta, Dutta, & Krajewska-Kulak, 2017).

In females the infertility induced by obesity is mainly related to PCOS (polycystic ovary syndrome). There is alleviated LH level in females having PCOS and these females reveal the condition of hypogonadism & hyperandrogenism (Nagae et al., 2021). There is decreased level of estrogen & gonadotropin in obese females that have no hyperandrogenism conversely on the other hand and all this proposes that in females the obesity may reduce the hypothalamic function (Iwata, Kunimura, Matsumoto, & Ozawa,

2017). Obesity severely effect the concentration of reproductive hormones such as adipokines mainly leptin which concentration is increases that cause insulin resistance and thus induce infertility in females.

There is briefly reviewed the mechanism of obesity in males on the quality of sperm in this article. Affected motility of sperm, DNA destruction of sperm, inflammatory cytokines secreted by fat tissue, alleviated aromatase, alleviated level of adipocytes & leptin, epididymitis and erectile dysfunction are included in the infertility of males induced by obesity. Decreased level of gonadotropin & plasma testosterone are severely related with obesity in males (Moore, Coolen, Porter, Goodman, & Lehman, 2018).

2. Obesity in relation to infertility

In females alleviated risk of pregnancy loss, subfertility, menstrual irregularities, severe oligo/anovulation are several difficulties in relation to ovarian & neuroendocrine functions supposed to cause by obesity (Kutlu, Özberk, & Görkemli, 2017).

In males environmental, endocrine & genetic factors control the infertility as infertility induced by obesity in males is considered multifactorial. Because of abnormal spermatogenesis the prime hormonal defect that is known as hypotestosteronemia that cause reproductive dysfunction in obese man.

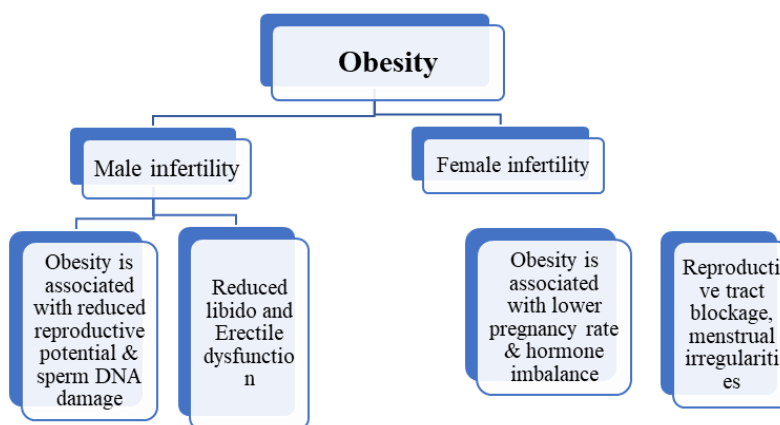


Figure 1: Infertility & Obesity

Obesity and infertility in females

In females the obesity in various ways affect the reproduction & infertility

- By deteriorating the delivery process in pregnancy & physiological process
- By disturbing spontaneous ovulation
- By disturbing the results of ART (assisted reproductive technology) and its accuracy

Obesity and reproductive hormones

On reproductive functions the adverse effects of obesity are well known for several years (Jungheim, Travieso, Carson, & Moley, 2012). To describe the fertility relation with obesity many mechanisms are involved though it is not too easy to clearly demonstrated the mechanism that how obesity affect reproductive system.

Adipokines:

Adipokines are the chemerin, ghrelin, omentin, visfatin, resistin, adiponectin & leptin that are principally secreted by adipocytes and are called as cytokines. In cell function & metabolism the worsening is led by abnormal cell signaling & inflammation that is caused by deviations in adipokines as adipokines are the signaling hormones (molecules). Reproductive disorders can cause by excessive adipose tissue though in normal development & reproductive function adipose tissue is essential.

Leptin level:

In obese females the hyperandrogenemia can happen when the leptin level & insulin resistance augmented. Likewise, the reproductive system is affected by steroidogenesis, HPG axis, adipokines level alterations & anovulation in obese females (Bellver et al., 2007). In both follicular fluid & blood the level of leptin is alleviated when the body mass index (BMI) increases as confirmed by the studies (Metwally, Li, & Ledger, 2007). So, in follicular fluid & serum there is augmented level of leptin associated with obesity. To induce the hypothalamic reproductive maturation the signal is provided by leptin as on HPG axis it has a stimulatory effect.

Table 1: On infertility of females the main effects of adipokines

Adipokines	Serum levels in obesity	Effects on reproduction in obesity
Leptin	Increases (leptin resistance occurred in obesity)	Inhibits insulin induced ovarian steroidogenesis
		Inhibits LH [*] -stimulated estradiol production by the granulosa cells
Adiponectin	Decreases	Plasma insulin levels increase
Resistin	Increases	Causes insulin resistance
Visfatin	Increases	Increased insulin sensitivity
Omentin	Decreases	Increased insulin sensitivity
Chemerin	Increases	Negatively regulates FSH [§] -induced follicular steroidogenesis

Leptin acts on the cell receptors of granulosa & theca and prevents ovarian steroidogenesis induced by insulin. Granulosa cells produce estradiol stimulated by LH (luteinizing hormone) and leptin inhibits LH. The growth & cleavage of early embryo is also regulated by leptin and on reproductive function it is another effect of leptin

Adiponectin level

The rate at which the weight is losses the adiponectin level is increase or decrease at that rate unlike the other hormones of the adipose tissue in obese females. Adiponectin reduces hepatic gluconeogenesis and in muscles & liver stimulates the uptake of glucose.

Resistin

Ghrelin & resistin mechanisms are not completely understood on reproductive functions. Resistin is secreted by adipose tissue and protein in nature. The sensitivity of insulin is reduced when the level of resistin is increased that leads to insulin resistance.

Visfatin

Fetal membranes, trophoblast, liver, muscle, lymphocytes, bone marrow, adipocytes & adipose tissue are various tissues and cell types from where the visfatin is secreted an adipokine (Fukuhara et al., 2005). The relationship is not completely understood between insulin, visfatin & obesity. From hepatocytes visfatin reduces release of glucose and in adipocytes it alleviates the uptake of glucose and illustrates insulin-mimetic effects as reported.

Chemerin

Metabolism of glucose & adipocytes there is effect of another adipokines that is known as chemerin. Polycystic ovary syndrome (PCOS) is the syndrome of irregular menstrual periods means there is no regulation in release of eggs (ovulation) from ovary and the pathogenesis of this syndrome chemerin play a vital role by impairing follicular steroidogenesis induced by FSH (follicle stimulating hormone). In the adipose tissue via the conversion of androgens to estrogens the adipose tissue inhibits the secretion of gonadotropin so that they affect the development of follicle. By the resistance of insulin nearly all adipokines effects on reproduction.

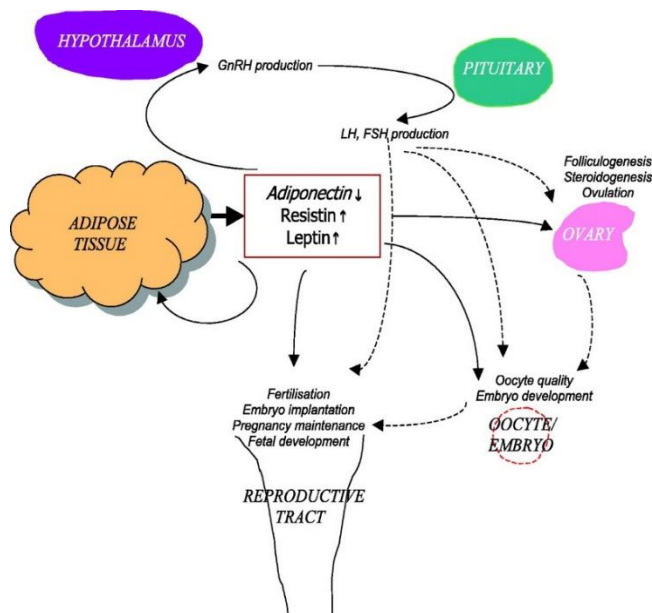


Figure 2: Between the reproduction of female & adipokines there show a potential relation. There is a reduction (↓) in the formation of adiponection & alleviation (↑) in the formation of resistin and leptin by expanded adipose tissue because of obesity. On the reproduction of female, the reproductive tract of female, embryo, oocyte, ovary, pituitary

& hypothalamus in relation with adipokines have indirect (discontinuous arrow) or direct effect (continuous arrow).

3. Obesity and menstrual irregularity

It was determined that those females with irregular menstrual cycles or anovulatory cycles of more than 36 days & hirsutism (having thick hair on face, neck, skin, chest, tummy, lower back, thigh or buttocks) were of heavier body weight greater than 13.6 kg or 30 lb as compared to those females who have normal menstrual cycles. Age of abnormalities in menstrual cycle and of obesity are mostly interrelated, in young females & adolescents. After regulating other perplexing factors, obesity at 7 years & obesity at 23 years both amplified the risk in menstrual problems independently by 33 years. High rate of menstrual problems is connected with underweight and Obesity.

Generally, the duration of menstrual cycle involves twenty-eight to thirty days. There is shown reduced fertility & disorders of ovulation in females having irregular or long cycle. There is a little chance of menstrual disorders when the BMI (body mass index) is twenty-two to twenty-three. When the body mass index increases to twenty-four to twenty-five then there is a double chance of menstrual irregularity and if the body mass index is thirty-five or more than thirty-five then the chances of menstrual irregularity become five times higher (Figure.1) (Rowland et al., 2002).

In contrary, the females having menstrual irregularity the obesity is the risk factor in them. The females having menstrual irregularity, the obesity frequency was forty-five percent and the females having normal cycle of menses in these the obesity frequency is nine to thirteen percent according to a study.

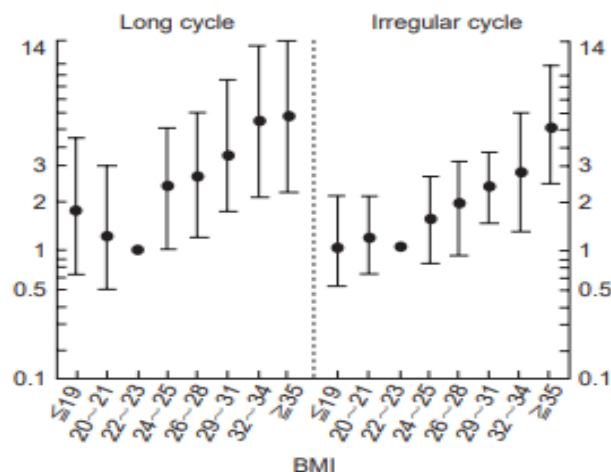


Figure 3: Association between obesity and menstrual disorders

4. Obesity & pregnancy outcomes

Weight gain & overweight during pregnancy

As the clinical point of view there seen a fear that during pregnancy an extra weight is gained by a female and there is already a weight problem with obese female. The association between weight gain during pregnancy, pre-pregnant weight & body mass index have been examined by several studies (Theron & Thompson, 1990). Between weight gain during pregnancy & pre-pregnant weight some studies found no constant relationship while other studies found a constant relationship. There found 'good' pregnancy results in 4674 females as estimated by Laros & Abrams. The body mass index groups of pre-pregnancy were listed as obese having body mass index greater than 28.9, overweight having body mass index 25.6 to 28.9, normal weight having body mass index 19.2 to 25.6 & under weight having body mass index less than 19.2. The group that are very obese gained two kilograms less while the group that are underweight gained 0.65 kilogram less as compare to the group of normal weight. Moreover, in the group of very obese the difference in the weight alleviation was much higher.

Duration of pregnancy and delivery complications

The females having normal weight when compared with obese women there is usually no occurrence of preterm delivery nor is the period of pregnancy significantly dissimilar (Galtier-Dereure, Boegner, & Bringer, 2000). In obese females the delivery time was longer as reported by Jonson et al though some studies revealed that on the period of delivery the obesity has no effect. Moreover, the frequency of labor induction is higher in obese females.

Additionally, there are large amount of planned & acute caesarean units in obese females. Gross et al., explained that inadequate expansion of induction miscarriage, fetal distress & cervix are most common suggestions. Large degree of caesarean units is a major problem in obese females as compared to obesity itself. However, among obese females, other types of supportive methods of delivery are common (Flamm, 2001). Problems due to surgery are more in obese females. If there are regular caesarean in obese females then it leads to enormous bleeding, infections and thrombosis (Galtier-Dereure et al., 2000). Because of overweight child, perineal tears chances are more in obese females, if delivery occur through vagina as compared to normal weight females (Samuelsson, Ladfors, Lindblom, & Hagberg, 2002).

5. Obesity and infertility in males

Multifaceted mechanisms are involved to estimate the relation between obesity and infertility like epigenetic fluctuations, inflammatory cellular response, hormonal disproportion, endocrine elements from adipose tissue and high scrotal temperature. Reproductive mechanism of hormones disturbs due to high BMI, then adipose tissues work as endocrine organs & hormones like adipokines are released from them. Spermatogenesis is disturbed by these hormones (both testicular & central ways). DNA mutation & increase in scrotal temperature due to high range of BMI and adipose tissue.

Obesity and hormonal imbalance on reproductive axis

GnRH (Gonadotropin-releasing hormone) from hypothalamus, FSH (follicle-stimulating hormone) and LH (luteinizing hormone) from pituitary gland are used to control the sperm creation. In Leydig cells of testis, LH control the testosterone production & under the control of FSH, development of spermatozoa by germ cells. Additionally, there is significant role of intratesticular testosterone in testis for spermatogenesis. In androgen-sensitive end tissues, processing of testosterone in dynamic form and deactivation to 17-ketosteroids in liver (Clavijo & Hsiao, 2018). Conversion of testosterone to estrogen is under the action of enzyme aromatase (cytochrome P450). Aromatase causes the decrease in the level of testosterone and results in male hypogonadism.

Serum hormone level in obese man

In obese males on the levels of serum hormone various consequences have been informed in studies. The level of luteinizing hormone continued normal while the level of free testosterone & total level of serum is reduced in proportion to body mass index as reported by some studies (Tsatsanis et al., 2015). In the testis the synthesis of testosterone is reduced because of over-activity of aromatase in obese people and this is all because of the alleviated estrogen level's negative feed-back effect on the gonadotrophic hormones. In contrast, reduction in the spermatogenesis & in Sertoli cells the takeover of the spermatogenesis is done by decreased FSH in response to alleviated level of estrogen. So, with the alleviation of body mass index the aromatization of testosterone to estrogen progresses hypogonadism in obese people. In obese males the levels of SHBG (sex-hormone binding globulin), luteinizing hormone serum level & testosterone decreases in further epidemiologic studies. Alleviated level of luteinizing hormone (LH) cause low level of testosterone related with age though low level of luteinizing hormone (LH) decrease the testosterone because of obesity as revealed by a significant discovery.

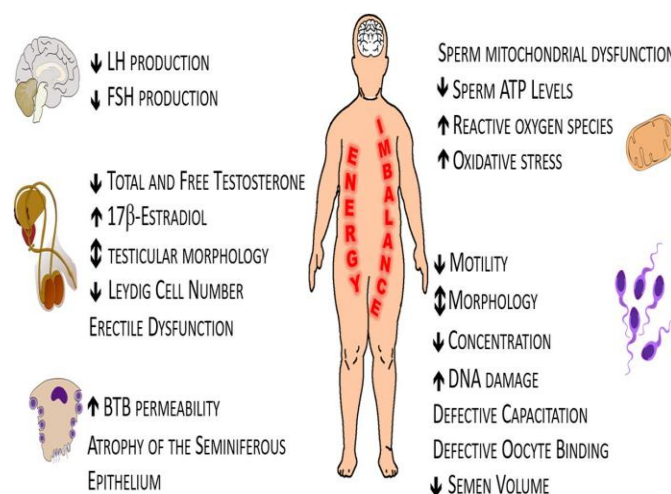


Figure 4: On the reproductive health & tract main effects of energy imbalance & obesity

The imbalance of energy affects the spermatogenesis & steroidogenesis by disturbing HPT (hypothalamic-pituitary-thyroid) and damages the testicular function. Moreover, by oxidative stress alleviation, decrease in the quality & production of sperm because the permeability of the blood-testis barrier is lost the energy imbalance damages the reproductive function of males.

↑ = increase, ↓ = decrease, ⇕ = alterations, LH = luteinizing hormone, FSH = follicle stimulating hormone, BTB = blood-testis barrier

How obesity effect on quality of sperm

During epididymis maturation & testis spermatogenesis the obesity can harm the molecular & physical structures of sperm. Implantation rates of embryo is reduced, quality of sperm is reduced (alleviation in damage of sperm DNA, affected motility and concentration & decreased acrosome reaction) in obese & overweight males as compare

to the males having normal weight. The risk factors involved in the infertility of males and reduction in the quality of sperm are high scrotal temperature because the fat content increases in the area of scrotum, imbalance in the level of hormones that cause reproductive tract inflammation that is very severe and all this is because of extreme visceral adiposity in obese men actually (Liu & Ding, 2017).

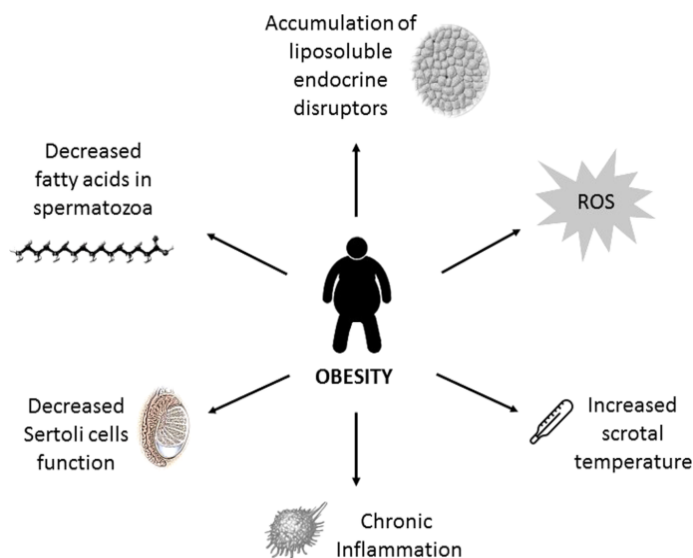


Figure 5: Alterations in sperm induced by physiology of obesity

There found controversy about motility, morphology & sperm count in human males influenced by obesity though with the parameters of sperm the relation of men obesity is revealed by animal & human models (McPherson & Lane, 2015). The males having abnormal weight in these the volume of semen reduced by 2 percent, total sperm count reduced by 2.4 percent & concentration of sperm reduced by 1.3 percent respectively for every 5 unit rise in the body mass index as compare to the males having normal weight as revealed by twenty-five studies meta-analysis. The conclusions propose that in infertility of men obesity could be a damaging factor.

Mechanisms implicated in obesity-induced male infertility

Among others endocrine disturbances with the severe inflammatory responses included in the complex pathophysiology of obesity. Pro-inflammatory responses drive M1-macrophage & Th1-lymphocyte induced by extreme deposition of visceral adipose tissues with obesogenic environment. Testes, pancreas, hepatic, cardiac & hypothalamus are the various tissue devastatingly affected by myokines, cytokines & adipokines that characterize inflammatory responses.

Inflammations that occur due to obesity are associated with two major co-morbidities; one is hypogonadism & second is male infertility. $\text{TNF}\alpha$ (tumor necrosis factor-alpha), MIP-1 (macrophage inflammatory protein), interleukin (IL12, IL6, IL1 β , IL8), TGF β (transforming growth factor-beta), neuroendocrine hormones (resistin & leptin), MCP-1

(monocyte chemotactic protein) are inflammatory mediators for immune response (Henkel, Samanta, & Agarwal, 2018).

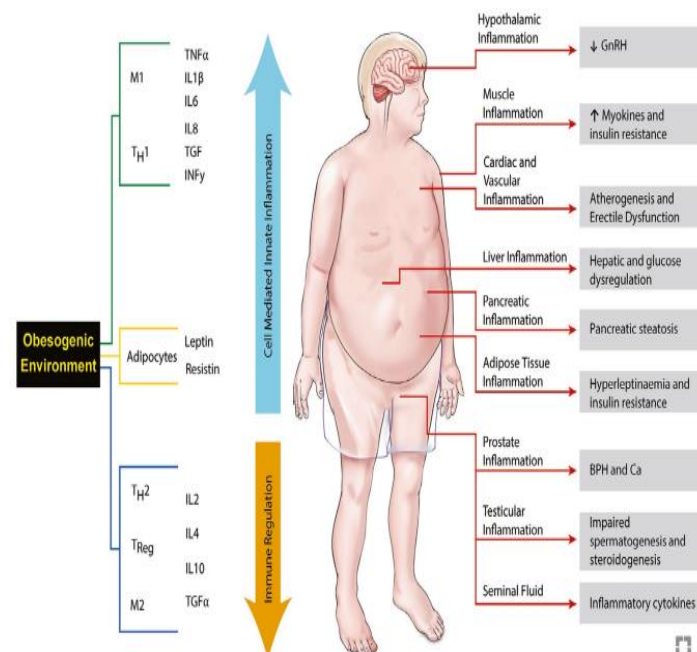


Figure 6: Obesity & low-grade systemic chronic inflammation

Inflammation induced by obesity involve such pathway that may cause the disturbance in mitochondrial function, activation of TLR4 (toll-like receptor 4), threonine kinase or serine kinase and stress in endoplasmic reticulum (Thaler & Schwartz, 2010). Oxidative stress in testis is due to dyslipidemia state, which also cause disturbance in sperm function in obese males. Modification of low-density lipoprotein functions by cellular process may cause LDL to play a role of ligand for such type of receptor that recognize macrophage like TLRs. Then, pro-inflammatory mediators are released by pro-inflammatory signaling pathways that are induced by it directly. Storage of cholesterol in cells is due to the activity of macrophages, monocytes and neutrophils. Inflammatory condition getting worse by amplification of TLR signaling (Tall & Yvan-Charvet, 2015). Inflammation in productive tract may provoke due to metabolic syndrome & obesity and it leads to pro-inflammatory cytokines (higher levels) in testes, ejaculate, prostate, epididymis and seminal vesicles in obese males. Thus, quality of semen deceases & it correlates inversely to hypogonadism indicators (Henkel et al., 2018). Oxidative stress is induced in case of hyperglycemia as well as stress on endoplasmic reticulum is also increased. Inflammatory responses due to obesity affect the endocrine regulation (of reproductive system functions) by upsetting the HPG axis & other hormones. Increase in level of estrogen and decrease in level of SHBG (sex hormone-binding globulin), testosterone & progesterone due to obesity in males and this high-level estrogen cause the inhibition of HPG axis and release of LH & FSH decreases (Henkel et al., 2018). Leptin

in obesity is most common and it also cause the stop in release of FSH & LH (Ojeda et al., 2006). Testicular dysfunction by GnRH & gonadotropin may cause infertility due to hormonal mechanism. Physical problems in obese males like increase in scrotal temperature & erectile dysfunction are also the reason of male infertility (Du Plessis, Cabler, McAlister, Sabanegh, & Agarwal, 2010).

6. Conclusion

In this review we discuss the role of obesity on infertility of females and male. Obesity have negative effects on reproductive system of males and females. Obesity effect reproduction and infertility of women by affecting spontaneous ovulation, by irregular menstrual cycles and by creating complications in pregnancy. Obese women have higher rate of caesarean sections. All adipokines (leptin, adiponectin, resistin, visfatin, omentin, ghrelin & chemerin) seems to have their effects on reproduction by causing insulin resistance in females. Male infertility that is induced by obesity considered multifactorial. Thus, instead of endocrine and genetic factors the environmental factors are also involved. The risk factors that induce infertility in males is that an obese man have decreased quality of sperm means there is increase of DNA damage, decrease concentration and motility of sperm & increased scrotal temperature because scrotum area is highly fatty. The inflammatory responses associated with obesity disturb the endocrine regulation of reproductive function through affecting the HPG (hypo-thalamic pituitary gland) axis and its cross talk with the hormones. The alterations in reproductive hormones induced by obesity in males are low level of sex hormone-binding globulin (SHBG), testosterone and progesterone & high level of estrogen that inhibit FSH & LH. Impaired regulations of testicular functions by GnRH & gonadotropins may explain the primary hormone mechanism of obesity associated male infertility.

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