

# Insights into the putative role of leptin in various traversing stages of women: A narrative review

G. M. Saranya\*, M. Ramesh Pathy

School of Bio Sciences and Technology, Vellore Institute of Technology (VIT) Vellore, Tamil Nadu, India.

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## ABSTRACT

From adolescence to adulthood, a woman goes through distinct phases in her life. The role of leptin in this journey is very crucial, as it supports her to cross different milestones in time. Leptin is an indispensable factor in the metabolic control of puberty, fertility, and pregnancy. Puberty is a chronic biological process that helps transform a child into an adult. In this process, sufficient amount of leptin is necessary for the initiation of puberty in girls. Apart from maintaining the energy homeostasis by regulating the food intake and energy expenditure, it also regulates various other hormones required for reproduction and regulation of the endocrine system. Malfunction of leptin alters the neuroendocrine pathways and causes a detrimental effect on reproductive disorders, such as PCOS, obesity, diabetes, anorexia, and infertility which are the most important intimation for female reproductive health worldwide. In this article, we aim to provide a synoptic view on the roles of leptin in the metabolic regulation of the reproductive axis, its hormonal regulations, permissive role for the onset of puberty, continuity of menstrual cycle and the putative roles of leptin during gestation, including its potential function as placental hormone in a female.

## INTRODUCTION

Leptin is an adipocyte hormone and is also called as the master hormone of the body which is produced mostly by adipocytes and by granulosa, theca cells and cumulus cells of ovarian follicles (Kamyabi and Gholamalizade, 2015; Catteau *et al.*, 2016). It is a 16-kDa protein of 167 amino acids plays a crucial role in the regulation of energy balance and body weight control (Farhood *et al.*, 2016). Circulating leptin binds to leptin receptor and functions as part of a signalling pathway, including Janus kinase 2 (JAK2)-signal transducer and activator of transcription 3 (STAT3), insulin receptor substrate (IRS)-phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), and 5' adenosine monophosphate-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC). Among these, the JAS/STAT3 plays an important role in the regulation of energy homeostasis (Catteau *et al.*, 2016). In human beings, leptin and leptin receptor genes are present at chromosomal locations 7q32.1 and 1p31.3

respectively. Mutation in the leptin and in its regulatory regions has been linked to type 2 diabetes mellitus development, metabolic disorders, hormonal imbalance and causes severe obesity that leads to infertility (Sanchez and Tena, 2013). It also regulates several endocrine functions and is involved in the regulation of immune and inflammatory responses, hematopoiesis, angiogenesis, reproduction, bone formation and wound healing (Nunziata *et al.*, 2017).

Due to the influence of sex hormones and larger subcutaneous fat, women likely to have higher leptin levels than men. Low level of leptin in women will affect puberty and reproduction when leptin concentrations are adequate, the body may reduce energy stores for the sake of reproduction. During low leptin concentration that energy stores are low so it gives a signal that the body should need food for energy balance and reproduction (Naylor and Petri, 2016). Leptin has a significant position in the global obesity, increasing obesity is positively correlated to a number of anovulatory cycles and it directly inhibits ovarian steroidogenesis, leading to inoperative follicular maturation (Sroga *et al.*, 2016). The risk of subfecundity and infertility, conception rates, miscarriage rates and pregnancy complications are increased in these women. They have poor

\*Corresponding Author

G. M. Saranya, Associate Professor, School of Bio Sciences and Technology, VIT Vellore, 632014.

E-mail: [mrameshpathy@vit.ac.in](mailto:mrameshpathy@vit.ac.in)

reproductive outcomes in natural as well as assisted conception (David *et al.*, 2014). In this review, we will focus on the pivotal role and association of leptin in a female during her various stages of life.

## METHODOLOGY

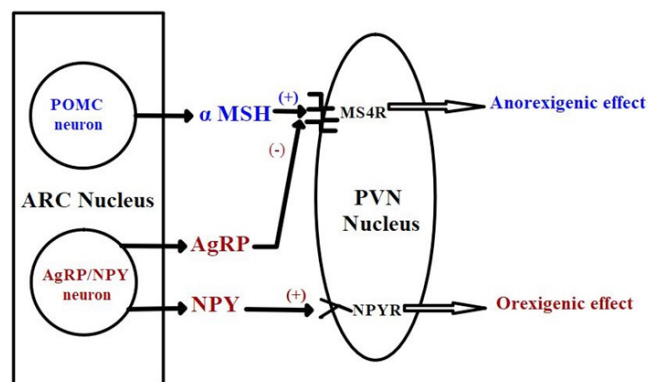
The review was gleaned following a thorough survey of reliable and legitimate publications like Science Direct, PubMed, PubMed Central, Google Scholar, Scopus and other scientific databases without any study design restriction. The inquiry was built by using the keywords since the investigation of the role of leptin in women is less and only a few relevant reports are cited. Surplus literature was analyzed from reference lists in the subsequent journals and review articles of interest. The significant facts were compiled, analyzed as per the essence of the study and original flow diagrams were made for better understanding. Further in this review, the confines in the existing literature on relations between leptin and its pivotal role in women health was utilized.

## LEPTIN AS HORMONE REGULATOR

Leptin acts as a satiety hormone as well as cell signaling hormone which is involved in regulation of body weight control through obstruction of food intake and amplification of energy expenditure (Blüher *et al.*, 2007; Leckle *et al.*, 2011). Two nucleus in the hypothalamus PVN (paraventricular nucleus) and ARC (arcuate nucleus) are responsible for maintaining homeostasis in our body (Gautron and Elmquist, 2011; Park and Ahima, 2015; Stieg *et al.*, 2015). Leptin enters the bloodstream via circulatory system and binds to receptors on the ARC nucleus and stimulate the POMC (proopiomelanocortin) neuron to produce  $\alpha$ -MSH (Alpha-melanocyte stimulating hormone), which in turn binds to the MS4R receptor of the PVN neuron to suppress the appetite (anorexigenic effect) and to increase the metabolic rate in order to achieve homeostasis. Also, leptin inhibits the release of appetite-stimulating factors by inhibiting the AgRP/NPY neuron which is responsible for the secretion of AgRP (Agouti-Related Protein) and NPY (neuropeptide Y) (Kelesidis *et al.*, 2010). NPY binds to the NPY receptor of PVN neuron and increase the appetite (orexigenic effect) and AgRP binds to the MS4R receptor and act as an antagonist to  $\alpha$ -MSH and thereby increase the appetite as shown in figure 1. So a deficiency of leptin leads to frequent hunger and in turn increases the risk of developing obesity (Vehapoğlu *et al.*, 2016; Kumari *et al.*, 2017).

Ghrelinergic cells in the gastrointestinal tract produce ghrelin, a hormone responsible for hunger in our body. It functions as an adiposity signal as well as a neuropeptide in the central nervous system, to stimulate hunger. Ghrelin increases the orexigenic effect by stimulating the AgRP/NPY neuron present in ARC nucleus. There is a relationship between the hormones ghrelin and leptin in the regulation of hunger in the human body (Cowley *et al.*, 2001; Budak *et al.*, 2006; Klok *et al.*, 2007). An increase in ghrelin will lead to hunger stimulation, while the increase in leptin will lead to its suppression. In normal condition ghrelin level is high before a meal and low after meals. In abnormal conditions, an elevated level of leptin concentration may cause leptin resistance which fools the brain to keep the ghrelin signal continuously stimulated. Administration of ghrelin in female rats

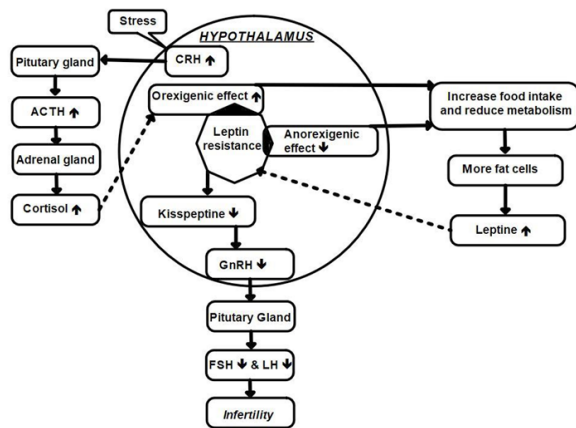
produces hyperphagia by suppressing the effect of leptin and increasing arcuate nucleus production of NPY and AgRP, leading to weight gain in the tested model (Nogueiras *et al.*, 2008; Perry *et al.*, 2012; Abizaid and Horvath, 2012).



**Fig. 1:** Anorexigenic and orexigenic effect induced by PVN nucleus in response to the ARC nucleus. Activation of the MS4R receptor by  $\alpha$ MSH induces anorexigenic effect (suppress appetite), and activation of NPY receptor by NPY induces orexigenic effect (induce appetite).

Leptin acts as an energy indicator which is required for normal hypothalamic control of reproduction. The increase of leptin concentration is one of the crucial factors for hormone secretion (Louis *et al.*, 2011; Paris *et al.*, 2017). For instance, increased leptin level is responsible for the gonadotrophin-releasing hormone (GnRH) secretion from hypothalamus which in turn stimulates pituitary gland leading to secretion of both follicle stimulating hormone (FSH) and luteinizing hormone in normal condition. Further these results in production and secretion of estrogen and progesterone in the ovary. Apart from causing obesity leptin deficiency and/or leptin resistance will also inhibit gonadotropin-releasing hormone (GnRH) secretion further absence of GnRH inhibits the secretion of FSH (Follicle stimulating hormone) and LH from pituitary which may in turn cause infertility as shown in figure 2. In female mice inactivation of the POMC gene or MC3R and MC4R receptors which lead subfertility at adult age (Roseweir *et al.*, 2008). The absence of leptin and insulin receptors from these cells causes irregularities of the estrous cycle, follicular abnormalities in the ovary and impairment of fertility (Blüher and Mantzoros, 2009; Ratra and Elias, 2014).

Yet another hormone which influences hunger, obesity, and fertility is cortisol. This neuroendocrine hormone is secreted by adrenal gland due to the abnormal factor-stress. In response to stress, the hypothalamus secretes corticotropin-releasing hormone (CRH) and NPY. A higher level of CRH will stimulate the pituitary gland to secrete ACTH which in turn will stimulate the adrenal gland to secrete cortisol. Both cortisol and NPY are responsible for orexigenic effect and hence stimulate appetite (Chou and Mantzoros, 2014). This increases the food intake and favors adipocytes to grow into mature fat cells and gets deposited deeply in the abdomen to form fat pads. It leads to intervention in the leptin – ghrelin signaling pathway by inducing leptin resistance (Leshan and Pfaff, 2014; Crujeiras *et al.*, 2015). This mechanism indirectly results in obesity and infertility as shown in figure 2.



**Fig. 2:** Increase in orexigenic effect and decrease in anorexigenic effect due to leptin resistance and stress will lead to decrease in GnRH secretion and infertility.

### LEPTIN AND ITS ROLE IN PUBERTY

The link between fat stores, puberty onset, and fertility, which was proposed by the Frisch hypothesis, was proved after the identification of leptin. Leptin is an undisputed factor in the metabolic control of puberty and fertility (Sanchez-Garrido and Tena-Sempere, 2013; Könnér and Brüning, 2012; Castellano *et al.*, 2016). Leptin plays a dynamic role in the process of puberty; it initiates the biological process required for the development of adulthood. However, the normal puberty onset plays an important role here in promoting the reproductive system development and maintaining the reproductive capacity (Elias, 2012; Hausman *et al.*, 2012; Manfredi *et al.*, 2016).

Puberty is regulated by interactions between kisspeptins and leptin and also the maturation of kisspeptin neurons. Suprachiasmatic nucleus (SCN) is a part of the hypothalamus which is called master clock of the body to regulate puberty (Beymer *et al.*, 2016). Kisspeptins are essential gatekeepers of mammalian puberty, and the relevance of energy homeostasis for the pubertal regulation, especially in females. Kisspeptin is found to be an intermediary between leptin signaling and GnRH function. Studies suggest that leptin/leptin receptor and kisspeptin/kiss1 receptor system plays an important role in regulating the puberty onset and the function of reproduction. Injecting leptin in prepubertal female mice hypothalamus stimulates GnRH secretion and subsequently, LH secretion resulting in an earlier onset of reproductive function and earlier maturation in the reproductive tract than that of controls (Luo *et al.*, 2016). By inducing fasting or food restriction in female rat it affects the signaling pathway of the leptin/leptinR/kisspeptin/kiss1r and it decreases the GnRH neuroendocrine activity it leads delay the puberty onset it suggests leptin important for initiation of kisspeptin pathways, puberty and fertility (Clarke *et al.*, 2015). Administration of leptin will increase the kisspeptin expression and stimulate the puberty in the female rat. These animal studies suggest that kisspeptin may stimulate GH from anterior pituitary (Semaan *et al.*, 2013; Tng, 2015).

Kisspeptins (Kp), encoded by Kiss1 gene with the ability to activate the G protein-coupled receptor, Gpr54. Inactivation of Gpr54 or Kiss1 perturbs puberty and which leads absence of puberty. Kisspeptin is an important key regulator for

the mammalian reproduction, kisspeptin, acting centrally via the kisspeptin receptor, stimulates the secretion of gonadotrophin releasing hormone (GnRH) (Gueorguiev *et al.*, 2001; Olaniyan *et al.*, 2013). Kisspeptin receptor gene expression has been present in both the ARC (arcuate nucleus) and AVPV (anteroventral periventricular nucleus) of the hypothalamus. Kisspeptin secreted from hypothalamus causes a chain reaction which leads to the release of neurotransmitters from the pituitary gland (Terasawa *et al.*, 2013). These neurotransmitter signals lead to the release of other hormones such as luteinizing hormone and follicle stimulating hormone. Neurokinin B [NKB] and dynorphin [DYN] are two other neuropeptides which act as key hypothalamic regulators in reproductive function. They are used for the GnRH secretion pathways as a self-switch on and self-switch off process. DYN inhibits kisspeptin release and NKB stimulates kisspeptin release (Rhie *et al.*, 2014; Skorupskaite *et al.*, 2014). Kisspeptin stimulates GnRH neurons to release GnRH from the hypothalamus into the hypothalamic-pituitary portal circulation which causes the release of gonadotrophs from the anterior pituitary.

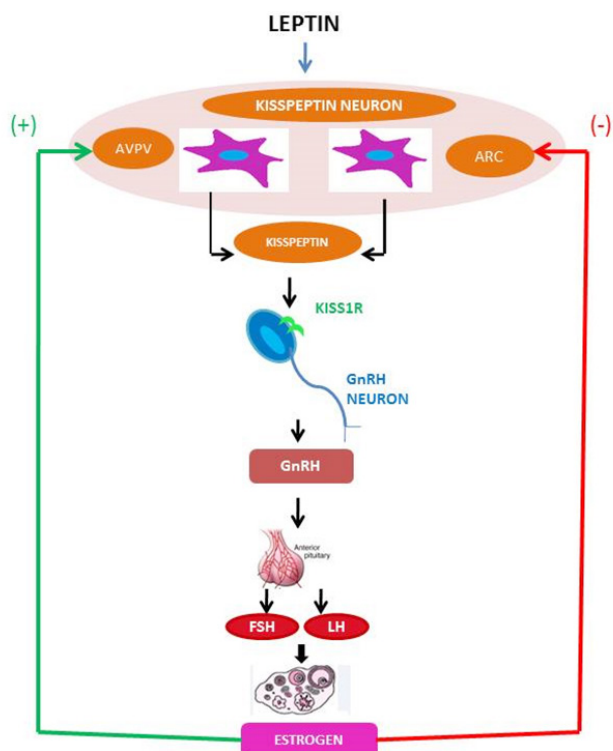
The expression of kisspeptin, kiss1r, GnRH, and leptinR were detected in the hypothalamic arcuate nucleus, surrounding the ventral surface of the third ventricle (3v) in the brain. The decrease of GnRH and GnRH mRNA levels subsequently caused the alteration of FSH and LH. Therefore, the changes in LH and FSH concentrations can cause abnormal development of follicle, ovulation, and luteinization. HPG axis was reactive during puberty onset and there was an increase in the expression level of GnRH and gonadal steroid hormone levels (Pan *et al.*, 2016). Kisspeptin signaling in the hypothalamus has been important for the regulation of the GnRH pulse generator. Kisspeptin does not affect feeding but has emerged as one of the major canals to relaying body metabolic status information to GnRH neurons (De Bond and Smith, 2014).

Estrogen exerts both positive and negative feedback mechanism on kisspeptin neuron as shown in figure 3. In positive feedback, estrogen exerts on kisspeptin neuron in AVPV, which is mediated through estrogen receptor and may account for the LH surge in the menstrual cycle. Normally estrogen allows the gonads to communicate with hypothalamus to regulate GnRH release, once activated HPG axis continuously work but it becomes deregulated by the lack of oocytes during menopause. This feedback effect of the estrogen regulates the expression was related with kisspeptin and kisspeptin encoding genes to mediate positive feedback effect of kisspeptin on GnRH release (Sheffer *et al.*, 2013; Javed *et al.*, 2015). In ARC, estrogen binds to estrogen receptor on kisspeptin neurons will inhibit kisspeptin and subsequently GnRH release (Roa *et al.*, 2008). Estrogen exerts negative feedback on GnRH release which is mediated via estrogen receptor. Estrogen receptor is not expressed in GnRH neurons while it is expressed in kisspeptin neurons. In the pubertal mice high amount of leptin on the GnRH, it will block the kisspeptin pathway, these observations illustrate the negative effect of obesity-induced female infertility (Han *et al.*, 2005; Luo *et al.*, 2016).

### EFFECT OF LEPTIN IN FEMALE REPRODUCTIVE HEALTH

Women reproductive health refers to the health of women during their reproductive years, which are the years they

can have a child. Disorders of reproduction include low birth weight, birth defects, preterm birth, developmental disorders, menstrual disorders, reduced fertility and impotence (Crain *et al.*, 2008). Leptin plays a significant role in the maintenance of female reproductive health. Leptin and leptin receptors (Ob-Rb) have been identified in the hypothalamus, gonadotrope cells in the anterior pituitary, granulosa, theca, and interstitial cells of the ovary and endometrium respectively. This multifocal expression of leptin and the dense presence of leptin receptors at all levels of the hypothalamus-pituitary-gonadal (HPG) axis indicates the role of leptin in nutritional regulation and infertility (Vázquez *et al.*, 2015; Pankov, 2015). Leptin regulation of reproduction involves a complex network of interactions at many levels to regulate the HPG axis (Goumenou *et al.*, 2003).

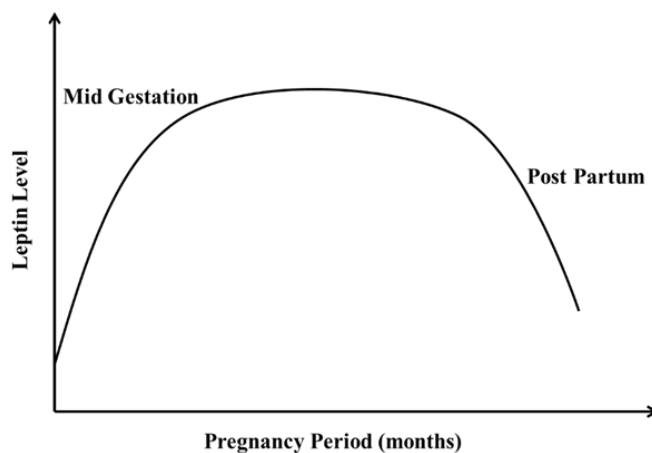


**Fig. 3:** Figure represents the role of kisspeptin and leptin in estrogen production from the ovary. Estrogen has a positive effect on AVPV neuron and negative effect in ARC neuron.

Leptin is performing a main role in reproductive and regulation of endocrine gland (Dardeno *et al.*, 2010). It acts as an important signal that depends on the adequacy of nutritional status in reproductive function because insufficiency of nutrition during adulthood can lead to a reduction of GnRH and causes infertility (Zhou and Rui, 2013; Naylor and Petri, 2016). Leptin acts as a facilitator of GnRH expression, elevated level of leptin concentration, not only stimulate release of GnRH from hypothalamus but also stimulates LH and FSH, which are responsible for synthesizing follicular development and ovulation, the high or low amount of ovarian steroidogenesis (17-beta-estradiol (E2) and progesterone (P4)) depending on leptin concentration (Dubern and Clement, 2012). Leptin function in the ovary, there is a potential consequence in the regulation of folliculogenesis and ovulation.

The intervention of leptin signaling may lead to a pathophysiological role in reproductive disorders and metabolic alterations (Jalilian *et al.*, 2016). Malfunction of leptin will alter the neuroendocrine pathways and causes a detrimental effect in reproductive disorders, such as PCOS, obesity, diabetes, and anorexia these are the most important intimation for female reproductive health worldwide (González *et al.*, 2000; Gao and Horvath, 2008; Brown and Clegg, 2013). Leptin secreted from adipose reservoir affects fertility, a higher concentration of leptin provides an impact on oocyte and embryo quality leading to the destruction of endometrial bed preparation that may be involved in pregnancy failure (Unuane *et al.*, 2011; Pérez *et al.*, 2015). Increases in follicular fluid leptin may negatively affect the embryo development, quality, implantation and pregnancy rates (Sam and Dhillo, 2010; Karoutsos *et al.*, 2017). Leptin might play a double-edged sword in reproduction both when leptin level is lower and higher than normal. It can exert a negative effect on reproduction, so it affects the normal functioning of ovary and development of the fetus (Patterson *et al.*, 2012; Tsouma *et al.*, 2014; Mutaz, 2015).

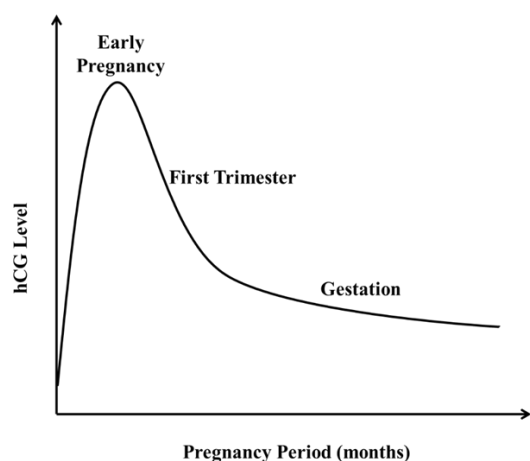
The change in concentration of different hormones related to metabolism and energy homeostasis during pregnancy have been studied (Briffa *et al.*, 2014; Farhood *et al.*, 2016). It is a condition where the normal functioning of the HPG axis is suppressed and in order to cope with the growing fetus's energetic demands, metabolic adaptations occur in mother. During gestation in humans, the increase in leptin level is attributed by both maternal adipose tissue and placenta (Henson and Castracane, 2000). In which, the placental leptin level is the key source of circulating leptin that leads to an increase in BMI comparatively (Salem *et al.*, 2016; Nishimura *et al.*, 2017). The pattern of circulating leptin concentration various during pregnancy, high level of leptin was observed in mid-gestation and it decreases subsequently in postpartum as shown in figure 4.



**Fig. 4:** Graphical representation of serum leptin level during pregnancy. Maternal leptin concentration significantly peaks at mid-gestation and gradually decreases during the postpartum period.

In humans, the maternal circulation facing syncytiotrophoblast and fetal circulation facing villous vascular endothelial cells were detected with placental leptin mRNA and a protein indicating the role of the placenta in the hyperleptinemia (Tafvizi and Masomi, 2016). The soluble isoform of leptin receptor

(Ob-Re) expressed by human placenta reaches circulation by various ways and binds to the free leptin and thereby maintains high leptin levels in the plasma also this prevents the binding of free leptin to the other isomer of leptin receptor Ob-Rb (Anum *et al.*, 2015). By maintaining the placental growth, fetal energy demands and a state of positive energy balance in mother, the energy accumulation during gestation is favored by an elevated level of maternal leptin which is linked to a state of central leptin resistance that works as a compensatory mechanism to store the energy resources in preparation to the metabolic demands of lactation (Herrid *et al.*, 2014). Human Chorionic Gonadotropin (hCG) is the placental hormone that increases placental leptin synthesis and secretion in early pregnancy (Joo *et al.*, 2010). The hCG levels increase rapidly during early pregnancy and decrease during the latter part of the first trimester and are maintained at low concentrations throughout gestation which is presented in figure 5.



**Fig. 5:** Graphical representation of Human Chorionic Gonadotropin (hCG) level during pregnancy. The highest peak during early pregnancy indicates the higher hCG level and the descending peak suggest a gradual reduction in hCG level during the gestation period.

The pattern changes of elevated hCG along with other hormones such as progesterone, prolactin, and placental lactogen, besides the loss of cyclical elevations in serum estradiol, initiates the leptin secretion in placenta and leptin resistance (Murphy *et al.*, 2009; Wauman *et al.*, 2017). The leptin production is maintained altogether by the placental production and increased estradiol levels during gestation (Llaneza *et al.*, 2014). Leptin has some pleiotropic effects that play a crucial role in fetal development and adequate placental function including implantation, placental angiogenesis, placental nutrient transport, immune modulation and trophoblast mitogenesis (Tong and Xu, 2012; Farr *et al.*, 2015). The leptin level in cord blood is in relation to the leptin level in fetal growth (Khalaf, 2010). The placental leptin modulates the transport of nutrients, especially amino acids and lipids from mother to fetus (Wasim, 2015). In the white adipose tissue (WAT) of obese pregnancies, the placental damage and dysfunction are stimulated in the placental stromal layer by the release of proinflammatory cytokines, such as IL-6 and TNF $\alpha$  by activated macrophages, as leptin functions as a pro-inflammatory signal (Zhou and Rui, 2013).

## LEPTIN IN MENOPAUSAL WOMEN

Menopause is a natural biological process; it is the cessation of the ovaries function and puts an end to the production of estrogen and progesterone. This ovarian function declines with age, which causes an increase in loss of bone mass, increase in adipose mass and decrease in muscle mass. Visceral leptin also plays a major role in maintaining neuroendocrine regulation and bone metabolism in postmenopausal women (Carter *et al.*, 2013). Aging in women is a crucial feature for developing leptin resistance which triggers metabolic dysregulations and also blunts normal central functions of leptin (Upadhyay *et al.*, 2015). Leptin resistance will lead to decrease in thermogenesis, which contributes to the negative metabolic changes associated with unhealthy aging. The estrogen plays a central role in regulating reproduction and also contributes to regulating energy balance. Estrogen is a vital component in the formation of bones, and also helps protect the cardiovascular system from heart disease. After the menopause, due to a deficiency in estrogen, the bones can become thin and fragile and highly prone to fractures and also which causes osteoporosis and heart attack, which is characterized by predominant abdominal fat accumulation (Sullivan *et al.*, 2017).

Osteoporosis, a multifactorial systemic skeletal disease characterized by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue results in bone fragility and increases the risk of breakage of bones (Kocyigit *et al.*, 2013; Ji and Xu, 2015). During the menopausal transition period, women will encounter a number of troublesome symptoms, such as hot flashes, night sweats, vaginal atrophy and dryness, dyspareunia, sleep disturbance, and mood swings (Lizzano and Guzman, 2014; Chen and Yang, 2015). Hypertension prevalence in postmenopausal women is higher than it is in premenopausal women and also the prevalence of obesity may be as high as 40% (Petzel, 2007). If estrogen replacement therapy is instituted soon after the onset of these changes, much of this bone loss, and subsequent fractures can be prevented. Estrogen, activated through the hypothalamic-pituitary-gonadal axis by leptin, itself stimulate the growth of human osteoblasts (Huang *et al.*, 2017). Estrogen deficiency promotes feeding and weight gain, and to some extent, it mimics some actions of leptin. So by the regulation of estrogen and leptin in the menopause women will be a better way for the alleviation of a post-menopausal symptom.

## CONCLUSION

The understanding about the relationship between metabolic systems, reproductive systems, neurohormonal causes of perturbations of puberty and fertility was made clear after the discovery of adipose-hormone; leptin in 1994. A woman drives diverse aspects throughout her life journey from adolescence to mature adult. Many studies have established that leptin deficiency or resistance can be related with anomalous reproductive function. Leptin deficiency and or leptin resistance will inhibit the secretion of FSH (Follicle stimulating hormone) and LH from pituitary which may, in turn, cause infertility. Inadequate nutrition leads intervention of leptin signaling may have a pathophysiological role in reproductive disorders and metabolic alterations. Leptin is a key player in regulating energy homeostasis, neuroendocrine function and metabolism, directing its action on hypothalamic-pituitary

axis, whose molecular and cellular aspects are progressively being disentangled.

Leptin also plays crucial roles in angiogenesis, immune function, puberty, fertility, and bone formation. In the female, minimal leptin threshold has a permissive role in nutritional and metabolic rate for the onset of puberty and continuity of menstrual cycle. It acts as an important signal that depends on the tolerability of nutritional status for reproductive function. The deviation of leptin from the normal threshold level may affect the neuroendocrine pathways and causes detrimental effects on reproduction. Elevation of leptin in the follicular fluid may negatively affect the embryo development, quality, implantation and pregnancy rates. Leptin acts as a novel placental hormone take part in the control of fetal growth and development. Leptin also has a crucial role in bone metabolism, after menopause bones can become fragile and cause low bone mass density (BMD). So in female leptin plays a pivotal role throughout her entire life to cross several landmarks on time.

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#### CONFLICT OF INTEREST

The authors declare that no conflicts for this article.

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