ISSN: 0975-833X

Available online at http://www.journalcra.com

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

International Journal of Current Research
Vol. 13, Issue, 06, pp.18037-18042, June, 2021

DOI: https://doi.org/10.24941/ijcr.41726.06.2021

RESEARCH ARTICLE **OPEN ACCESS**

OBESITY AND PATHOPHYSIOLOGY OF REPRODUCTION

***Padmasana Singh**

Department of Zoology, Indira Gandhi National Tribal University, Amarkantak 484887

ARTICLE INFO

Article History:
Received 29th March, 2021
Received in revised form
17th April, 2021
Accepted 24th May, 2021
Published online 30th June, 2021

Key Words:

Obesity, Leptin, Hyperinsulinemia, Insulin resistance, anovulation, PCOS.

ABSTRACT

Android obesity leads to development of several chronic diseases like type 2 diabetes, cardiovascular disease, hyperlipidemia, irregular menstrual cycle, infertility and miscarriage. Disturbance circulating metabolic hormones like leptin and insulin and sex hormones are main cause of these abnormalities. Overfeeding causes hyperinsulinemia and insulin resistance which in turn causes excessive androgen production. During puberty, critical amount of fat and high insulin decreases two binding proteins, SHBG and IGF binding protein that increases circulating free sex steroids. These free sex steroids are responsible for sexual maturation at puberty. Insulin causes androgen production but long-term exposure to insulin causes polycystic changes in ovary. Increased GnRH together with high LH pulse frequency and decreased negative feedback to LH is also reported. Hyperinsulinemia and high LH are responsible for high androgen production from the ovary but aromatase activity in not that much upregulated. That leads to high circulating androgen and anovulation in PCOS.

Citation: Padmasana Singh. "Obesity and pathophysiology of reproduction", *2021. International Journal of Current Research, 13, (06), 18037-18042.*

INTRODUCTION

Excessive body fat in compare to lean body mass of sufficient magnitude that has adverse health effect is defined as obesity. There has been a sharp increase of obesity in the world that drew the attention of the researchers. >60% of American adults are overweight or obese. The prevalence of obesity is not only in adults but also growing in children predisposing them to a host of many chronic diseases (Flegal *et al.*, 2005). Obesity is associated with many endocrine abnormalities, such as abnormal circulating hormone concentrations, changes in the pattern of hormone secretion and its metabolism, altered hormone transport, and abnormal action on target tissue (Kahn and Flier, 2000). Previously it was thought that these changes were secondary to obesity, but recently it become evident that they may play a crucial role in the development of different metabolic abnormalities (Wajchenberg, 2000). Together these metabolic alterations due to obesity is associated with multiple reproductive health problems. To study the relationship between obesity and reproduction is of great importance for several reasons: 1) obesity play a cardinal role in the development of various reproductive disorders in women such as amenorrhea, anovulation, hyperandrogenism, and polycystic ovary syndrome (PCOS), etc. (Pasquali *et al.*, 2003); 2) obesity has a profound impact on sex hormone secretion and metabolism (Pasquali *et al.*, 2001); 3) in females changes in androgens levels may favor the development of specific endocrine disorders (Pasquali and Vicennati, 2001); 4) sex hormone imbalance may favor infertility (Pasquali *et al.*, 2003); 5) androgens play a central role in the distribution of body fat; and 6) high androgen in obesity may favor the susceptibility to develop type II diabetes mellitus and cardiovascular disease. The present overview summarizes the basic information available on the obesity disorders, hyperandrogenism, obesity hormones like leptin and insulin and their role in reproduction and PCOS.

Obesity and reproductive disorder: Obesity is increasing worldwide and rapidly growing threat to the health of people. The relationship between increasing adiposity and the development of chronic diseases such as type 2 diabetes, cardiovascular disease and some cancers has been recognized for many years. Mechanism of adiposity and is important for understanding disturbances in the glucose and lipid metabolism. Excess fat in the upper part of the body that is "central or abdominal obesity" considered as "android or male-type obesity" (Vague, 1947). This male type obesity may have increased risk for disorders such as diabetes, hyperlipidemia,

*Corresponding author: ***Padmasana Singh,***
Department of Zoology, Indira Gandhi National Tribal University, Amarkantak 484887.

hypertension, and atherosclerosis (Wajchenberg, 2000). This may also lead to reproductive disorders like irregular menstrual cycles, reduced fertility, increased risk of miscarriage and hormone-sensitive carcinoma (Krischner, 1982). These abnormalities are related to distinct changes in the circulating sex and metabolic hormones.

Obesity and Androgens: It is well known that in both pre- and post-menopausal women, increase body weight and fat deposition is associated with changes in sex steroid imbalance. Such imbalance involves change in the concentration of both androgens and estrogens, their carrier protein and sex hormone-binding globulin (SHBG). Changes in SHBG concentration leads to alteration in the delivery of androgen and estrogen to target tissues. Follicular androgens serve as estrogen precursors. Apart from serving as a substrate for estrogen synthesis, androgen has some other functions in the ovary is not clear. To answer this, it is important to understand the distribution and function of androgen receptors in the ovary. Hyperandrogenism (HA) in women is associated with android obesity which is the major characteristic feature of polycystic ovary syndrome (PCOS) (Balen, 2004). In order to understand the cause of HA, there have been considerable number of studies on mechanism of androgen production and its regulation in the theca cells. From these studies, we have learned that the metabolic abnormalities that appear due to high fat deposition is the cause of elevated androgen production. The most important one among these metabolic abnormalities is hyperinsulinemia and insulin resistance (Dunaif, 1997). Receptors for insulin and insulin-like growth factor-I (IGF-I) are abundant in the human ovary (Franks *et al.,* 1999). It led to the hypothesis that excess insulin cause excessive ovarian androgen production.

Leptin in obesity and reproduction: Body fat is the primary source of leptin synthesis. Leptin was first discovered in 1994 form the adipose tissue of ob/ob mice (Zhang *et al.,* 1994). The circulating leptin molecule is of 146 amino acid with a molecular weight of 16 kDa. The leptin receptor belongs to the class I cytokine receptor family (Tartaglia *et al.,* 1995). Multiple splice variant of leptin receptor with different length of intracellular domain are produced from the same gene. The long isoform is predominantly expressed in the hypothalamus and the short form is widely expressed. It signals via the JAK/STAT and the MAPK pathways. The amount of leptin synthesized and released in circulation depends upon the amount of fat in the body and the leptin together with insulin signals to the brain for fat deposition. Both leptin and insulin acts on the peripheral reproductive tissues for anabolic activity that play a crucial role in reproduction (Poretsky *et al.,* 1999). It is also a potent satiety element (Halaas *et al.,* 1995). It acts on the hypothalamus via its receptor and suppress food intake. It also increases the insulin sensitivity on the peripheral tissues and therefore modulates glucose metabolism (Abrams and Pickett, 1999). Apart from fat, there is difference in the circulating leptin level between the gender. Serum leptin is considerably high in women than in men of equal body weight. The gonadal steroid directly acts on the adipose tissues and are responsible of this difference in the level of serum and that influence the site of fat deposition. Glucose metabolism links food intake and leptin synthesis in adipose tissue. The leptin release is now shut down by negative feedback through sympathetic nervous system. Other regulators of leptin synthesis include glucocorticoids, cytokines and agonists of peroxisome proliferator-activated receptor- γ (PPAR-γ), although the physiologic role of these factors is not fully understood. The major function of leptin is to inform the brain about the energy stored in the body. With this information, brain modulate the body to maintain energy balance through food intake and energy expenditure which is important for survival and successful reproduction. Therefore, leptin play a crucial role in the physiology of reproduction. Leptin has drawn the attention of reproductive biologists. They believe that it is an indication of nutritional status that allows reproductive processes to. Leptin coordinate with both appetite and reproduction. It also acts on hypothalamus which express various neuropeptides (Clarke and Henry, 1999). The short form of leptin receptor is found in both the ovary (Karlsson *et al.,* 1997) and the testis (Hoggard *et al.,* 1997). Within the ovary, leptin inhibits the insulin-induced secretion of progesterone and androstenedione from cultured bovine thecal cells (Spicer and Francisco, 1998) and estrogen and progesterone from bovine granulosa cells (Spicer and Francisco, 1997). Leptin showed an inhibitory effect on combined IGF-I and FSH-stimulated estrogen production from rat granulosa cells (Zachow and Magoffin, 1997) and LH-stimulated estrogen secretion form cultured human granulosa cells (Karlsson *et al.*, 1997).

Obesity and insulin: Hormonal responses of obesity are now well understood. Overfeeding produces a significant increase in plasma insulin, IGF-I and androgen (Morovat *et al.,* 1994). All these hormones facilitate fat accumulation in response to excess energy (Spiegelman *et al.,* 1993). Study has shown a positive correlation between body mass and plasma insulin levels (Boswell *et al.,* 1994). The action of insulin on peripheral tissues is anabolic. Plasma insulin serves as a signal to the central nervous system about the body fat content (Schwartz *et al.,* 1992; Woods *et al.,* 1990). Studies on animals like squirrel, marmots and bats have demonstrated that circulating insulin level increased at the time of maximum body mass and body fat (Florant *et al.,* 1985; Doval and Krishna, 1998). The increase in insulin levels is associated with increased insulin resistance in peripheral tissue (Tokuyama *et al.,* 1991). These studies thus suggest that increase in body mass cause hyperinsulinemia (HI), which in turn may induce insulin resistance and fat accumulation.

Role of insulin in reproduction: Insulin receptor is expressed in human ovaries (Jarrett *et al.,* 1985; Poretsky *et al.,* 1985) suggesting its role in the regulation of ovarian function. It has been demonstrated from *in vitro* studies that insulin directly stimulate androgen production from ovarian stroma cells of PCO (Barbieri *et al.,* 1986). IGF is ubiquitously present and expressed in brain, pituitary and ovarian tissue (Monget and Martin, 1997). Therefore, there may be possibility that some of the reproductive responses are mediated by autocrine and paracrine effects of the IGF family rather classical endocrine actions. Frisch and Revelle (1970) hypothesized that puberty in human depends upon achieving a critical body weight, later Frisch and McArthur (1974) showed a better correlation between puberty and body fat. Thus, it has been hypothesized that ovulation in mammals is dependent upon certain amount body fat (Bronson and Manning, 1991). Some evidences reveal that insulin resistance, with compensating HI, is a normal phenomenon during puberty (Amiel *et al.,* 1991). HI amplifies protein anabolism and favors somatic cell growth. Insulin influences growth by modulating IGF-I action (Monget and Martin, 1997). It has been suggested that increase in insulin level during puberty affects sexual maturation by augmenting

the level of free sex steroid by decreasing the concentration of SHBG (Nobels and Dewailly, 1992). Rising insulin during puberty also suppresses IGF-binding proteins, thus freer IGF is available (Peiris *et al.,* 1989). Both insulin and IGF are known to have direct effect on gonadal steroidogenesis (Cara and Rosenfield, 1988). These studies thus suggest that insulin performs regulatory function in sexual maturation and growth by influencing the two key binding proteins IGF-binding proteins and SHBG. A substantial clinical and experimental data obtained in human beings and animal, both *in vitro* and *in vivo*, show that insulin and IGF play important role in ovarian physiology (Adashi *et al.,* 1985; Poretsky and Kalin, 1987;). It has been shown that insulin treatment, irrespective of gonadotropin secretion, increases ovulation rates of cycling gilts (Cox *et al.,* 1987), stimulates follicular steroid synthesis and decreases follicular atresia (Morley *et al.,* 1989). In the ovary, insulin stimulates steroidogenesis, up regulates receptor for gonadotropins and affects key steroidogenic enzymes, such as P450 side chain cleavage enzyme and aromatase (Krishna and Abhilasha, 2000; Poretsky, 1991). Both insulin and IGF-1 receptors have been identified in animal and human ovarian cells (Doval and Krishna, 1998; Monget and Martin, 1977).

Several *in vitro* studies have demonstrated that insulin stimulates ovarian steroidogenesis both in granulosa and thecal cells and helps in the production of androgen, estrogen and progesterone (Barbieri *et al.,* 1986; Poretsky and Kalin, 1987). Insulin may also be affecting ovarian steroidogenesis through IGF-1 (Poretsky, 1989). The possible mechanism by which insulin or IGF-1 stimulates steroidogenesis can be broadly classified into nonspecific or specific effects. The non-specific effects are the classic actions of the hormones on glucose transport, amino acid uptake, and DNA synthesis. This would improve cell viability and consequently enhance steroidogenesis. The specific effects include its action on steroidogenic enzymes, synergism between insulin/IGF and LH or FSH, or modulation of LH receptor etc. (Nestler and Jakubowicz, 1996). The effect of insulin on androgen production in women has been extensively studied (). In PCOS patients, a positive correlation has been reported between insulin and androgen (Nestler and Jakubowicz, 1996), while some failed to find such a relationship. The level at which insulin and IGFs act on ovarian cells to promote steroidogenesis has not been fully elucidated, but it appears to act at both transcriptional and posttranscriptional levels including increase in the stability of specific mRNAs. The thought that insulin acts on gonadotrophs for its function can be explained by a variety of clinical observations like amenorrhea, delayed puberty, anovulation, low pregnancy rate and early menopause in insulin dependent diabetes mellitus (IDDM). These diseases can only be understood if it is accepted that insulin is necessary for ovarian steroidogenic. But, prolonged stimulation of the ovary by insulin possibly produces morphological changes, such as hyperthecosis or polycystic changes. The idea that insulin affects ovarian steroidogenesis explains the state of HA accompanies PCOS and other insulin resistant states.

Polycystic ovary syndrome: PCOS is one of the most prevalent cause of infertility in females affecting 6-10% of women of reproductive age world-wide. It is defined as hyperandrogenism inclusive of anovulation without adrenal or pituitary disorders or ovarian tumors. It is a complex, multifactorial syndrome with heterogeneous clinical features and is characterized by increased GnRH pulse frequency, LH hypersecretion, hyperandrogenism, acne, hirsutism, underlying metabolic disorder such as hyperinsulinemia and anovulation. Studies suggest higher insulin in synergy with LH might be responsible for higher ovarian androgen production. Several hypothalamic neurons coordinate and maintains the synchronized pulsatile secretion of GnRH. Any change in GnRH pulse frequency and amplitude affect the LH and FSH secretory pattern. Such severe disturbance in pulsatile GnRH secretion is observed in women with PCOS. In anovulatory PCOS women, LH:FSH ratio is typically high. High LH increases androgen production in the theca cells, whereas aromatase activity in not upregulated in granulosa cells. This leads to overproduction of androgen in the ovary. About 80–85% of women with PCOS have clinical hyperandrognism which is further exacerbated by the concomitant presence of obesity and metabolic abnormalities. Hyperandrogenism (HA) in women is associated with android obesity which is one of the major characteristics of PCOS (Balen, 2004). Obesity has a profound effect on both pathophysiology and clinical symptoms. However, it is not necessarily a defect intrinsic to PCOS as 40–50% of women with PCOS are not obese. Other important metabolic factor associated with PCOS is hyperinsulinemia and insulin resistance. This hyperinsulinemia may modulate steroidogenesis and high androgen production from the ovary which ultimately cause premature follicular atresia and thus anovulation. Sometimes despite normal insulin binding, primary defects in insulin-mediated glucose transport, GLUT4 production and adrenergic signaling in adipocytes have been reported in many patients. LH hypersecretion together with increased LH pulse frequency due to increased hypothalamic GnRH and decreased steroidal negative feedback on LH secretion have been reported in 70% of women with PCOS. Apart from the metabolic and endocrinological factors, genetic and environmental factors also contribute to the development of PCOS. However, it is believed that the multiple genes and multiple factor such as intra-uterine environment, lifestyle, food and more recently gut and uterine microbiota (Thackray, VG. 2019) may exaggerate the complications. Since PCOS patients are presented with varied clinical features, therefore their treatment is symptomatic and not monotherapeutic.

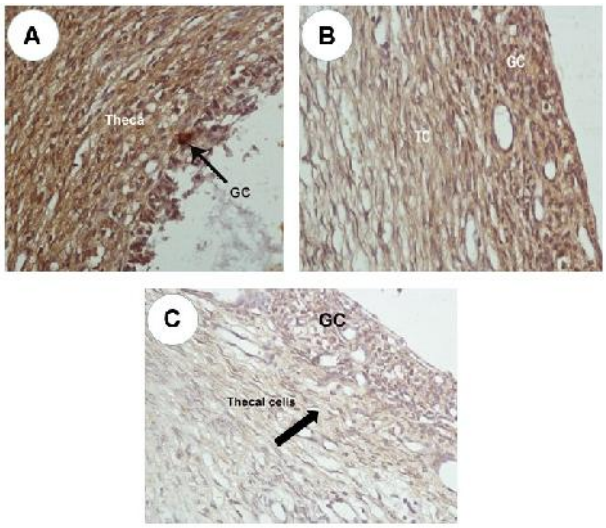

Fig. 1: Ovarian sections of women with PCOS were immunostained for GnRH I and GnRH I-receptor to demonstrate their localization (Fig. 1). GnRH I immunoreactivity was mainly localized in the large cystic follicles. Immunohistochemical localization of GnRH I (Fig A & B) and GnRH I-receptor (Fig C) in the ovary of PCO woman. (A) & (B) Strong GnRH I immunoreactivity in the granulosa cells (arrows). (C) GnRH I-receptor immunoreactivity in the theca cells (arrow)

Distribution of GnRH I and its receptors in the ovary of PCOS women: In an attempt to determine the role of GnRH in PCOS, we examine the localization of GnRH and its receptor in the ovaries from women with PCOS. The PCOS ovaries collected from the patients, undergone surgery for hysterectomy and the tissues were processed for immunohistochemical localization for GnRH and GnRH receptor. Ovarian sections of women with PCOS were immunostained for GnRH I and GnRH I-receptor to demonstrate their localization (Fig 1). GnRH I and GnRH I-receptor immunoreactivity was mainly localized in the large cystic follicles. Within the follicle, strong GnRH I immunoreactivity was noted in the granulosa layer and moderate in the theca layers of the follicle (Fig 1 A, B). GnRH I-receptor immunoreactivity was mainly found in the granulosa cells. A mild immunostaining of GnRH I-receptor was also noted in the theca layer (Fig 1 C) of PCO ovary of the woman. We also found moderate immunoreactivity for GnRH I and GnRH I-receptor in cumulus oophorus and strong immunoreactivity in the oocytes of cystic follicles of PCO mouse model (Singh, *et al.*, 2016). GnRH I, GnRH II and type I GnRH-R has also been localized in the human ovary suggesting its autoregulatory role in follicular development and corpus luteum functions (Choi, *et al.*, 2006**)**. Our data suggests the possibility of involvement of GnRH in the development of cystic follicles.

Conclusion

Obesity is rapidly growing in the population in a number of countries worldwide and has become threat to the health of people. Significant associations between obesity and several reproductive disturbances have also been seen. Such reproductive disturbances include irregular menstrual cycles, reduced spontaneous and induced fertility, increased risk of miscarriage and hormone-sensitive carcinomas. Distinct changes in the circulating sex hormones appear to underline these abnormalities. Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders associated with obesity. Clinical and biochemical evidence of hyperandrogenism (HA) has been described in obese PCOS women with menstrual disturbances, but relevance of these findings to the mechanism of anovulation is not obvious. Obesity may not only affect the ovulation, but also the outcome of pregnancy in fertile women. The various factors that mediate the effects of obesity and the mechanism responsible for communicating obesity or nutritional status to the reproductive system are complex and are poorly understood. Further studies are needed to establish the relevance of presence of GnRH and GnRH receptor in the different compartments of antral follicles of PCO.

Key Points

- Obesity leads to high circulating leptin, hyperinsulinemia, and insulin resistance.
- High leptin inhibits steroidogenesis in the ovary.
- In PCOS patients, a positive correlation has been reported between insulin and androgen production form the ovary.
- Obesity may not only affect the ovulation, but also the outcome of pregnancy in fertile women.
- There is possibility of involvement of GnRH in the development of cystic follicles.

Source of funding: This work was partially supported by Grant-in aid from DBT-BIOCARE (BT/PR20038/ BIC/ 101/537/2016) and DST-SERB (EMR/2016/007290) to PS.

Glossary of Abbreviations
HA - Hyperandrogenism
HI - Hyperinsulinemia
IDDM - Insulin dependent diabetes mellitus
IGF-I - insulin-like growth factor-I
PCOS- polycystic ovary syndrome
PPAR-γ - peroxisome proliferator-activated receptor- γ
SHBG- sex hormone-binding globulin

REFERENCES

Abrams, B., & Pickett, KE. 1999. Maternal nutrition. In: *Maternal-fetal medicine* 4th edn., pp. 122-131. Eds RK Creasy and K Resnik. Philadelphia, Pennsylvania, USA: W.B. Saunders Company.

Adashi, EY., Resnick, CE., D'Ercole, AJ., Svoboda ME., van Wyk, JJ. 1985. Insulin-like growth factors as intraovarian regulators of granulosa cell growth and function. Endocrine reviews., 6(3):400-20.

Amiel, SA., Caprio, S., Sherwin, RS., Plewe, G., Haymond, MW., Tamborlane, WV. 1991. Insulin resistance of puberty: a defect restricted to peripheral glucose metabolism. The Journal of Clinical Endocrinology & Metabolism., 72(2):277-82.

Balen, A. 2004. The pathophysiology of polycystic ovary syndrome: trying to understand PCOS and its endocrinology. Best practice & research clinical obstetrics & gynaecology., 18(5):685-706.

Barbieri, RL., Makris, A., Randall, RW., Daniels, G., Kistner, RW., Ryan, KJ.1986. Insulin stimulates androgen accumulation in incubations of ovarian stroma obtained from women with hyperandrogenism. The Journal of Clinical Endocrinology & Metabolism., 62(5):904-10.

Boswell, T., Woods, SC., Kenagy, GJ. 1994. Seasonal changes in body mass, insulin, and glucocorticoids of free-living golden-mantled ground squirrels. General and comparative endocrinology., 96(3):339-46.

Bronson, FH., & Manning, JM. 1991. The energetic regulation of ovulation: a realistic role for body fat. Biology of Reproduction., 44(6):945-50.

Cara, JF., Rosenfield, RL. 1988. Insulin-like growth factor I and insulin potentiate luteinizing hormone-induced androgen synthesis by rat ovarian thecal-interstitial cells. Endocrinology., 123(2):733-9.

Choi, JH., Gilks, CB., Auersperg N., Leung PKC. 2006. Immunolocalization of Gonadotropin-Releasing Hormone (GnRH)-I, GnRH-II, and Type I GnRH Receptor during Follicular Development in the Human Ovary. The Journal of clinical endocrinology and metabolism., 91 (11): 4562–4570

Clarke, IJ., & Henry, BA. 1999. Leptin and reproduction. Reviews of reproduction. 4(1):48-55.

Cox, NM., Stuart, MJ., Althen, TG., Bennett, WA., Miller, HW. 1987. Enhancement of ovulation rate in gilts by increasing dietary energy and administering insulin during follicular growth. Journal of animal science., 64(2):507-16.

Doval, J., & Krishna, A. 1998. Ovarian androstenedione production is enhanced by insulin during the period of

delayed ovulation in a vespertilionid bat, Scotophilus heathi. Reproduction., 114(1):63-8.

Dunaif, A. 1997. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocrine Reviews 18 774-800.

Flegal, KM., Graubard, BI., Williamson, DF., Gail, MH. 2005. Excess deaths associated with underweight, overweight, and obesity. Jama., 293(15):1861-7.

Florant, GL., Lawrence, AK., Williams, KR., Bauman, WA. 1985. Seasonal changes in pancreatic b-cell function in euthermic yellow-bellied marmots. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology., 249(2): R159-65.

Franks, S., Gilling-Smith, C., Watson, H., Willis, D. 1999. Insulin action in the normal and polycystic ovary. Endocrinology and metabolism clinics of North America., 28(2):361-78.

Frisch, RE., McArthur, JW. 1974. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science., 185(4155):949-51.

Frisch, RE., Revelle, R. 1970. Height and weight at menarche and a hypothesis of critical body weights and adolescent events. Science.,169(3943):397-9.

Halaas, JL., Gajiwala, KS., Maffei, M., Cohen, SL., Chait, BT., Rabinowitz, D., Lallone, RL., Burley SK., Friedman, JM. 1995. Weight-reducing effects of the plasma protein encoded by the obese gene. Science., 269(5223):543-6.

Hoggard, N., Mercer, JG., Rayner, DV., Moar, K., Trayhurn, P., Williams, LM. 1997. Localization of Leptin Receptor mRNA Splice Variants in Murine Peripheral Tissues by RT-PCR and in-situ Hybridization. Biochemical and biophysical research communications. 232(2):383-7.

Choi, JH., Gilks, CB., Auersperg, N., Leung, PC. 2006. Immunolocalization of gonadotropin-releasing hormone (GnRH)-I, GnRH-II, and type I GnRH receptor during follicular development in the human ovary. The Journal of Clinical Endocrinology & Metabolism., 91(11):4562-70.

Jarrett, JC., Ballejo, G., Tsibris, JC., Spellacy, WN. 1985. Insulin binding to human ovaries. The Journal of Clinical Endocrinology & Metabolism., 60(3):460-3.

Kahn, BB., Flier, JS. 2000. Obesity and insulin resistance. Journal of Clinical Investigation 106 473-481.

Karlsson, C., Lindell, K., Svensson, E., Bergh, C., Lind, P., Billig, H., Carlsson, LM., Carlsson, B. 1997. Expression of functional leptin receptors in the human ovary. The Journal of Clinical Endocrinology & Metabolism., 82(12):4144-8.

Kirschner, MA., Schneider, G., Ertel, NH., Worten, E. 1982. Obesity, androgens, estrogens, and cancer risk. Cancer Research 42 3281-3285.

Krishna, A., & Abhilasha, S. 2000. Proliferative activity of follicles and serum steroid concentration in Scotophilus heathi (vespertilionid bat) during periods of delayed ovulation. Canadian journal of zoology., 78(8):1301-8.

Monget, P., & Martin, GB. 1977. Involvement of insulin-like growth factors in the interactions between nutrition and reproduction in female mammals. Human Reproduction., 12(suppl_1):33-52.

Morley, P., Calaresu, FR., Barbe, GJ., Armstrong, DT. 1989. Insulin enhances luteinizing hormone-stimulated steroidogenesis by porcine theca cells. Biology of reproduction., 40(4):735-43.

Nestler, JE., & Jakubowicz, DJ. 1996. Decreases in ovarian cytochrome P450c17{alpha} activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. New England Journal of Medicine 335 617-623.

Nobels, F., & Dewailly, D. 1992. Puberty and polycystic ovarian syndrome: the insulin/insulin-like growth factor I hypothesis. Fertility and Sterility 58 655-666.

Pasquali, R., & Vicennati, V. 2001. Obesity and Hormonal abnormalities. In International text book of obesity pp 225-239. Eds P Bjorntorp Chichester, UK: John Wiley and Sons.

Pasquali, R., Casimirri, F., Venturoli, S., Paradisi, R., Mattioli, L., Melchionda, N., Labò, G.1983. Insulin resistance in patients with polycystic ovaries: its relationship to body weight and androgen levels. European Journal of Endocrinology., 104(1):110-6.

Pasquali, R., Pelusi, C., Genghini, S., Cacciari, M., Gambineri, A. 2003. Obesity and reproductive disorders in women. Human Reproduction Update 9 359-372.

Peiris, AN., Aiman, EJ., Drucker, WD., Kissebah, AH. 1989. The relative contributions of hepatic and peripheral tissues to insulin resistance in hyperandrogenic women. The Journal of Clinical Endocrinology & Metabolism., 68(4):715-20.

Poretsky, L., & Kalin, MF.1987. The gonadotropic function of insulin. Endocrine reviews. 8(2):132-41.

Poretsky, LF., Grigorescu, F., Seibel, M., Moses, AC., Flier, JS. 1985. Distribution and characterization of insulin and insulin-like growth factor I receptors in normal human ovary. The Journal of Clinical Endocrinology & Metabolism., 61(4):728-34.

Poretsky, L. 1989. Specificity spill over at the hormone receptor. The New England journal of medicine., 321(7):474.

Poretsky, L. 1991 On the paradox of insulin-induced hyperandrogenism in insulin-resistant states. Endocrine Reviews., 12(1):3-13.

Schwartz, MW., Figlewicz, DP., Baskin, DG., Woods, SC., Porte, Jr D. 1992. Insulin in the brain: a hormonal regulator of energy balance. Endocrine reviews.,13(3):387-414.

Singh P., Srivastava RK., Krishna A. 2016. Effects of gonadotropin-releasing hormone analogs on ovarian activity in the animal model for polycystic ovary. The Journal of Steroid Biochemistry and Molecular Biology., 163:35–44.

Spicer, LJ., & Francisco, CC. 1997. The adipose obese gene product, leptin: evidence of a direct inhibitory role in ovarian function. Endocrinology.,138(8):3374-9.

Spicer, LJ., & Francisco, CC. 1998. Adipose obese gene product, leptin, inhibits bovine ovarian thecal cell steroidogenesis. Biology of Reproduction., 58(1):207-12.

Spiegelman, BM., Choy. L., Hotamisligil, GS., Graves, RA., Tontonoz, P. 1993. Regulation of adipocyte gene expression in differentiation and syndromes of obesity/diabetes. The Journal of biological chemistry (Print)., 268(10):6823-6.

Thackray, VG. 2019. Sex, microbes, and polycystic ovary syndrome. Trends in Endocrinology & Metabolism., 30(1):54-65.

Tokuyama, K., Galantino, HL., Green, R., Florant, GL. 1991. Seasonal glucose uptake in marmots (Marmota flaviventris): the role of pancreatic hormones.

Comparative biochemistry and physiology. A, Comparative physiology., 100(4):925-30.

Vague, J. La 1947. différentiation sexuelle facteur déterminant des formes de l'obésité. Presse méd., 30:339-40.

Wajchenberg, BL. 2000. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocrine reviews., 21(6):697-738.

Woods, SC., DP, FL., Schwartz, MW., Porte, Jr D. 1990. A re-assessment of the regulation of adiposity and appetite by the brain insulin system. International journal of obesity., 14:69-73.

Zachow, RJ., Magoffin, DA. 1997. Direct intraovarian effects of leptin: impairment of the synergistic action of insulin-like growth factor-I on follicle-stimulating hormone-dependent estradiol-17β production by rat ovarian granulosa cells. Endocrinology., 138(2):847-50.

Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., Friedman, JM. 1994. Positional cloning of the mouse obese gene and its human homologue. Nature.372(6505):425-32.

****