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The Known and Unknown of Leptin in Pregnancy and Gynaecological Problems

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Abstract

Leptin is a vital peptide hormone secreted by the adipose tissue, which has been regarded for years as an exclusive regulator of energy and satiety homeostasis. It's role in pregnancy was recognized only during the last three decades. Leptin is now proven to play a wide range of roles in reproductive biology, from maternal physiology to implantation and from paracrine effects in placenta to regulation of conceptus development and fetal growth. The role of leptin in pregnancy was suggested by the findings that plasma levels during gestation are greater, it is synthesized within the fetoplacental unit, and due to its interaction with common pregnancy pathologies. It is involved in regulation of GnRH and LH secretion and in puberty and lactation. Leptin disorders can lead to reproductive disorders, including infertility, recurrent pregnancy loss and polycystic ovarian syndrome. We review the known and unknown of leptin in metabolic regulation of the reproductive axis.

Historical Perspective

1950

The Jackson laboratory first discovered an autosomal recessive mutation ob/ob

1958

Harvey G: "The effects of lesions in the hypothalamus in the parabiotic rats". J. Physiol 1958; 145; 336-52. Demonstrated Leptin first as a satiety factor.

1973

Coleman D. Effects of Parabiosis of obese with Diabetes & normal mice. Diabetologia 1973; 9 – 249-298

1994

Jeffrey Friedman's team at Rockefeller University cloned the ob gene that codes for Leptin

1994

Zhang et al discovered the 16 kDa, now glycosylated polypeptide of 146 amino acids called "LEPTIN"

Leptin: Derived from the Greek word 'Leprus' meaning thin

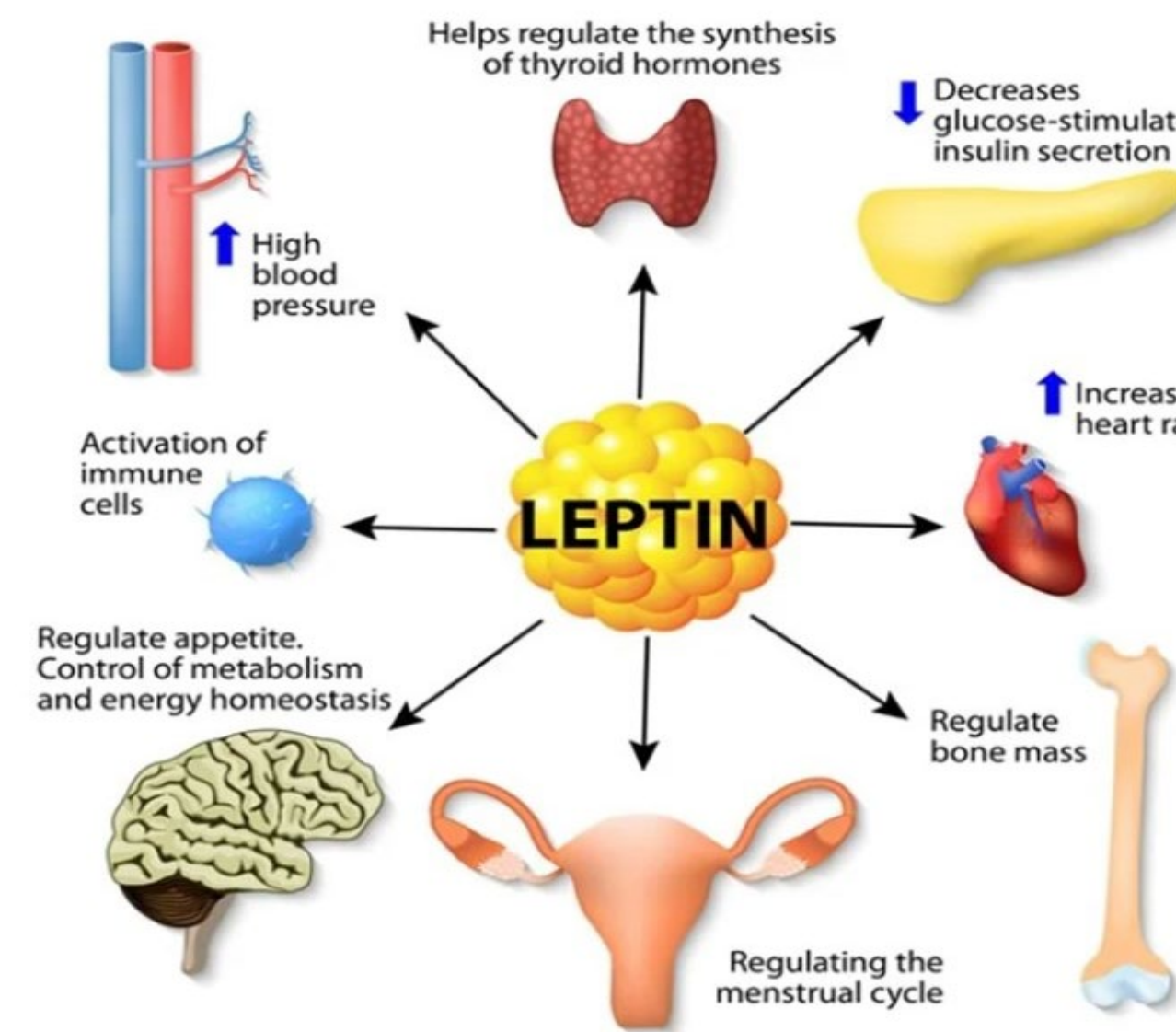
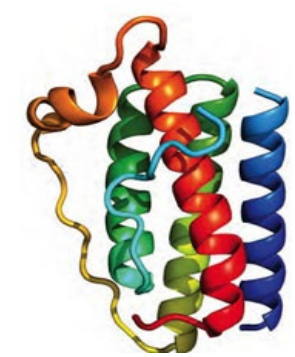


Figure 1: The physiologic roles of Leptin

- Protein with tertiary structure of a cytokine
- Encoded by *ob* gene located on chromosome 7
- Expressed predominantly by adipocytes; smaller amounts secreted by stomach epithelial cells and in the placenta
- Leptin receptors are highly expressed in:
 - Hypothalamus- regulates body weight
 - T- lymphocytes and vascular endothelial cells
- Four isoforms; Ob-Rb is expressed in endometrium, myometrium, placenta & umbilical cord.

Leptin in Pregnancy

Leptin hormone is produced, and leptin receptors are expressed by the human placenta. Human placental leptin is identical to adipose tissue leptin. Leptin increase precedes the increase in BMI.

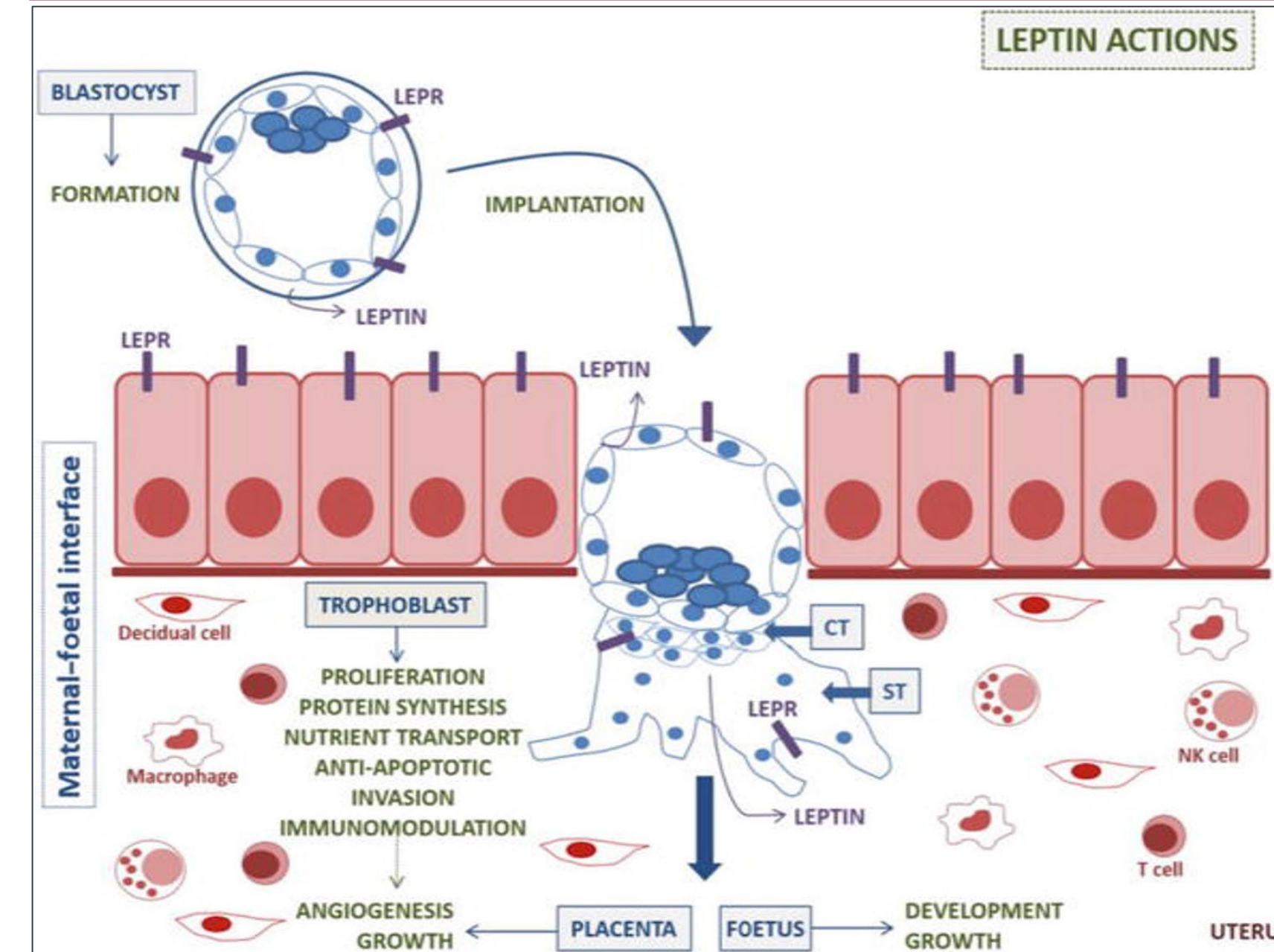


Figure 2: Leptin is produced by syncytiotrophoblasts (95% of total placental leptin) and fetal vascular endothelial cells. Amniocytes of the amniotic membrane and maternal decidua release leptin into the amniotic fluid.

Leptin in Diabetes

- Leptin production is stimulated by hyperinsulinemia
- Dramatic increase in fetal and placental leptin concentration correlates with higher inflammatory cytokines, IL6 & TNF- α .
- Mitotic activity and growth signals through Mitogen-activated protein kinase activation $\rightarrow$ macrosomia

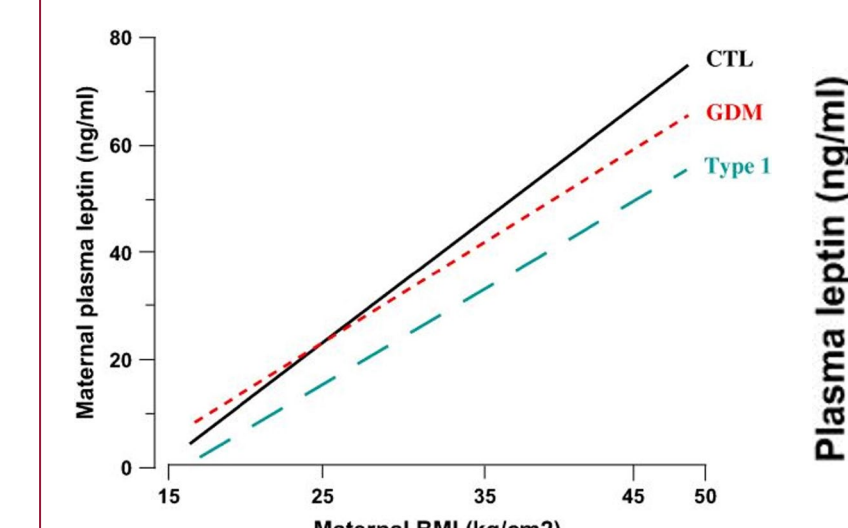


Figure 4: Correlation with BMI¹

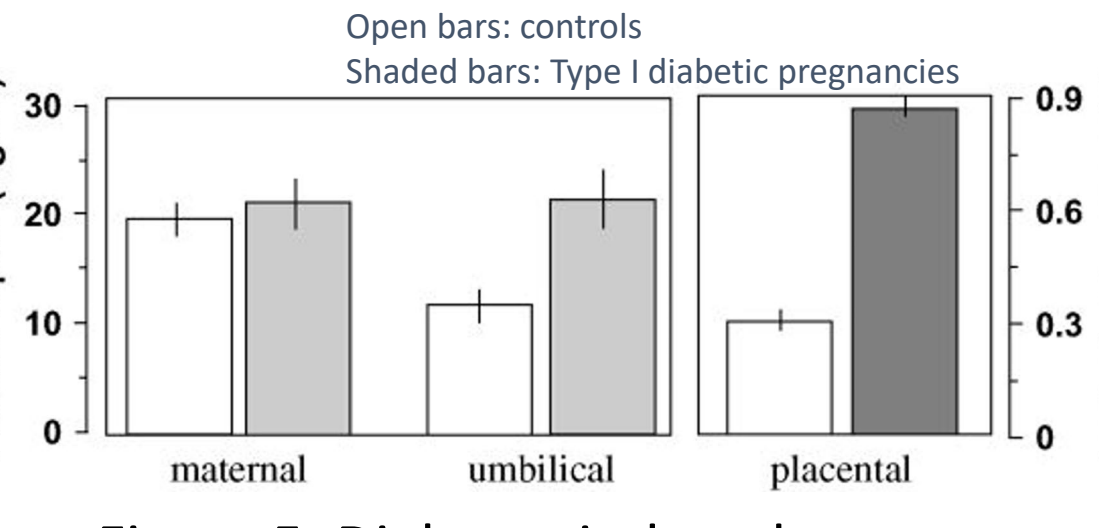


Figure 5: Diabetes induced modifications of leptin concentration¹

Leptin in Disorders of Placental Growth

- Molar pregnancy and choriocarcinoma are associated with maternal leptinemia; leptin levels decrease after evacuation
- Decreased leptin levels – intrauterine growth restriction (fat mass only 3-5% of total body weight)

- Estrogen regulates leptin release; 95% to maternal and 5% to fetal circulation.
- Leptin is present in the placenta from week 7 of gestation, plateaus at mid-pregnancy and returns to pre-pregnancy levels 24 hours after delivery

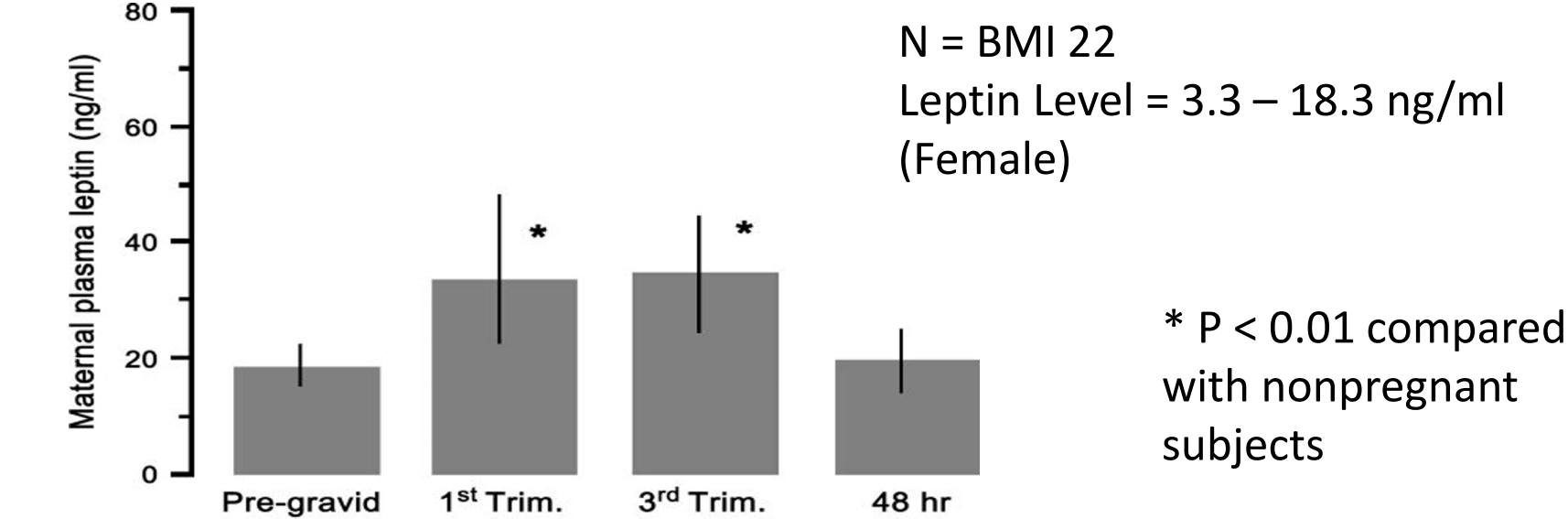


Figure 3: Pregnancy associated changes in maternal leptin concentration¹

Functions and Regulation of Leptin

- Leptin provides a link between the immune and endocrine system responses of the placental cells
- Contributes to placental angiogenesis, erythropoiesis & induces placental growth to produce hCG
- Suppresses rejection of developing fetus
- Regulates fetal growth (maternal leptin does not significantly cross placenta. Fetal leptin is produced by fetal adipose tissue² from 18 weeks gestational age)
- Insulin acts as a regulator of placental gene; hypoxia is also a stimulus. Leptin resistance, like insulin, can occur

Leptin in Pre-eclampsia

- Increased placental synthesis but low umbilical concentration; increased maternal leptin concentration
- Leptin may also modify arterial thrombosis after endothelial injury through interaction with platelet leptin receptors

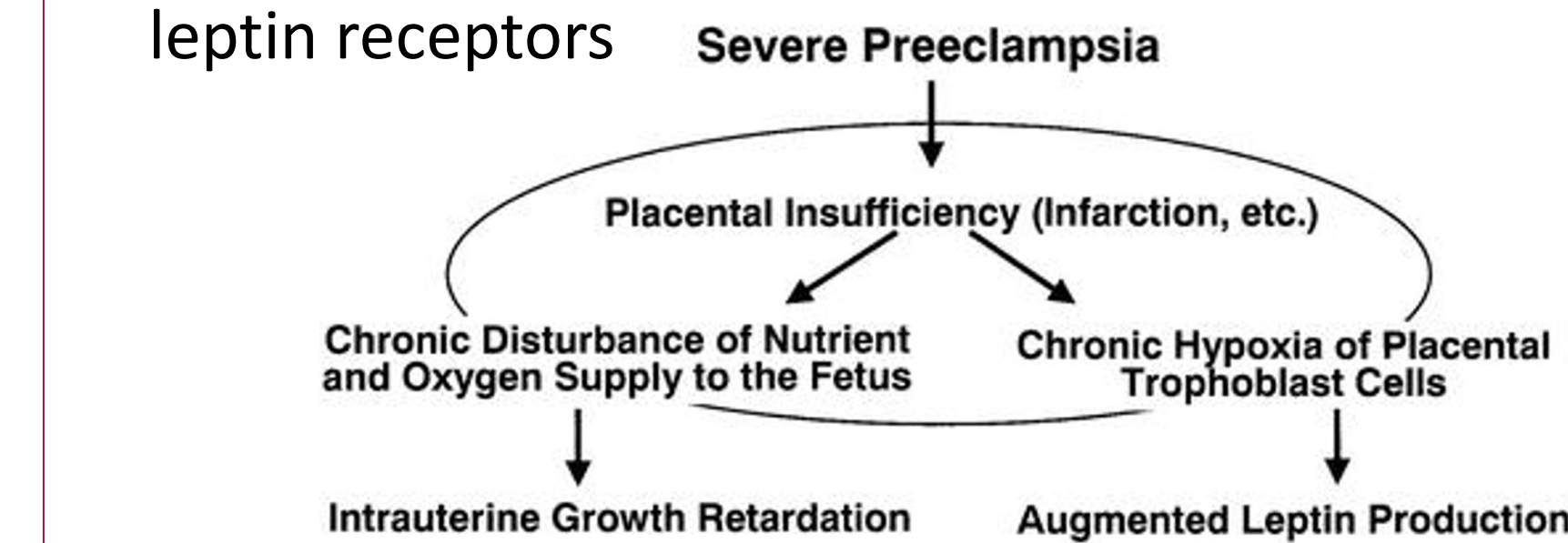


Figure 6: Hyperleptinemia due to chronic placental hypoxia induced by severe pre-eclampsia (Leptin – a non-invasive marker of pre-eclampsia)

Leptin in Gynaecological Disorders

- **Leptin in puberty and menstruation**
 - Cyclical variation in serum leptin concentration correlating with pulses of menstrual cycle
 - Lower leptin level due to heavy exercise & decreased body fat; lower leptin level can lead to amenorrhoea; resumption with recombinant leptin therapy
 - Leptin receptor deficiency caused by LEPR gene mutation can lead to hypogonadotrophic hypogonadism, delayed puberty / no puberty

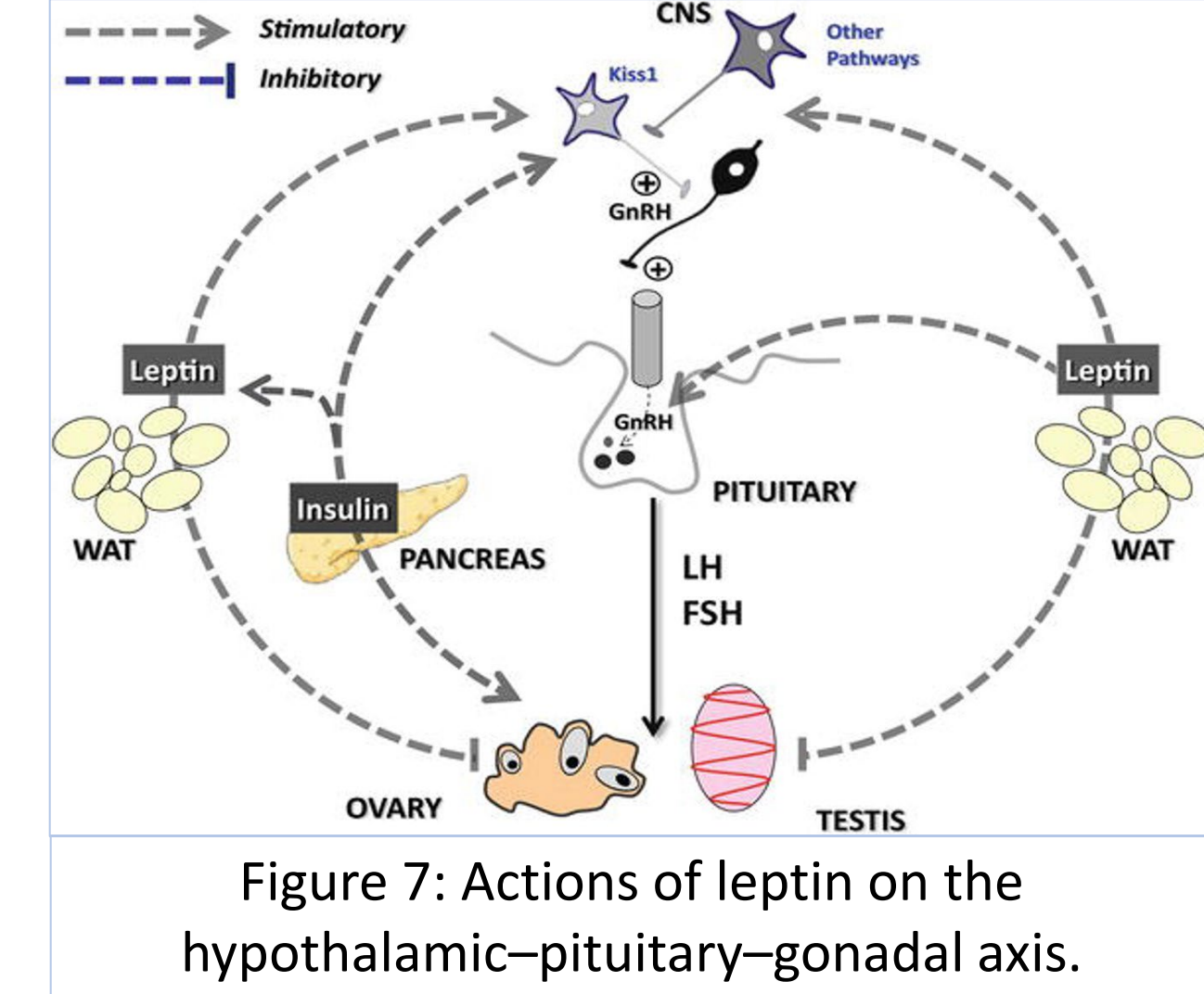


Figure 7: Actions of leptin on the hypothalamic-pituitary-gonadal axis.

- **Role in infertility**
 - Central Nervous System: Controls reproduction by acting on hypothalamus; leptin receptors are present in GnRH producing cells; release of FSH & LH from pituitary is governed by central pathway involving leptin
 - Ovaries: High leptin levels suppress oocyte maturation
 - Endometrium: Receptivity of endometrium blunted under the effect of leptin (in obese women) as well as normal decidualisation
 - Embryo: Affects implantation and growth of developing embryo; lower success rates of in-vitro fertilization in obese women
- **Leptin in Polycystic Ovarian Syndrome (PCOS):** Increased LH levels are associated with increased leptin levels in PCOS (studies sparse on a direct cause for PCOS)
- **Leptin and recurrent pregnancy loss (RPL):** Leptin signaling pathway defects - a possible cause of idiopathic RPL; raised serum leptin levels in women with RPL; however, low level also seen; link between leptin and RPL is inconclusive

The UNKNOWN of Leptin

- Reason for elevated leptin levels during normal pregnancy?
 - Is excess leptin beneficial or detrimental for the fetus?
 - Does leptin participate in fetal programming of obesity and adult disease?
- Does leptin regulate fetal fat accretion or does such control require interaction between adipose tissue and central brain targets in utero?
- Role of increased maternal leptin level and fetal umbilical prolactin level is not clear

Conclusion

- Leptin is the cross-talk molecule linking human reproduction and nutrition
- Will ob protein be useful for treating human obesity?
- Recombinant leptin therapies and leptin sensitizers should be grounds for further research to address the serious effects of leptin and leptin resistance on reproduction.

¹Am J Obstet Gynecol 2006; 194: 1537-45

²J Clin Endocrinol Metab 2001; 86:2409-13