Chapter

Leptin and Female Reproductive Health

Shyam Pyari Jaiswar and Apala Priyadarshini

Abstract

Leptin is a peptide hormone, secreted primarily by the adipose tissue, placenta being the second leptin-producing tissue in humans. Apart from playing an integral role in food intake regulation and energy balance, leptin is an important signalling molecule affecting human reproduction. Accumulated evidence suggests that leptin has potential roles in the regulation of GnRH and LH secretion, puberty, pregnancy, and lactation. Deregulation of leptin levels has been associated with several reproductive disorders including infertility, recurrent pregnancy loss, and polycystic ovary syndrome. This chapter illustrates the importance of leptin in female reproductive health, its role in the metabolic regulation of reproductive axis and its eventual pathophysiological implications in prevalent reproductive disorders.

Keywords: leptin, pregnancy, reproduction

1. Introduction

Human reproduction is an energy demanding process which requires the complex interaction of biological molecules and neuroendocrine pathways primarily revolving around the hypothalamic–pituitary–ovarian (HPO) axis [1, 2]. The size of body fat and energy stores and the metabolic state of the individual are two of the key elements which determine the appropriate functioning of human reproduction, including the onset of puberty [1, 3].

In a severely undernourished state, the energy stores of the body are deviated to support the indispensable functions for survival, hence compromising the reproductive ability [4, 5].

It has long been observed that the extreme situations of body fat metabolism, that is, obesity and cachexia are both associated with derangement of female reproductive function including infertility, recurrent pregnancy loss (RPL) and polycystic ovary syndrome (PCOS) [1].

The presumptions on the existence of a missing link between the energy homeostasis of the body and female reproductive health culminated in the year 1994, with the discovery of leptin, an adipose tissue derived hormone that maintains the homeostatic control of the body fat stores [1, 6, 7]. Leptin has now been recognised to control and influence the functioning of the HPO axis also exerting a negative feedback effect on the hypothalamus.

2. Leptin: Structure and function

Leptin (derivative of Greek word "leptos" which means thin) is an adipose tissue derived hormone. It a known biomarker of adiposity, its levels rising proportionately with body fat stores [3, 8].

Leptin comprises a 167 amino acid polypeptide chain. This 16 kDa protein is encoded by the obesity gene (Lep^{ob} gene) situated on chromosome 7 [2, 8].

The preliminary function of leptin was recognised to control energy homeostasis via a negative feedback mechanism to the brain, to reduce the intake of food when the body fat stores were sufficient [3, 9].

However, recent literature elucidates that leptin can control and regulate the functioning of HPO axis, has a putative role as a placental hormone and can directly affect the reproductive function of gonads.

In this chapter, the role of leptin in female reproductive health will be illustrated under the following sections:

a. Leptin in normal pregnancy

b. Leptin in pathological pregnancy:

   i. Pre-eclampsia (PE)

   ii. Gestational diabetes mellitus (GDM)

   iii. Fetal growth restriction (FGR)

c. Leptin in puberty and infertility

d. Leptin in menstruation

e. Leptin in PCOS

f. Leptin in recurrent pregnancy loss (RPL).

3. Leptin in normal pregnancy

3.1 Source of leptin in pregnancy

Placenta is the other leptin producing tissue in humans apart from adipose tissue and compelling evidence suggests that both leptin hormone and leptin receptors are expressed in human placenta [1, 8–10]. Leptin is produced by the syncytiotrophoblast cells of the placenta (contribute 95% of total placental leptin) and the vascular endothelial cells on the fetal side (5%) [8, 11, 12]. The amniocytes of the amniotic membrane and the maternal decidua also release leptin into the amniotic fluid [13].

Even though pregnancy is a state of enhanced fat stores, the major proportion of leptin in maternal circulation is contributed by the placenta [1, 11]. Leptin has both endocrine and autocrine actions in the placenta and placental leptin is similar to its adipose tissue derived counterpart in terms of structure and function [10, 11, 14].

Increased blood levels of leptin (by two folds) have been demonstrated in pregnant as compared to non-pregnant women [8]. Presence of leptin has been observed

in placenta from 7 weeks of gestation onwards. Leptin levels increase by 30% at as early as 12 weeks of gestation, plateau at mid pregnancy and return to pre-pregnant levels 24 hours after delivery [8, 11]. The clarification for increased leptin concentration during pregnancy is the release of plasma soluble leptin receptors by the placenta which bind the circulating leptin, hence delaying its clearance [1, 11].

3.2 Functions of leptin in pregnancy

3.2.1 In mother

Pregnancy is an anabolic state where adequate energy stores are required to cater to the nutritional demands of the growing fetus. However, pregnancy is a state of leptin resistance and the role of leptin in pregnancy deviates considerably from its classical role of controlling food intake [15, 16].

The functions can be elaborated as follows (**Figure 1**) [8, 17]:

1. Plays an integral role in implantation and formation of blastocyst.

2. Activation of enzymes for lipid oxidation to generate growth substrates in the form of free fatty acids for growing fetus.

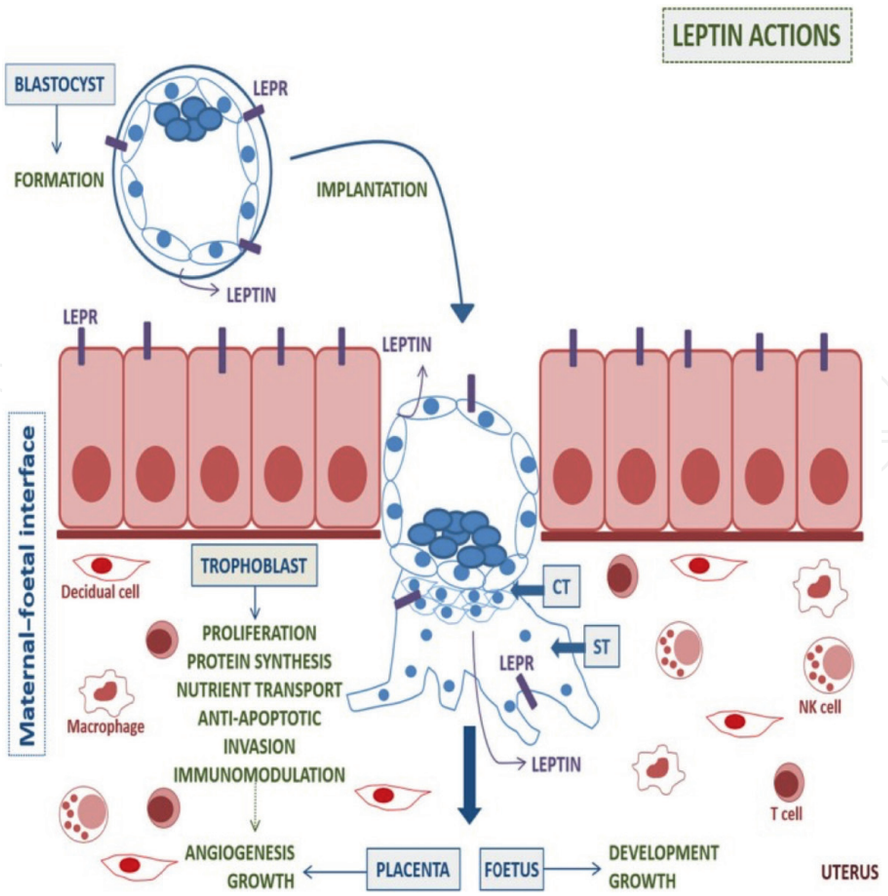

Figure 1.
Actions of leptin seen at maternal-fetal interface. ST, syncytiotrophoblast; CT, cytotrophoblast [17].

3. Placental transfer of these substrates to meet the energy demands of the fetus including amino acid uptake by the fetus.

4. Placental leptin has a paracrine action in the placenta itself. It contributes to placental angiogenesis, induces placental growth and stimulates the trophoblasts to produce hCG.

5. As an immunomodulator, it suppresses maternal immune mediated rejection of the developing fetus [17].

3.2.2 In fetus

Fetal leptin is predominantly fetal in origin and is present in fetal blood from 18 weeks of gestation [8, 18]. Maternal leptin does not cross the placenta to affect fetal functions due to its high molecular weight [19].

However, the umbilical cord blood leptin concentrations correlate strongly with fetal fat mass serving as a good indicator for the same [8, 10, 11, 20]. Fetal leptin levels increase as gestational age increases [21]. Female foetuses have higher serum leptin levels than their male counterparts due to the suppression of leptin by testosterone in males [22].

Leptin receptors have been reported to be expressed in fetal tissues, for example, bone, kidney, and hypothalamus and fetal leptin supports fetal endocrine functions, for example, angiogenesis and erythropoiesis.

4. Leptin in pathological pregnancy

4.1 Leptin and pre-eclampsia (PE)

Pre-eclampsia is a multisystem disorder of unknown aetiology characterised by hypertension ≥140/90 mm Hg after 20 weeks of gestation with proteinuria. Pre-eclampsia complicates around 5% of all pregnancies. The pathophysiology involves defective trophoblastic invasion of maternal spiral arteries leading to reduced placental blood flow and hence hypoxia [23].

Pre-eclamptic pregnancies have higher serum leptin levels (eight folds) specifically in the second half of gestation as compared to normal pregnancy. In PE, plateau of leptin does not occur and leptin levels continue to rise till term, falling only after delivery. The increase in the serum leptin levels are a consequence of placental

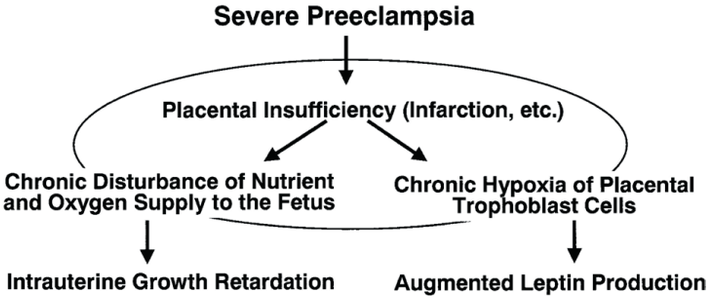

Figure 2.
Schematic diagram representing hyperleptinemia as a consequence of chronic placental hypoxia induced by severe pre-eclampsia [9].

hypoxia induced stress (**Figure 2**). This rise in leptin levels precedes the clinical onset of disease hence can also be considered as a potential predictive marker of PE. Apart from serum, amniotic fluid also shows a higher concentration of leptin than normotensive pregnancies. Leptin being an angiogenic hormone promotes placental vasculogenesis and trans placental nutrient transfer compensating for the placental insufficiency to some extent [8, 11, 17, 24].

The serum leptin levels rise in linear proportion with the severity of the disease [8, 9]. Studies have also suggested that leptin concentrations are higher in term PE as compared to preterm PE [17].

However the cord blood leptin levels are lower which denote a reduced fetal fat mass often associated with PE [11]. Pre eclamptic pregnancies complicated with FGR have higher maternal leptin levels than those without FGR suggesting a greater degree of placental insufficiency [8].

The data available is conflicting and the modulation of leptin in relation to pre-eclampsia is a fertile ground for further studies.

4.2 Leptin and fetal growth restriction (FGR)

Fetal growth restriction may be defined as the failure of the fetus to reach its genetically determined growth potential. FGR complicates 5–10% of all pregnancies and is associated with significant perinatal morbidity and mortality [25].

Studies linking the role of leptin in FGR have yielded conflicting results. A recent meta-analysis involving 1734 women showed no difference in the leptin levels between maternal blood of FGR pregnancies and healthy pregnant women [26].

However evidence suggests that the maternal serum leptin levels are higher in pregnancies complicated with FGR and fetal cord blood levels are lower compared with normal pregnancies. The higher maternal levels are a consequence of increased placental production of leptin triggered by placental insufficiency and hypoxia [27]. The lower cord blood levels reflect a lower fetal fat mass seen in FGR and also suggest a plausible role of leptin as a growth factor [28].

4.3 Leptin and gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is one of the most common metabolic complications occurring during pregnancy with a high risk of maternal and perinatal morbidity, also leading to long term sequelae [29]. It may be defined as glucose intolerance of variable severity with its onset or first recognition during pregnancy [30]. Prevalence of GDM is higher in obese women as compared to women with a normal pre-pregnancy BMI [12].

GDM is associated with increased levels of leptin in the placenta and increased expression of placental leptin receptors. The rise in serum leptin levels has been noted in the first trimester of pregnancy itself, illustrating its possible role as a predictive marker for GDM (4.7 fold greater risk of developing GDM). Not only in serum, higher leptin levels have also been measured in the amniotic fluid of women with GDM, each 1 ng/dl rise in amniotic fluid leptin increasing the risk of developing GDM by 4% [31].

It has been observed the higher umbilical cord leptin levels were present in macrosomic foetuses of diabetic mothers correlating with the increased fetal fat mass. Leptin may also contribute to the increased placental size seen in GDM. Moreover, leptin also stimulates placental protein synthesis and transfer of nutrients to the fetus

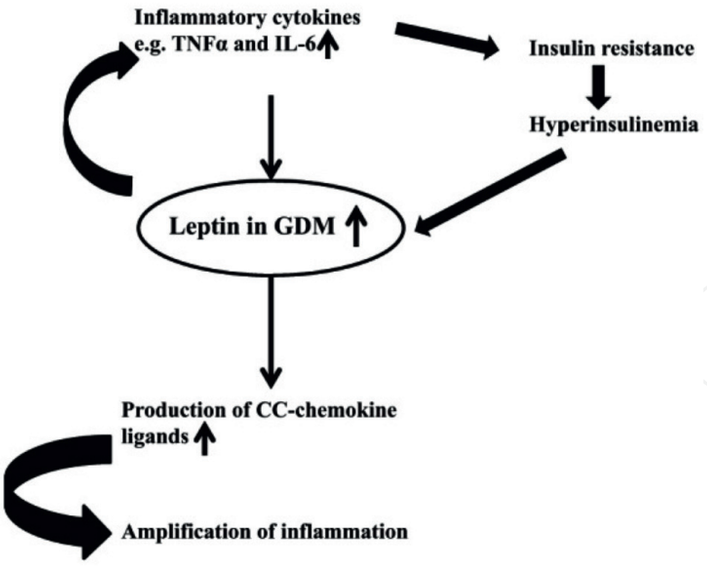

Figure 3.
Association of increased leptin production with chronic inflammatory state, insulin resistance and hyperinsulinemia seen in GDM. TNF-α, tumour necrosis factor alpha; IL-6, interleukin-6 [30].

as can be speculated by increased expression of glycerol transporter aquaporin-9 in the placentae of women with GDM [32].

The enhanced placental production of leptin has also been correlated with a higher production of inflammatory cytokines interleukin-6 and tumour necrosis factor-alpha and therefore linked with the chronic inflammatory state seen in GDM. IL-6 and TNF-α enhance the placental expression of leptin. Leptin in turn stimulates the monocytes for enhanced production of IL-6 and TNF-α resulting in a vicious cycle [11, 17, 30, 33].

The production of leptin is stimulated by hyperinsulinemia seen in GDM. Therefore, increased leptin levels are also associated with the increased insulin resistance seen in GDM during the second half of pregnancy (**Figure 3**) [33].

Studies evaluating novel bioactive therapeutic agents comprising macro and micronutrients which exert anti-inflammatory actions may be a potential cure for inflammation induced leptin resistance at the level of the hypothalamus seen in GDM. This will lead to improved leptin sensitivity at the centre and decreased insulin resistance at the peripheral level [32].

5. Leptin in puberty and infertility

Robust data reveal that obesity is associated with precocious puberty and cachexic women often experience delayed puberty [34]. The association of obesity with puberty as well as infertility led the researchers to investigate the mediator and connecting factor linking obesity with reproduction.

Rat models with deficiency of leptin or leptin receptors failed to attain puberty, elaborating the significance of leptin for reproductive function. The serum levels of leptin rise continuously throughout the entire period of pubertal development. Leptin regulates female pubertal development more closely as compared to males where minimal leptin levels are sufficient to sustain reproductive function [1].

The actions of leptin on various levels of the HPO axis are detailed (**Figure 4**):

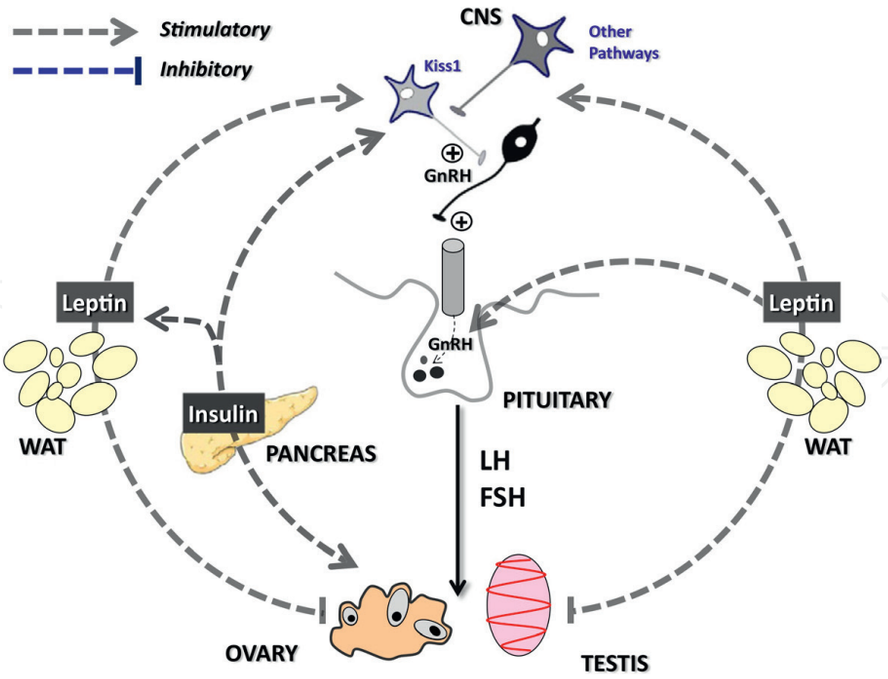

Figure 4.
Figure representing the actions of leptin on the hypothalamic–pituitary–gonadal axis. Both stimulatory and inhibitory effects are depicted. GnRH, gonadotropin releasing hormone; LH, luteinising hormone; FSH, follicle stimulating hormone; WAT, white adipose tissue [1].

5.1 Effects on the central nervous system

The primary site where leptin acts to control the reproductive function is the hypothalamus. Leptin receptors are present on the GnRH producing cells in the hypothalamus [1]. Leptin through its central action on the hypothalamus stimulates the production of GnRH and therefore may be a crucial determinant of the integrity of the HPO axis [35]. In mammals the effect of melatonin is also mediated by leptin, as observed by reduced litter size in leptin deficient mice [36]. The administration of daily dose of leptin to normal female mice resulted in advancement in the timing of opening of the vagina by some days [37].

Kisspeptin, a neuronal substance produced by the kiss1 neurons in the hypothalamus stimulates the release of GnRH. Physical stress conditions result in the inhibition of kiss1 neurons thereby resulting in the suppression of HPO axis. Studies have shown that leptin directly acts on the kiss1 neurons to release kisspeptin hence causing GnRH release [1].

The release of follicle stimulating hormone (FSH) and luteinising hormone (LH) from the pituitary gland is also governed by central pathways involving leptin [38]. Although increased leptin levels are seen in women with excessive body weight, obesity per se is associated with leptin resistance at the level of the hypothalamus. This leptin resistance further aggravates the hyperleptinemia via feedback mechanisms. Although leptin resistance is observed at the centre, the peripheral tissues, for example, the ovaries not only remain sensitive to leptin, but are also subjected to higher levels seen in obesity [35, 39].

5.2 Effects on the ovary

Normal leptin levels (10–20 ng/ml) are required for the synthesis of oestrogen and progesterone from the theca and granulosa cells of the ovary. Leptin is also

essential for the normal growth and maturation of the oocyte. The follicular fluid of the maturing Graafian follicle contains leptin, the concentration of which is dependent on the serum leptin concentrations. Higher serum levels of leptin (50–200 ng/ml) were associated with suppression of oocyte maturation and reduced follicular count. Leptin may also play a role in ovulation as can be speculated by a surge in leptin levels occurring at the same time as the LH surge prior to ovulation. Therefore, hyperleptinemia also contributes to infertility by inhibition of ovulation. The role of leptin also extends to the maintenance of corpus luteum after ovulation [3, 38–40].

Hence it can be summarised that decreased leptin levels seen in energy deficient states may be a threat to fertility due to the suppression of HPO axis. However, hyperleptinemia in obese females also causes infertility due to the direct inhibitory action on the gonads.

5.3 Effects on the endometrium

The receptivity of the endometrial epithelium is blunted under the effect of leptin. Studies in mice have revealed that the normal decidualisation of the endometrium is also diminished in obese women. Leptin controls the remodelling of the endometrial epithelium by mediating its proliferation as well as apoptosis [35].

5.4 Effects on the embryo

The effects of leptin on fertility are not confined to the pre-conceptional phase. It also affects the implantation and development of the growing embryo as can be interpreted from lower success rates of IVF in women with hyperleptinemia [39]. Although in vitro studies have demonstrated the positive effects of leptin on growth and proliferation of trophoblastic stem cells, higher levels seen in obese women are a deterrent to the embryonal development [39, 41].

6. Leptin in menstruation

Hyperleptinemia may also be a determinant of menstrual function, again through its effects on the HPO axis [38]. It is well known that heavy exercise and decreased body fat (resulting in lower leptin levels) can lead to cessation of menses. Studies have demonstrated resumption of menses in women with hypothalamic amenorrhoea when treated with recombinant leptin [42, 43].

A cyclical variation has been observed in the serum leptin concentrations correlating with the phases of the menstrual cycle. In the early follicular phase, the concentration of leptin in serum is 14.9 ng/ml, which increases to 20.4 ng/ml in the mid-luteal phase [3]. Data have shown that a mid-cycle surge is seen in leptin levels corresponding to the mid-cycle LH surge. A recent study demonstrated that a 10% rise in leptin level throughout the menstrual cycle resulted in an increase in serum estradiol and luteal progesterone level [44].

The cyclicity of leptin levels in reproductive aged women in contrast to the constant levels in men and post-menopausal females further exemplify the role of leptin in regulation of menstrual cycle [44].

7. Leptin in polycystic ovary syndrome (PCOS)

PCOS is a heterogeneous disease, characterised by chronic oligo/an-ovulation, hyperandrogenism and polycystic ovaries on morphology. It is one of the most common endocrine disorders of women of reproductive age group affecting 5–10% of these women. It is also the most common cause of anovulatory infertility.

Since a vast majority of these patients are obese and have metabolic derangements, several studies have been conducted investigating the role of leptin in PCOS which have yielded conflicting results [1, 17].

It has been observed that the increased LH levels seen in PCOS patients are also associated with increased leptin levels [45]. Since nearly half of these women present with obesity, hyperleptinemia is a common association in PCOS. Several studies have elucidated elevated levels of leptin in PCOS [46, 47]. Others have linked leptin with the insulin resistance seen in PCOS [48]. Leptin has also been associated with the pro-inflammatory and hyperandrogenic state seen in PCOS [49].

Since hyperleptinemia is observed in several clinical manifestations associated with PCOS, it may be speculated that leptin may have a role in the etiopathogenesis of the disease. However, studies directly demonstrating leptin as one of causative factors of PCOS are still sparse.

8. Leptin and recurrent pregnancy loss (RPL)

Recurrent pregnancy loss may be defined as three or more consecutive spontaneous pregnancy losses occurring before the 20th week of gestation irrespective of previous live births [17]. Known causes include anatomical abnormalities, genetic causes, endocrine derangements, environmental factors, and immunological diseases. However, despite a thorough evaluation of the patients, the cause remains unknown in upto 50% of patients. Defects in the leptin signalling pathway have been evaluated as one of the possible causes of idiopathic RPL. Studies have demonstrated raised serum leptin concentrations in women with RPL as compared to controls. In contrast, reduced leptin levels were also observed in women having first trimester abortions. A recent study revealed similar leptin concentration in RPL cases and controls [50–53].

In conclusion, data linking recurrent pregnancy loss with leptin is largely inconclusive, though there is significant evidence suggesting positive association of hyperleptinemia with RPL.

9. Conclusion

It may be concluded that leptin is the cross-talk molecule linking human reproduction and nutrition. More than 25 years after its discovery, leptin is now known to mediate a paraphernalia of functions relating to the reproductive capacity. Leptin exerts its actions in several ways at multiple levels of the pathway of reproduction including the hypothalamus, ovary, and the placenta. It plays a crucial role in essential processes in the establishment of a normal pregnancy such as trophoblastic invasion, placentation, and transfer of nutrients to the developing embryo. The pathological significance of leptin in human reproduction may be elucidated by the fact that deregulation of leptin levels is responsible for the genesis of a wide variety

of disorders associated with pregnancy and reproduction including GDM, FGR, PE, PCOS, RPL and infertility. Recombinant leptin therapies and leptin sensitisers should be the ground for further research to address the devastating effects of abnormal leptin levels and leptin resistance on human reproduction.

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