Diploma Thesis

The Role of Placental Hormones in the Regulation of Maternal Metabolism During Pregnancy

submitted by

Lisa-Catharina Lindheim

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Department of Obstetrics and Gynecology

under supervision of

Ao.Univ.-Prof. Dr.phil. Gernot Desoye

and

Dr.rer.nat. Ursula Hiden

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Graz, 29.8.2012 *Lisa Lindheim*

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Für meine Mama

Abstract

Of the multitude of functions performed by the human placenta during pregnancy, the alteration of maternal metabolic processes by the secretion of various hormones and cytokines is of great relevance and importance. In response to the secreted products of the placenta, the maternal metabolism shifts from a balanced to an anabolic and later to a catabolic state so as to provide the best possible conditions for the growth and development of the fetus. Hyperphagia, hyperlipidemia, hyperinsulinemia, and subsequent insulin resistance are among the changes that can be observed. This review provides a comprehensive overview of the known and unknown aspects of the placental regulation of maternal metabolism and also addresses the hormonal changes that can be observed in common pathologies of pregnancy.

Research was conducted using the international online database PubMed. Preliminary research allowed for the selection of 16 hormones and cytokines, which were then individually researched. This process ultimately yielded 116 sources published between the years 1982 and 2012.

A large amount of evidence exists supporting the role of estradiol, progesterone, PGH, hPL, leptin, TNF-α, and adiponectin in the initiation and amplification of hyperphagia, hyperlipidemia, hyperinsulinemia, and insulin resistance. The peptide hormones hCG, CRH, hCT, PTH-rP, and ghrelin have a minor role in these changes. The relatively recently identified adipokines visfatin, resistin, apelin, and chemerin also have metabolic effects, but have not yet been sufficiently researched to make any statements about their exact role and significance during gestation. Many contradictions exist regarding their physiological concentrations, regulation, and relation to pregnancy-related pathologies. Many adipokines are secreted in abnormal concentrations in gestational diabetes mellitus, preeclampsia, and intrauterine growth restriction, but so far only studies with leptin, TNF-α, and adiponectin have shown consistent results.

In conclusion, the adipokines represent an interesting point for future research, as they are often a sign of an impending or current pathological condition of the mother or the fetus. However, the great individual variability of adipokine concentrations will be an obstacle to overcome before they can be widely used as a screening or diagnostic tool.

Zusammenfassung

In einer Schwangerschaft ist die Anpassung der mütterlichen Stoffwechselprozesse durch die von der Plazenta sezernierten Hormone und Zytokine von groβer Wichtigkeit. In Gegenwart dieser Faktoren wechselt die Schwangere von einer ausgeglichenen auf eine anabole und später eine katabole Stoffwechsellage um die optimalen Bedingungen für das Wachstum und die Entwicklung des Föten zu schaffen. Hyperphagie, Hyperlipidämie, Hyperinsulinämie und die daraus folgende Insulinresistenz sind typische Veränderungen. Diese Arbeit bietet einen Überblick über die bekannten und unbekannten Aspekte der Regulation des mütterlichen Metabolismus durch die Plazenta und erörtert die Hormonveränderungen, die in Schwangerschaftspathologien beobachtet werden können.

Die Literaturrecherche in der internationalen online Database PubMed ergab nach anfänglicher Suche 16 Hormone und Zytokine, welche nachfolgend genauer recherchiert wurden. Es wurden 116 Quellen, zwischen 1982 und 2012 publiziert, ausgewählt.

Die vorliegende Evidenz lässt auf eine Rolle für Estradiol, Progesteron, PGH, hPL, Leptin, TNF-α und Adiponektin in der Entwicklung und Verstärkung von Hyperphagie, Hyperlipidämie, Hyperinsulinämie und Insulinresistenz schlieβen. Die Peptidhormone hCG, CRH, hCT, PTH-rP und Ghrelin spielen bei diesen Veränderungen eine untergeordnete Rolle. Die relativ neu entdeckten Adipokine Visfatin, Resistin, Apelin und Chemerin haben ebenfalls metabolische Effekte, sind jedoch derzeit noch nicht ausreichend bezüglich Ihrer Funktion und Signifikanz erforscht. Es existieren viele Widersprüche hinsichtlich ihrer physiologischen Konzentrationen, Regulation und Zusammenhang mit Schwangerschaftspathologien. Viele der Adipokine werden in pathologischen Zuständen wie Gestationsdiabetes, Präeklampsie und intrauteriner Wachstumsrestriktion in abnormen Konzentrationen produziert, jedoch haben bis jetzt nur Studien mit Leptin, TNF-α und Adiponektin übereinstimmende Resultate gezeigt.

Adipokine stellen ein interessantes zukünftiges Forschungsthema dar, da sie oft ein Zeichen einer inzipienten oder schon bestehenden Pathologie der Mutter oder des Föten sind. Allerdings ist die groβe individuelle Variabilität der Konzentrationen der Adipokine ein Problem, welches es zu überwinden gilt bevor diese als Screening- oder diagnostische Parameter genutzt werden können.

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Abbreviations

11β-HSD	11β-hydroxysteroid dehydrogenase
ACTH	adrenocorticotropic hormone
APJ receptor	apelin receptor
BMI	body mass index
CG	chorionic gonadotropin
CNS	central nervous system
CRH	corticotropin-releasing hormone
E2	17β-estradiol
ESR1 and 2	estrogen receptors 1 and 2
FFA	free fatty acid(s)
FSH	follicle stimulating hormone
GDM	gestational diabetes mellitus
GH	growth hormone
GH-N	pituitary growth hormone
GHSR	growth hormone secretagogue receptor
GH-V	placental growth hormone
GLUT	glucose transporter
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotropin
hCS	human chorionic somatomammotropin
hCT:	human chorionic thyrotropin
HDL	high-density lipoprotein
hPL	human placental lactogen
IGF-I	insulin-like growth factor I
IL	interleukin
IUGR	intrauterine growth restriction
LDL	low-density lipoprotein
LH	luteinizing hormone
LPL	lipoprotein lipase
M-CSF	macrophage colony-stimulating factor

mRNA	messenger RNA
NPY	neuropeptide Y
PBEF	Pre-B cell colony-enhancing factor
PGH	placental growth hormone
PL	placental lactogen
PTH-rP	parathyroid hormone-related protein
TBG	thyroxin-binding globulin
TG	triglyceride(s)
TNF-α	tumor necrosis factor-α
TNFR1 and 2	tumor necrosis factor-α receptor 1 and 2
TSH	thyroid-stimulating hormone
VLDL	very low-density lipoprotein

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I. Introduction

This paper will discuss the effects of placental hormones on the metabolism of the mother during pregnancy. Firstly, the metabolic changes of each trimester of pregnancy will be addressed, followed by a description of the research method that was used. Then, each of the selected hormones will be discussed as to its history, physiological concentrations, functions, regulation, interactions with other hormones, and pathological implications. Finally, there will be a discussion stating the merits and limitations of the paper, as well as suggestions for future research.

A. Maternal metabolism in pregnancy

The metabolic changes occurring during pregnancy can be divided into an anabolic and a catabolic phase. The anabolic phase corresponds to the first and second trimester of pregnancy and is directed at nutrient storage and the buildup of reserves, which are then mobilized in the catabolic phase of the third trimester when they are needed for fetal growth and to prepare the mother for the demands of lactation (1,2).

1) The first trimester

In the past, it was thought that the fetus acts as a "parasite" upon the mother, feeding off her and depleting her reserves (3). However, it has since been observed that the metabolic changes in early pregnancy happen long before the fetus reaches a size that would allow it to significantly impact maternal nutrient stores (3). Therefore, maternal changes occur in preparation for the later demands of the fetus, not as a consequence of them. Rather, these changes are brought about by hormones secreted by the corpus luteum, placenta, and maternal organs.

One of the earliest changes that can be observed in the mother during pregnancy is the development of hyperphagia. In the rat, hyperphagia can begin on the fourth day of pregnancy, even before implantation, and a similar situation can be assumed in humans (4,5). Food intake in pregnant women increases by 10-15% in the first trimester (1). The mechanism causing this change is not fully elucidated, but the hormones progesterone, prolactin, and human placental lactogen are probably involved as they are secreted in

larger than normal quantities during this time (5,6). As a consequence of hyperphagia, body weight and fat mass increase (3,6-9). An estimated 3.3 kg of fat is stored in the first 15 weeks of pregnancy (3). These fat stores become essential to maternal tissues later in pregnancy, since most of the circulating glucose is used by the placenta and fetus in the third trimester (3).

Meanwhile, peripheral insulin sensitivity remains stable or slightly increased in the first trimester, providing optimal conditions for glucose and lipid uptake (3,7,8). There is a 60-120% increase in first phase insulin response and simultaneous increased β-cell activity and hyperinsulinemia (1,3,6,7,10). The consequence of this anabolic state is a decrease in fasting glucose levels accompanied by a temporary low plasma lipid concentration in the first eight weeks of pregnancy (3,7). After eight weeks, lipid levels begin to rise and do so continuously until term(1,3). Amino acid levels decline in the first trimester and remain low throughout gestation (1,3). This is due to increased amino acid uptake by the placenta, increased use of amino acids for gluconeogenesis in the liver, and increased trans-placental transfer of amino acids (3). Unlike glucose, which moves passively across the placenta along a concentration gradient, amino acids enter the fetal circulation via active transport (2). Thus, fetal plasma amino acid levels are high despite low maternal levels (2).

2) The second trimester

Although the second trimester still represents the anabolic phase of pregnancy, it differs from the first due to the development of insulin resistance around mid-gestation. While insulin sensitivity is normal or high during the first trimester, it begins to decline soon thereafter (7). In the second trimester, peripheral insulin response decreases by 45-70% and postprandial hyperglycemia becomes apparent (3,6). Furthermore, fasting glucose production in the liver increases by 30%, a sign of impaired hepatic insulin sensitivity (3). Meanwhile, hyperphagia persists, further promoted by the adipokine leptin, and fat depots continue to increase to an estimated 4.8 kg by the end of the second trimester (11). Intestinal calcium absorption increases (1).

There are several factors which contribute to the development of insulin resistance. The first are the placental hormones, most of which are secreted in ever increasing quantities as the pregnancy progresses. Initially, human placental lactogen,

progesterone, estrogen, and placental growth hormone were believed to be the main causes of insulin resistance (6,12,13). However, the current opinion is that adipokines such as TNF-α, leptin, and adiponectin play a more significant role (6,12,14). Insulin resistance has a way of potentiating itself by creating a feed-forward mechanism by which decreased insulin sensitivity leads to decreased lipid uptake and this hyperlipidemia further causes insulin sensitivity to decline [see Figures 1 and 2] (1,3). To counter the metabolic stress caused by the placental hormones, β-cell mass and insulin secretion are augmented (6). However, β-cells are damaged by free fatty acids and gradually lose their functionality the longer the insulin resistance persists (15). Notably, maternal insulin levels return to normal 24 hours after the expulsion of the placenta, further supporting the view that placental hormones are responsible for insulin resistance (16).

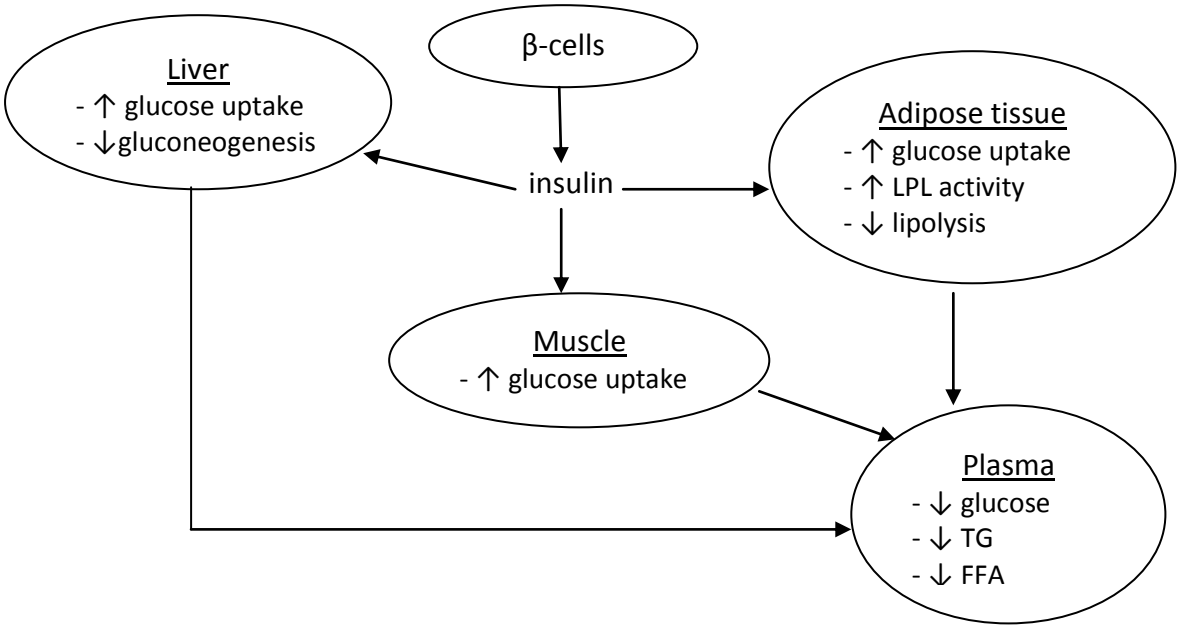

Figure 1: Physiological response of muscle, liver, and adipose tissue to insulin after feeding (15). LPL = lipoprotein lipase, TG = triglycerides, FFA = free fatty acids

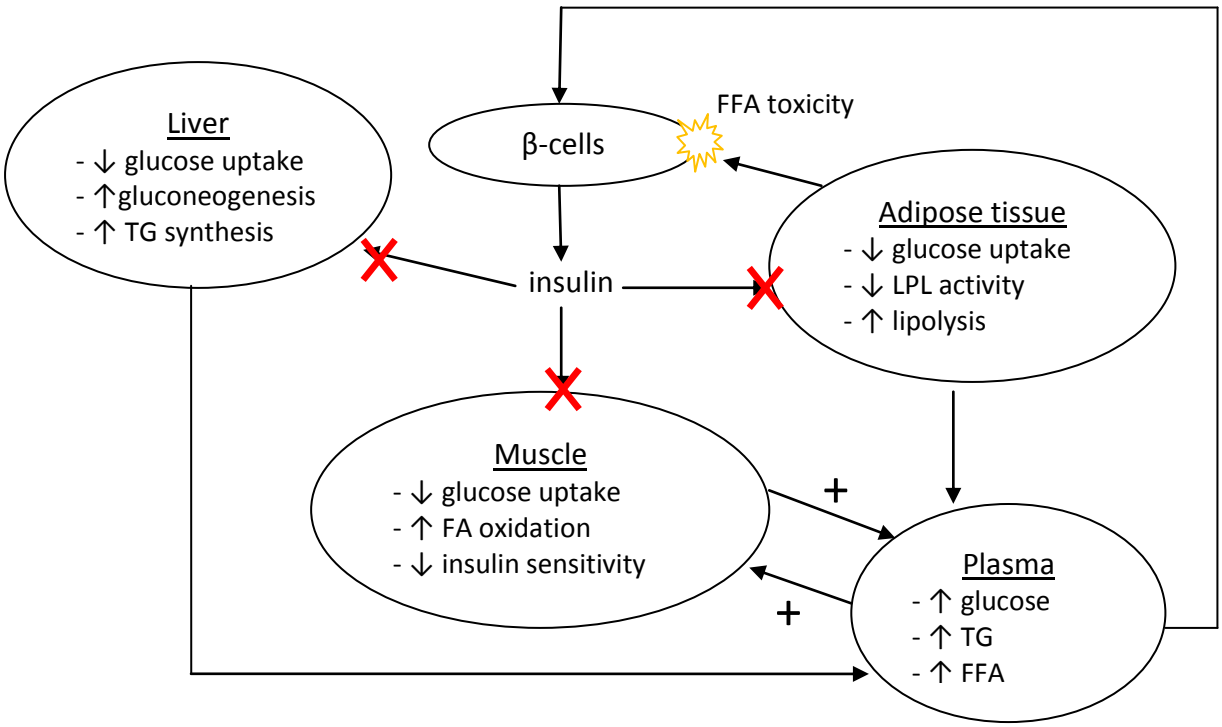

Figure 2: Effects of insulin resistance on maternal metabolism during the second half of pregnancy (15). LPL = lipoprotein lipase, TG = triglycerides, FFA = free fatty acids

Norbert Freinkel has described two states which are characteristic for maternal metabolism during the second half of pregnancy. The first is "accelerated starvation". This term was first described when Freinkel studied a group of pregnant women and discovered that after a 14-hour fast, these women had significantly lower plasma glucose and higher free fatty acid levels than non-pregnant control women [see Figure 3] (17). These changes result from the constant metabolic demands of the fetus in addition to those of the mother. Freinkel showed that pregnant women have a profoundly different metabolism than non-pregnant women and that even a skipped breakfast can have a pronounced and detrimental effect on the mother and the fetus. Further changes observed during accelerated starvation are enhanced ketogenesis and decreased plasma amino acids (3).

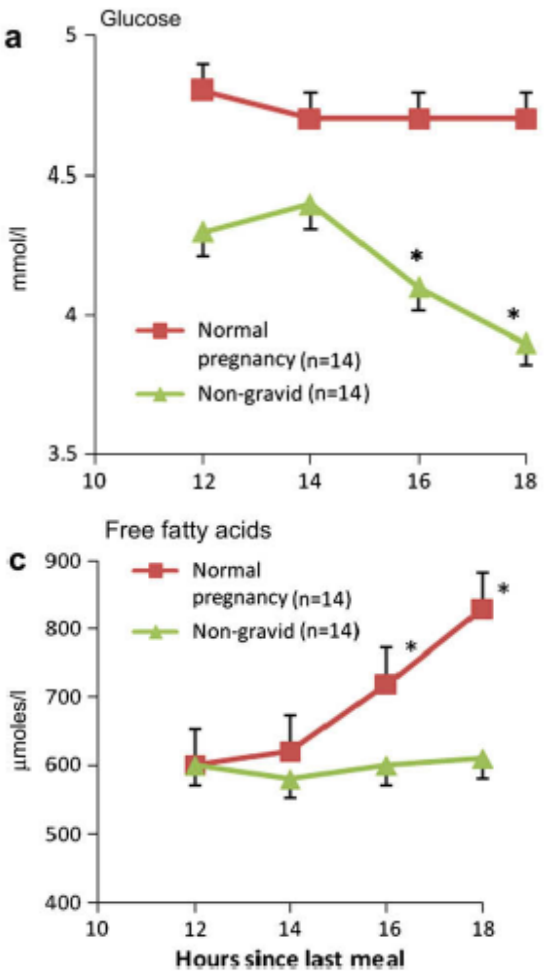

Figure 3: Changes in plasma concentrations of glucose and free fatty acids in non-gravid (n=14, triangles) and healthy pregnant (n=14, squares) women between 12 h fasting and 18 h fasting during the third trimester. Adapted from Hadden and McLaughlin (3)

The second concept, "facilitated anabolism", describes an adaptive mechanism by which the mother seeks to constantly ensure an adequate supply of nutrients to the fetus (3). This occurs mainly through augmented hepatic gluconeogenesis as a result of insulin resistance, despite elevated levels of insulin and fatty acids after feeding (3). Facilitated anabolism enables the mother to utilize fatty acids as her main source of energy, while glucose is spared for the fetus (3). Furthermore, a high concentration gradient guarantees an effective transfer of glucose across the placenta and must be maintained throughout feeding and fasting periods (3).

3) The third trimester

The catabolic state which is characteristic of late gestation is achieved through changes in insulin production and sensitivity combined with a continuing increase in maternal food uptake (1). Accelerated starvation and facilitated anabolism become very

apparent in late pregnancy. Total body insulin sensitivity is reduced by 45-70%, insulin secretion is twice as high as in the non-pregnant state with a 10-15% increase in pancreatic β-cell mass, and basal glucose levels are reduced despite increased hepatic glucose production (1,3,7,10). Maternal skeletal muscle, cardiac muscle, and adipose tissue reduce their glucose uptake, relying on free fatty acids and ketones as their energy source (1,2). In late pregnancy, the placenta uses up to 40-60% of the maternal glucose and oxygen for its own metabolism (2,8).

As the fat depots of the mother dwindle to supply the demands of herself, the placenta, and the growing fetus, feeding and fasting periods must be optimally utilized. The main goal is to effectively store nutrients during meals, while ensuring adequate supply to the fetus during fasting periods through a quick mobilization of reserves (1). Immediately after feeding, maternal glucose and free fatty acid concentrations are elevated, allowing effective nutrient transfer to the fetus (1). At the same time, lipolysis and ketogenesis are suppressed and amino acid uptake is increased, facilitating fat storage and protein synthesis (1,8,10). In fasting periods, when plasma glucose is low, the mother can quickly release the stored fatty acids and ketones and use them as an alternate energy source, sparing glucose for the fetus (1,3,8,10). Hepatic glucose production is also increased during fasting periods due to hepatic insulin resistance (3).

Finally, the maternal lipid profile needs to be addressed. Phospholipid, total cholesterol, free cholesterol, and triglyceride concentrations increase throughout gestation (1,8,10,18). An increase in plasma free fatty acids and glycerol can also be observed (10). At term, triglyceride levels have tripled compared to week eight of gestation, while total cholesterol, LDL-cholesterol, and HDL-cholesterol increase to a lesser extent (1,18). In late gestation, VLDL concentrations have risen by 100-150%, while total cholesterol levels show an increase of 20-30% (1). This is due to increased lipolysis and decreased lipoprotein lipase activity (1,2,10)

	First trimester	Second trimester	Third trimester
Food intake	↑	↑↑	↑↑
Fat mass	↑	↑↑	↑↑
Insulin production	↑	↑↑	↑↑↑
Glucose tolerance	↔ or ↑	↓	↓↓
Insulin sensitivity	↔ or ↑	↓	↓↓
Free fatty acids	↓ then ↑	↑↑	↑↑↑
Triglycerides	↓ then ↑	↑↑	↑↑↑
Cholesterol	↔	↑	↑↑
Amino acids	↓	↓	↓

Table 1: Maternal metabolic changes during early, mid-, and late pregnancy (1,3,7,8,18)

II. Materials and Methods

The main goal of this paper is to summarize and discuss the metabolic effects of placental hormones in the mother during pregnancy. The best way to tackle this is in the form of a review. From December 2011 to (but not including) April 2012, research was conducted using the international online database PubMed, ultimately yielding 116 sources published between 1982 and 2012. Of these, 73 are studies and 43 reviews.

In the initial stage of research, basic knowledge of placental formation, structure, and function as well as an overview of the metabolic changes that occur during pregnancy were obtained through PubMed using the search terms "placenta", "pregnancy", "metabolism", "changes", "maternal", "effect", "physiological", and "insulin resistance", either on their own or in combination.

After basic knowledge had been established on the subject, the next task was to compile a list of placental hormones with metabolic functions. This second stage of research was also executed via PubMed using the search terms "placental", "hormone", "endocrine", "trophoblast", "syncytiotrophoblast", "regulation", "metabolic", "function", "maternal", "pregnancy", "physiological", and "secretion", alone or in combination. The limits used were "female", "human", "adult", and "english". Publications which were not accessible for free were acquired using the literature delivery service of the Medical University Graz. Once several sources had been found, their respective bibliographies were used to identify further useful publications. Only placental hormones with an effect on the maternal metabolism were considered. This eliminated placental hormones with functions exclusively on the fetal metabolism along with placental hormones and cytokines that are present in the maternal circulation during pregnancy but do not have a direct metabolic effect. An inclusion of these hormones and cytokines would by far exceed the scope of this investigation.

Once the relevant hormones and cytokines had been identified, further research was done on each individually, using the search terms "estrogen", "estradiol", "progesterone", "hCG", "hPL", "placental growth hormone", "CRH", "hCT", "PTH-rP", "ghrelin", "leptin", "leptin resistance", "TNF-alpha", "visfatin", "PBEF", "adiponectin", "resistin", "apelin", and "chemerin", in combination with the search terms mentioned in

the second stage of research. Once again, the bibliographies of the relevant articles were considered. The works of the authors Freemark, Hauguel-de Mouzon, Evain-Brion, Guibourdenche, Murphy, and Lowry were closely examined upon recommendation by the supervising professor, Dr. Desoye.

III. Results

A. Steroid Hormones

1) Estrogens

This group is comprised of the steroid hormones 17β-estradiol (E2), estrone, and estriol (19). While in humans estrone and estriol are only present in low concentrations, E2 is recognized as the dominant estrogen and is present at high levels during gestation (19,20). The production of estrogens during pregnancy is of interest, as it occurs as a collaboration between the maternal and fetal metabolism [see Figure 4]. Placental cholesterol-derived pregnenolone is converted in the fetal adrenal glands to dehydroepiandrosterone and then to dehydroepiandrosterone sulfate in the fetal liver, which is then metabolized to androstenedione and testosterone in the placenta (19,21). These products are subsequently converted into estrone and estradiol and secreted back into the maternal circulation (19). This gives rise to the concept of the fetoplacental unit as a site of hormone production during pregnancy.

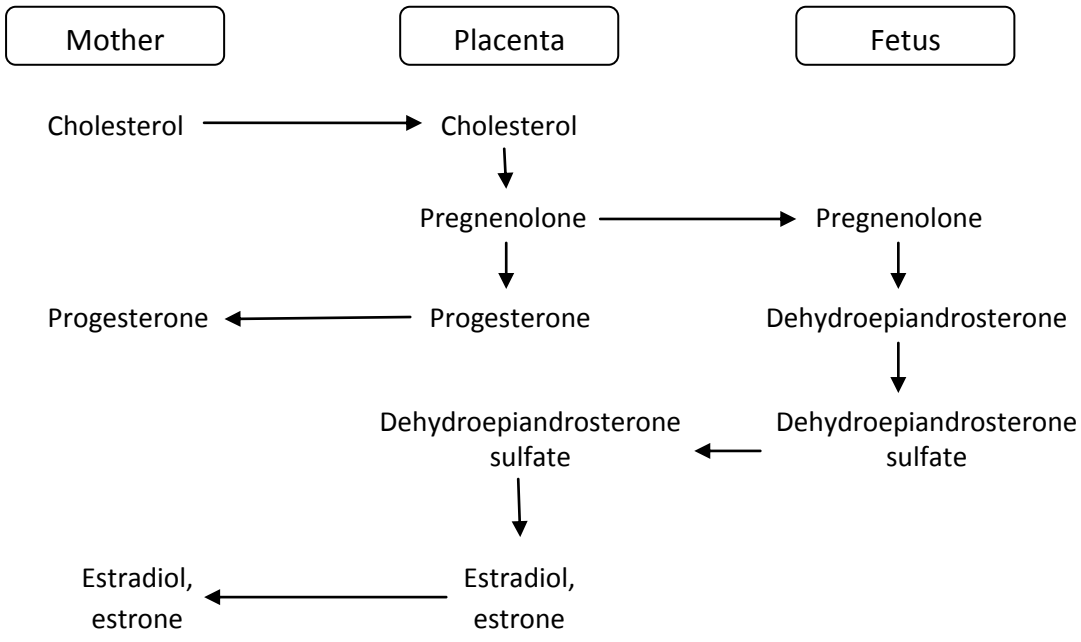

Figure 4: Synthesis of estradiol and estrone by the fetoplacental unit, placental progesterone synthesis (8,19,21)

Once released into the maternal circulation, E2 exerts its effect in two different ways. The first is the classical interaction with intracellular estrogen receptors (ESR 1 and ESR 2), which act as ligand-activated transcription factors (20). Once activated by E2, the ESRs dimerize and go on to modulate gene expression and protein synthesis (19,20). These genomic actions occur slowly and induce long-term changes in maternal tissues. However, some effects of E2 occur so rapidly that they cannot be explained by means of this classical pathway. Recently, it has been proposed that E2 can also exert an immediate, or non-genomic, cellular effect by binding to membrane receptors on the outside of cells and activating protein kinase pathways (19,20). This can either cause a rapid change in membrane properties (charge, ion channels) or influence gene expression by means of a non-genomic-to-genomic signaling inside the cytoplasm (20). The changes caused by estrogens during pregnancy are thought to be a combination of genomic and non-genomic actions (19).

i. Levels during pregnancy

Estrogen production begins to increase rapidly once the placenta is large enough to take over the function of the corpus luteum. This has been described to occur between the sixth and ninth week of pregnancy (1,19,22). From this point onward, concentrations continuously rise until term, reaching levels three to eight times higher than in the non-pregnant state, according to one author [see Figure 5] (19). Another study found that estradiol levels were 16 times higher at term than at week eight of pregnancy (18). In late pregnancy, physiological concentrations have been reported at 30-50 nmol/l and 20 ng/ml (13,23).

ii. Functions [see Table 3]

Among the many functions of estrogens during pregnancy, including the regulation of fetal growth, the onset of parturition, placental steroidogenesis, glycoprotein synthesis, and neuropeptide production, the modulation of maternal lipid metabolism must be addressed (23). It has been shown numerously that E2 causes a rise in plasma lipid levels during mid- to late gestation (1,7,8,24,10,25). One review reported a rise in maternal plasma triglycerides by 50-300% and a rise in total cholesterol by 50-60%, while another states that plasma triglycerides rise by 200-310%, total cholesterol by

30-65%, and HDL-cholesterol by 15-40% (8,25). Yet another review puts the rise in HDL-cholesterol at 20-30% (1). Perhaps the authors used measurements taken from different times during the pregnancy. Since estrogen concentrations continuously rise until term, it can be expected that the changes in lipid levels are more pronounced in late gestation. Another reason for the discrepancy could be that some of the women studied already had altered lipid profiles before becoming pregnant. LDL-cholesterol concentrations also increase during pregnancy, almost doubling between weeks eight and 36 and decreasing somewhat thereafter (18).

Another pronounced effect of E2 on plasma lipid levels is the increase in very low-density lipoprotein (VLDL) in late pregnancy (8,10). Freemark reports that VLDL levels are 2-2.5 times higher in women at term than in non-pregnant women (1). The increase can be attributed to a higher hepatic production of VLDL as a response to stimulation by estrogen (8). Another contributing factor to hyperlipidemia in pregnancy is an estrogen-mediated reduction of hepatic lipase and lipoprotein lipase (1). This prevents lipids from being broken down and absorbed in peripheral tissues and their reduced clearance leads to increased transport back to the liver and repackaging into VLDL (1). By inhibiting lipolysis, the estrogens also promote lipid storage and weight gain (7).

In early pregnancy, insulin sensitivity can be slightly elevated (3,7,8,13). Ryan and Enns have suggested that this brief improvement of insulin sensitivity may be due to enhanced insulin binding mediated by estradiol (13). The situation is quite different in mid- and late pregnancy. García-Arencibia et al. have shown that estradiol reduces insulin receptor gene expression and glucose transport, implicating the estrogens in the induction of insulin resistance in the latter part of pregnancy (26). Hyperlipidemia is also considered a contributing factor to insulin resistance. However, the contribution of estradiol to the development of insulin resistance is relatively minor compared to that of several other pregnancy hormones.

Finally, E2 exerts a function on the thyroid gland during pregnancy. In early pregnancy, a rise in the hepatic production and secretion of thyroxin-binding globulin (TBG), the major thyroid hormone transport protein, has been observed as a result of elevated estrogen levels (27). Around mid-gestation, TBG levels peak at 2.5 times the normal level and remain stable until term (27). This rise is one of the changes that must occur in the normal human thyroid during pregnancy to adjust to the altered metabolic

demands of the mother during this time (27). Pregnancy is a state requiring higher levels of thyroid hormones and a proportional increase in TBG is necessary for the mother to remain euthyroid (27).

iii. Regulation and interactions with other hormones

Estrogen is produced continuously throughout pregnancy, initially by the corpus luteum and later by the fetoplacental unit (19). Production rate is generally thought to be influenced by luteinizing hormone from the pituitary gland, as well as substrate availability on the maternal (cholesterol) and fetal (androgens) side (22). Estrogen production has been found to be down-regulated by leptin and possibly by human chorionic gonadotropin (7,22,28). There may also be a role for human placental lactogen in the modulation of estrogen production through induction of dehydroepiandrosterone secretion, although this hypothesis remains to be confirmed (9).

E2 acts on several other hormones of pregnancy. It up-regulates leptin at the transcriptional level and also through non-genomic actions in maternal adipocytes and placental explants (19,24,29-31). However, Henson et al. state that while adipose tissue leptin production is up-regulated by estradiol, placental leptin is down-regulated (30). The discrepancy may be due to differences in the E2 concentrations that were administered. There is some evidence that estradiol increases the expression of both the long form of the leptin receptor in the hypothalamus and the soluble leptin receptor (30).

Estradiol suppresses placental corticotropin-releasing hormone concentrations (32). Simultaneously, cortisol binding protein levels double during pregnancy in the presence of estrogen, extending the half-life of cortisol in the blood stream (32). Overall, cortisol levels are increased by 200-300% during pregnancy, suggesting that the suppressive action of estrogen is rather weak (32). Finally, E2 has a suppressive effect on resistin, a novel adipokine which is thought to contribute to insulin resistance (33). The implication of estrogen-mediated down-regulation of resistin is unclear.

iv. Pathologies

Since estradiol is thought to have a positive effect on trophoblast differentiation, abnormalities in estrogen production are associated with impaired placental growth and

function (19). Decreased estradiol levels have been observed in women with preeclampsia [see Table 2] (34).

2) Progesterone

Like the estrogens, progesterone is produced continuously throughout pregnancy, first by the corpus luteum and later by the placenta. While pregnancy can be maintained at low estrogen concentrations, this is not true for progesterone, making it arguably the most important steroid hormone of pregnancy (22). Following implantation, the corpus luteum is stimulated to sustain progesterone secretion by rising concentrations of hCG (21). After six to ten weeks of pregnancy, hCG concentrations decline and progesterone synthesis is relocated to placental trophoblast cells (1,6,21,22,35). There, cholesterol is converted to pregnenolone and then to progesterone in the placental mitochondria [see Figure 4] (8).

i. Levels during pregnancy

While progesterone concentrations are initially low during the phase of luteal production, they rise exponentially once the placenta takes over as the main site of steroid synthesis and continue to increase until term [see Figure 5] (1,6,21). At term, progesterone concentrations have been reported at 150 ng/ml in one study, while another has estimated a production rate of 300 mg/day at term (13,35). A further study declares progesterone secretion to be eight times higher at term than at week 14 (21). Finally, yet another study found progesterone levels to be seven times higher at term than at week eight of pregnancy (18).

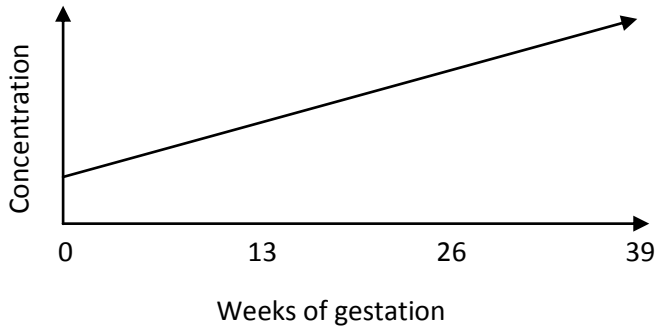

Figure 5: Time course of estrogen and progesterone concentrations during pregnancy (1)

ii. Functions [see Table 3]

Progesterone is considered the most important hormone for the maintenance of pregnancy, as it promotes uterine quiescence and suppresses maternal immune response to prevent rejection of the fetus (6,21,24,35,36). It is generally accepted that progesterone is the main stimulant of hyperphagia in pregnancy, increasing food intake and body weight throughout gestation (5,6). Hyperphagia is one of the maternal adaptive mechanisms to ensure adequate nutrient reserves for the metabolic demands of mother and fetus during pregnancy and lactation. Progesterone further contributes to weight gain by inhibiting lipolysis and promoting fat storage (1,3,7). In concert with other gestational hormones, progesterone thus contributes to the hyperlipidemia and free fatty acidemia of pregnancy. This metabolic change is one of the factors leading to insulin resistance around mid-pregnancy (1).

The rise in progesterone is proportional to the decrease in insulin sensitivity observed during the second half of pregnancy, pointing to a role for progesterone in this process (37). In late gestation, when levels are highest, progesterone contributes to insulin resistance by reducing insulin binding, glucose transport, and GLUT-4 expression in skeletal muscle and adipose tissue (1,6,12,13). This leads to postprandial hyperglycemia and increased transfer of glucose to the fetus. Progesterone also reduces hepatic insulin sensitivity and induces hepatic triglyceride lipase activity, augmenting gluconeogenesis and hyperlipidemia, thereby further adding to hyperglycemia (1,18).

It has been suggested that progesterone plays a part in inducing leptin resistance by inhibiting central nervous system response to leptin (5). However, the exact mechanism appears to be unclear.

iii. Regulation and interactions with other hormones

The mechanisms regulating progesterone secretion are not fully elucidated. Interestingly, progesterone concentrations are only weakly correlated with placental mass, indicating the presence of alternate regulatory mechanisms (21). Estrogen, insulin, insulin-like growth factor, and epidermal growth factor have been reported to increase progesterone synthesis, while transforming growth factor-β1 has been reported to have an inhibitory effect (21).

It has been observed that progesterone decreases placental leptin production (4,24). This effect can be explained through the anti-inflammatory actions of progesterone during pregnancy. Since leptin is an adipokine, it probably falls into the category of pro-inflammatory cytokines suppressed by progesterone. The same is true for resistin (33). Increasing concentrations of progesterone are associated with decreasing levels of hCG and CRH (23,38). Since the drop in hCG levels coincides with the placental take-over of steroid production from the corpus luteum it is difficult to say whether the rise in progesterone inhibits hCG, lower levels of hCG promote progesterone secretion, or both events occur as a consequence of a third hormone or other influence. The decrease in CRH in the presence of progesterone is likely due to competitive antagonism at the glucocorticoid receptor (38).

iv. Pathologies

High progesterone levels are associated with states of insulin resistance. Therefore, progesterone concentrations are elevated above the normal range in pregnancies with diabetes mellitus or gestational diabetes [see Table 2] (37). There is also a connection between low progesterone levels and the inability to sustain a pregnancy (21). Progesterone is the most important hormone for maintaining a safe environment during pregnancy and concentrations lower than normal in the first ten weeks of gestation are predictors of an impending abortion in 83% of pregnancies (21).

	GDM	PE	IUGR
Estrogen	?	↓	↓
Progesterone	↑		

Table 2: Changes in steroid hormone levels in pregnancy-related pathologies (19,34,37). A question mark represents unclear or conflicting data while a blank space indicates a lack of data on the topic.

B. Peptide Hormones

1) hCG

Human chorionic gonadotropin (hCG) is a glycoprotein hormone and considered by some to be the "key hormone of human pregnancy" because of its importance in the process of implantation and trophoblast differentiation (35,39). Human CG is secreted initially by the blastocyst and later by villous trophoblast cells in a pulsatile manner (40). Two types of pulsatility can be observed, short-term pulses lasting less than one hour and long-term pulses occurring every few hours (41). To date, the earliest stage of proven hCG production is the 8-cell embryo (40). In the maternal circulation, hCG binds to the LH/hCG receptor, a G-protein-coupled receptor (39,40).

i. Levels during pregnancy

Human CG is among the first hormones produced by the human embryo and large quantities are secreted during implantation and the early stages of pregnancy, detectable as early as eight days after fertilization (40,42). Unlike other gestational hormones, hCG levels do not increase until term, but rather peak early on at eight to twelve weeks and subsequently decline in the second trimester [see Figure 6] (13,39,42,43). This peak generally lasts less than one week, after which levels remain stable until term, increasing slightly near term (27,43). Desoye et al. reported hCG levels of 57-60 IU/ml in the first and 8-13 IU/ml in the second trimester, and an increase again in the third trimester (18). In late pregnancy, hCG levels have been reported at 180 mg/l by one author (13). Concentrations of hCG are directly proportional to syncytiotrophoblast formation (23,44).

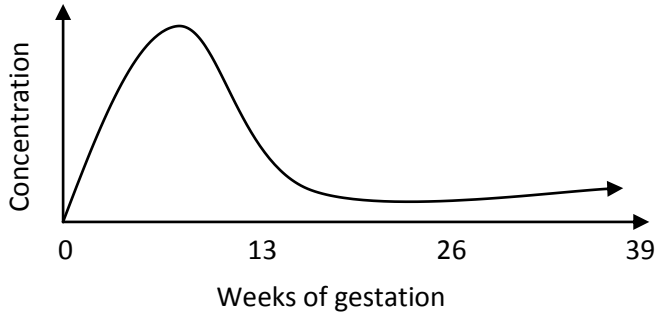

Figure 6: Time course of hCG concentrations during pregnancy (13,27,39,42,43)

ii. Functions

As mentioned earlier, hCG plays a key role in the implantation of the blastocyst and in stimulating the differentiation of cytotrophoblast cells to syncytiotrophoblast cells (35,43). Furthermore, because they share a receptor, hCG acts as a "super-agonist of LH", maintaining the corpus luteum and thus the secretion of estrogen and progesterone in the first six weeks of pregnancy (21,35,40,43).

Human CG has a close structural similarity to thyroid-stimulating hormone (TSH), and the receptors of the two molecules are also very similar (39). This allows hCG to displace TSH from the TSH receptor and exert a thyroid stimulating activity in the first trimester (27,39). Fortunately, the potency of hCG at the TSH receptor is much lower than that of TSH itself, so it does not normally cause hyperthyroidism or thyrotoxicosis (39). In addition to increased iodide uptake, an increase in T_3, and T_4 is observed, with maximum concentrations occurring at the time of the hCG peak (39). A weak suppression of TSH has also been measured (39). Thus, hCG acts as a weak thyroid stimulator during the first trimester of pregnancy.

iii. Regulation and interactions with other hormones

Many factors have been implicated in the regulation of hCG production and release. Because of the pulsatile nature of hCG secretion by trophoblast cells, three different qualities may be influenced: pulse frequency, pulse amplitude, and total hCG secretion (41). GnRH causes a decrease in pulse frequency, but an increase in total hCG secretion (41). Other promoters of hCG secretion include epidermal growth factor, leukemia inhibitory factor, IL-1, IL-6, TNF, M-CSF, and activin (23,36). Inhibitors of hCG secretion are progesterone, inhibin, and transforming growth factor (23,36).

A point of contention is the regulation of hCG secretion by leptin. While many authors have claimed that leptin causes a rise in hCG production, others have disputed this (23,28,30,36,40,41,45). Coya et al. state that experiments which showed an increase in hCG release after administration of leptin were carried out using unphysiologically high leptin concentrations and further point out the discrepancy between the early hCG and late leptin peaks (28). A recent study provides an explanation, stating that leptin promotes hCG secretion only in the first trimester and not at term (40). Conversely and

less controversially, hCG has been shown to up-regulate the production of leptin in early pregnancy, acting at the transcriptional level (24,30,40).

iv. Pathologies

Several pathologies are associated with overly high hCG concentrations. Choriocarcinomas and molar pregnancies can secrete significant amounts of hCG, leading to excessive thyroid stimulation and thyrotoxicosis in 25-64% of cases (27,39). In pregnancies with hCG concentrations rising above normal levels, the increased thyroid stimulation can cause hyperemesis gravidarum and, in extreme cases, also thyrotoxicosis (27). Pregnancies with trisomy 21 fetuses also show abnormally high hCG concentrations, reflecting a pathological trophoblast differentiation (46).

2) hPL

Human placental lactogen, initially known as human chorionic somatomammotropin (hCS), is a polypeptide hormone derived from a gene cluster encoding five closely related proteins (47). These are pituitary growth hormone (GH-N), placental growth hormone (GH-V), and three lactogens, hPL-A, hPL-B, and hPL-L (9). Of these, hPL-A is the most abundant during pregnancy, with levels three to six times higher than hPL-B, while hPL-L has not been identified in maternal blood (9,48). Apart from GH-N, which is synthesized in the pituitary gland, all hormones of this family are produced by the placental syncytiotrophoblast (9,35,48). Human PL has a structural similarity of 85% to GH-N and 17% to prolactin, but functionally it is a stronger lactogen than somatogen (5,6,9). Human PL binds to the growth hormone receptor with low affinity, but to the prolactin receptor with a higher affinity than prolactin itself (9,13). GH and prolactin receptors are present in many maternal and fetal tissues, including liver, white adipose tissue, skin, cartilage, ovary, adrenal glands, kidney, breast, and pancreas (9). There also exists a distinct PL receptor in the fetal skeletal muscle to which hPL can bind (9).

i. Levels during pregnancy

Human PL production begins very early in pregnancy. In the placenta, it can be detected as early as five to ten days after implantation, and in the maternal circulation

after six weeks (9). Human PL concentrations correlate closely with placental mass and are higher in twin pregnancies and in pregnancies with female fetuses (6,9,35,46,48,49). Accordingly, hPL concentrations rise linearly after six weeks and peak at 30-35 weeks to remain stable until term [see Figure 7] (6,9). One study reports hPL levels 30 times higher in late than in early pregnancy (50). In another study, hPL concentrations were measured at week eight at 33 ng/ml, while in week 38 the measurement was 7.1 µg/ml (18). Maximal hPL secretion has been estimated from 5-10 µg/ml to 1-3 g per day (6,46,47). Handwerger states that hPL has the highest term secretion rate of any polypeptide hormone (9). Although hPL does not cross the placenta, a small amount is secreted directly into the fetal circulation (9). At term, this amounts to 20-30 ng/ml (9,35).

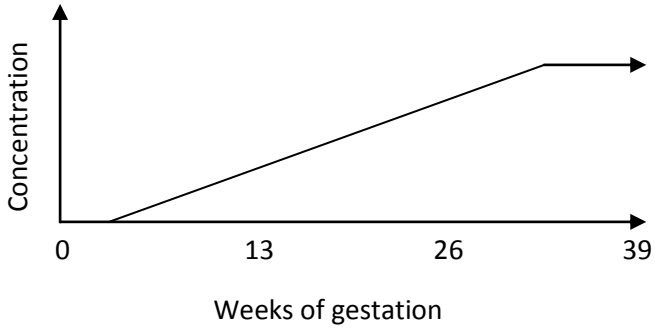

Figure 7: Time course of hPL concentrations during pregnancy (1,6,9)

ii. Functions [see Table 3]

Human PL has a profound impact on maternal metabolism in all phases of gestation. For many years, hPL was thought to be the dominant factor in the development of insulin resistance in mid-gestation. In recent years, however, many hormones have emerged as potential regulators of insulin sensitivity during pregnancy, and it seems likely that insulin resistance is the result of the combined effects of these.

In early pregnancy, hPL contributes to weight gain and the accumulation of fat stores by promoting hyperphagia, glucose uptake, and incorporation of glucose into glycogen, glycerol, and fatty acids (1,9). In the catabolic phase of the third trimester, hPL causes increased lipolysis and fat mobilization, especially during fasting periods (1,7,9). Human PL has also been suggested as a promoter of leptin resistance in mid-pregnancy, although the exact mechanisms of action are not fully elucidated (4,5).

Human PL acts as an insulin antagonist, decreasing insulin sensitivity in a dose-dependent manner. As pregnancy progresses and hPL concentrations rise, insulin sensitivity worsens (9,28,51,52). In late pregnancy, hPL reduces glucose transport, while increasing ketone, glycerol, and free fatty acid levels in the maternal circulation (8,9,13). It is therefore an important contributor to insulin resistance. However, hPL is also one of the most important hormones counteracting insulin resistance during pregnancy.

Starting in early to mid-pregnancy, hPL promotes the production and secretion of insulin (1,9,13,28,50,53). Under the influence of hPL, pancreatic β-cell replication increases, resulting in enhanced β-cell mass and pancreatic growth (1,6,9,28,53). Human PL also increases the lifespan of β-cells (6,53). As a consequence, insulin levels are twice as high in the third trimester than at the beginning of pregnancy (6). In the first half of pregnancy, this increased insulin production successfully counteracts the diabetogenic effects of hPL and other gestational hormones, delaying insulin resistance. However, in late pregnancy this compensation is no longer sufficient and insulin resistance emerges.

Lastly, in preparation for parturition and lactation, hPL promotes breast development and nesting behavior in the mother (9).

iii. Regulation and interactions with other hormones

The exact mechanisms regulating hPL secretion are not known (9). It seems that hPL production is not related to plasma glucose, amino acid, or fatty acid levels (9). However, levels are increased during fasting (9). A likely explanation for the regulation of hPL is the presence of factors acting in an autocrine or paracrine manner (9). Some of the suspected promoters of hPL secretion are 1,25-dihydroxyvitamin D_3, IL-1, IL-6, retinoic acid, thyroid hormone, and pre-β HDL (9). Earlier studies have proposed a stimulatory effect of phospholipase A_2 and arachidonic acid on hPL release (9).

Human PL itself has a regulatory role on some other gestational hormones. With prolactin, hPL stimulates the release of parathyroid hormone-related protein (PTH-rP) and cortisol (9). It may have an effect on estrogen production by inducing fetal dehydroepiandrosterone secretion (9). Coya et al. demonstrated that hPL causes a time- and dose-dependent decrease in leptin concentrations *in vitro* (24).

iv. Pathologies [see Table 4]

Human PL levels are elevated in conditions associated with impaired insulin sensitivity, such as diabetes mellitus and gestational diabetes (1,9). On the other hand, very low hPL levels can be observed in pregnancies complicated by preeclampsia, maternal hypertension, and IUGR (1,6,9). In these cases, the decreased hPL production can be seen as a sign of placental dysfunction and insufficiency (6).

There have been reports of pregnancies in which the gene locus encoding for hPL was fully deleted in the fetus (48,49,54). Surprisingly, these pregnancies were able to be carried to term and showed a normal outcome, although some authors have found an association between hPL-gene deletion and fetal growth retardation (54). Due to the close similarity of the lactogenic and somatogenic hormones, it can by hypothesized that in the case of a complete absence of one hormone, others can partially or completely take over its functions (48,49).

3) Placental Growth Hormone

Like hPL, placental growth hormone (PGH, GH-V) is a polypeptide hormone which is secreted by the placental syncytiotrophoblast during pregnancy (35). Due to its close genetic similarity to hPL and pituitary growth hormone (GH-N), PGH also binds to somatogenic and lactogenic receptors, albeit with different affinities. The molecular structure of PGH is more similar to GH-N than to the lactogens, differing by only 13 amino acids (1,9,47). The affinity of PGH for the somatogenic receptor is equal to that of GH-N, while its lactogenic potential is seven times lower (1,9,48,49,55).

i. Levels during pregnancy

Like hPL, placental GH is a marker for syncytiotrophoblast formation; levels therefore correlate with placental size and development (47,48,55). Levels are also higher in twin pregnancies and when the fetus is female (48,56,57). PGH can be detected as early as five weeks of pregnancy, but levels can vary significantly in the mothers (44,58). The first detection of PGH can therefore be anytime between five and 21 weeks (9,44,56,58). From then on, PGH concentrations continually rise until the third trimester, peaking at 34-37 weeks and then remaining stable or declining slightly until term [see Figure 8] (1,6,47,48,58). Maximum levels have been reported from 2.6-40 ng/ml,

reflecting the great individual variation throughout gestation (6,9,54,56,58). Most authors agree that placental GH does not cross the placenta and cannot be detected in the fetal circulation (1,9,35,47-49,53,55). However, Mittal et al. detected the hormone in umbilical cord blood (58).

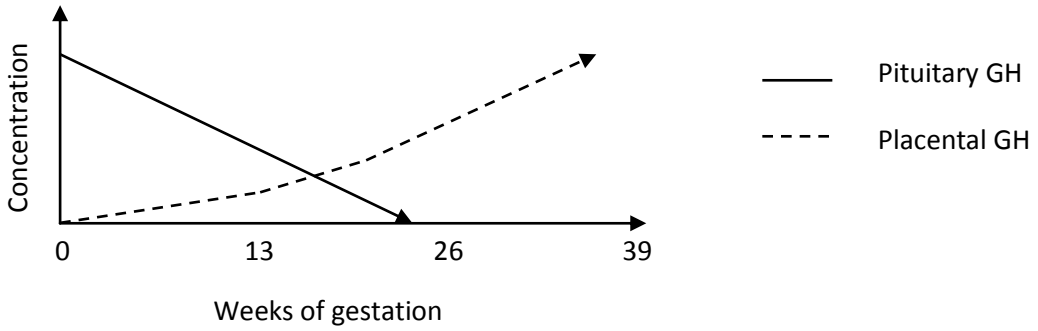

Figure 8: Time course of placental growth hormone and pituitary growth hormone concentrations during pregnancy (1,6,47)

ii. Functions [see Table 3]

Once a certain concentration has been reached between 10-24 weeks of pregnancy, PGH begins to gradually replace maternal pituitary growth hormone as the dominant somatogenic hormone in the maternal circulation (6,48,53). At around mid-gestation, GH-N disappears completely and does not return until after delivery [see Figure 8] (46,47). Due to its close similarity, PGH takes over many of the functions of GH-N, but since it is present in very high concentrations in late pregnancy, it also causes some substantial changes in maternal metabolism (9,57). PGH essentially acts as an insulin antagonist, stimulating maternal gluconeogenesis, lipolysis, and weight gain (6,16,47-49,55). In periods of fasting, PGH is one of the hormones ensuring a constant supply of nutrients to the fetus by mobilizing fuel and increasing nutrient transport across the placenta (56). In rats, PGH has been shown to increase body weight and fasting insulin levels while decreasing insulin sensitivity, and the assumption is that the effect is similar in humans (1,48,53,55). Thus, placental GH is one of the factors responsible for the development of insulin resistance, and it is considered a very dominant one by many (1,48,53).

Another function of PGH during pregnancy is the regulation of insulin-like growth factor I. IGF-I levels closely correlate with PGH levels and exhibit a steady rise of about

56% during pregnancy (1). In addition to its role in regulating fetal growth, IGF-I stimulates the growth of maternal tissues such as uterus, breast, and thyroid gland (1,9,35,58). It also increases maternal cardiac output and blood volume (1,9).

Finally, PGH probably also has autocrine or paracrine regulatory effects on the placenta, as suggested by the presence of GH receptors in the villous trophoblast (46,48,49).

iii. Regulation and interactions with other hormones

Unlike GH-N, placental GH is not secreted in a pulsatile manner and its secretion is not controlled by growth-hormone-releasing hormone (GHRH) (6,9,47-49,53, 55). However, many studies have shown a stimulatory effect on PGH secretion by hypoglycemia, as well as an inhibition by glucose (1,6,9,16,47-49). This reflects the importance of PGH as a nutrient provider for the fetus in times of low supply. PGH secretion is inhibited by insulin, cortisol, ghrelin, and possibly leptin and up-regulated by visfatin (44,57).

Short-term administration of PGH leads to an increase in leptin, but leptin is decreased during chronic exposure to PGH, most likely due to the decrease in fat mass mediated by PGH (57). PGH decreases adiponectin levels (1).

iv. Pathologies [see Table 4]

Many studies have found a correlation between PGH levels and fetal size and development, while other authors found no relationship. Therefore, the role of placental GH in diabetic pregnancies is uncertain. However, it is clear that PGH levels are decreased in pregnancies with IUGR (1,6,9,16,17,47,49,55). This observation could be explained as a consequence of inadequate fetal growth due to low levels of PGH and IGF-I, but the low PGH levels could also be the result of placental insufficiency due to some other reason. Evain-Brion states that low levels of PGH can be associated with fetal malnutrition. One author claims that PGH levels are increased in women suffering from preeclampsia (58). However, there is not yet much information on this topic.

Like hPL, PGH can be absent during pregnancy due to a gene deletion (56). Nevertheless, the pregnancy can proceed and be carried to term, but maternal plasma

typically shows circulating levels of GH-N throughout as a substitute for the missing placental hormone (55,56).

	Hyperphagia	Fat storage	Insulin sensitivity	Insulin production	Plasma lipids
Estrogen		?	↑ in early, ↓ in late gestation		↑
Progesterone	↑	↑	↓		↑
hPL	↑	↑	↓	↑	↑
PGH		↑ in early, ↓ in late gestation	↓		↑

Table 3: Effects of estrogen, progesterone, hPL, and PGH on maternal metabolism during pregnancy (1,6,9,13,26,56). A question mark represents unclear or conflicting data while a blank space indicates a lack of data on the topic.

4) CRH

Corticotropin-releasing hormone (CRH), also known as corticotropin-releasing factor (CRF), is a polypeptide hormone which is usually derived from the hypothalamus, but is also secreted in significant concentrations by the placenta during human pregnancy (38). Placental CRH is identical in size, structure, and biological activity to hypothalamic CRH (38,59). However, unlike hypothalamic CRH, its release does not follow a circadian rhythm, as the two hormones are controlled differently (32). During mid and late pregnancy, CRH is produced in large quantities by the cytotrophoblast, syncytiotrophoblast, and fetal membranes (38,59,60). It is secreted into the maternal and, to a lesser extent, the fetal circulation (38,59,61). CRH exerts its effects by binding to one of two G-protein-coupled receptors, corticotropin-releasing hormone receptor 1 and 2 (32).

i. Levels during pregnancy

CRH becomes detectable in maternal plasma at 8-20 weeks of gestation (32,59). As with many other placental hormones, CRH levels can vary greatly between individual women and are higher in twin pregnancies (32,59). After their first appearance, CRH

concentrations rise steadily until shortly before term and then rapidly until parturition [see Figure 9] (59). It is generally agreed that maximum levels of CRH are seen immediately before or during gestation, possibly at the time of maximal cervical dilation (60). However, the reported levels vary greatly. Goland et al. found an exponential increase of CRH levels during the last six weeks of pregnancy to concentrations of 1 ng/ml and more, while mean CRH concentrations after 18-20 weeks were reported at 350 pg/ml (59). Several authors found a two- to threefold increase of CRH levels throughout pregnancy, while Frim et al. have found a 100-fold increase just in the last six to eight weeks of pregnancy (1,32,38,60). Robinson et al. measured a 20-fold increase in CRH concentrations five weeks before term, as compared to non-pregnant levels (61).

CRH is also secreted directly into the fetal circulation, but fetal cord CRH concentrations are about 20 times lower than those in the mother (60).

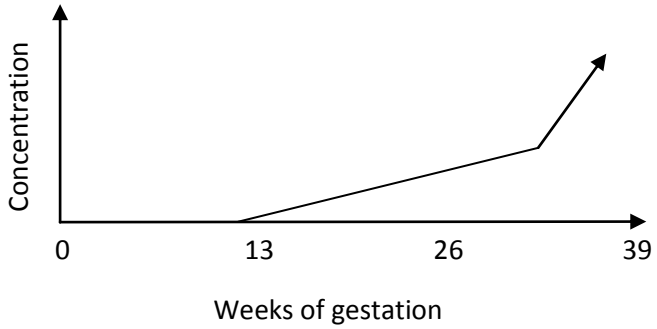

Figure 9: Time course of CRH concentrations during pregnancy (32,59)

ii. Functions

Since it is structurally identical to hypothalamic CRH, placental CRH performs many of the same functions, namely stimulation of ACTH release (32,53). Pregnancy is considered a state of hypercortisolism (59). This state is characterized by a stimulation of hepatic gluconeogenesis and inhibition of insulin-dependent glucose uptake in skeletal muscle (1). CRH also exerts important local effects, contributing to "the aseptic anti-inflammatory process of implantation and the anti-rejection process that protects the fetus from the maternal immune system" (32). Furthermore, CRH regulates placental blood flow, myometrial contractility, and prostaglandin release (60).

In late pregnancy, CRH levels continue to rise, but ACTH response decreases, indicating a down-regulation of the CRH receptor in response to chronically high concentrations (38,59). Shortly before birth, CRH levels are extremely high and it has been proposed that CRH acts as a "pregnancy clock", determining the timing and initiation of labor (32,59).

iii. Regulation and interactions with other hormones

Unlike hypothalamic CRH, placental CRH release is not down-regulated, but rather stimulated by cortisol (32,38,61). Both maternal and fetal cortisol production cause a rise in placental CRH concentrations (61). CRH concentrations also rise in the presence of IL-1, NPY, acetylcholine, noradrenaline, vasopressin, angiotensin II, and oxytocin (60). As mentioned earlier, estrogen down-regulates CRH levels while increasing cortisol binding globulin (32,38,59). Several authors have found that progesterone decreases CRH levels (38,60).

Not much is known about the effects of CRH on other gestational hormones. One author has suggested that CRH might stimulate the release of hCG from the placenta by an autocrine or paracrine mechanism (61).

iv. Pathologies [see Table 4]

High CRH levels are associated with all forms of maternal and fetal stress. Several studies have confirmed increased CRH levels in preterm labor, pregnancy-induced hypertension, and IUGR (38,60,61). Additionally, psychological stress can cause CRH levels to increase (38,61). Other pregnancy-associated pathologies have not yet been thoroughly investigated in regard to CRH levels.

5) Ghrelin

Ghrelin is a peptide hormone which has garnered some interest in recent years. It is produced by many different tissues, including stomach, ovary, pancreas, neutrophils, hypothalamus, and the placenta (16,62,63). Ghrelin is a ligand for the growth hormone secretagogue receptor (GHSR), which is present in the central nervous system, adipose tissue, endocrine organs, muscle tissue, and gastrointestinal tract (62,63).

i. Levels during pregnancy

Ghrelin levels follow an interesting pattern during pregnancy. Concentrations are low in the first trimester, peak at mid-gestation, and subsequently decline to lower than non-pregnant levels in the third trimester, becoming nearly undetectable in some cases [see Figure 10] (1,16,62). After parturition, ghrelin levels once again rise to normal values (62). Fuglsang et al. measured ghrelin levels in pregnant women after a period of fasting (62). Maximum levels were observed at week 18 at 1.2 µg/l, and a concentration of 0.87 µg/l was observed at term (62). Another publication states that ghrelin levels are 30% lower in women in the third trimester of pregnancy than in non-pregnant women (63).

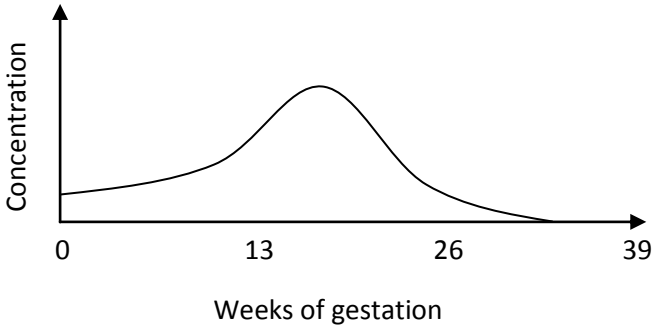

Figure 10: Time course of ghrelin concentrations during pregnancy (1,16,62)

ii. Functions

Ghrelin acts as an orexigenic hormone, increasing food uptake and promoting weight gain and fat accretion by stimulating the differentiation of preadipocytes (16,62,63). Ghrelin is also believed to be a contributing factor to insulin resistance by stimulating hepatic gluconeogenesis while inhibiting pancreatic insulin secretion (63).

iii. Regulation and interactions with other hormones

Not much is known about the regulation of ghrelin, but its release might be stimulated by fasting, while insulin causes a decrease in ghrelin concentrations (16,63).

On the other hand, ghrelin down-regulates insulin secretion, promoting hyperglycemia (16). Placental GH, leptin, and resistin are decreased in the presence of

ghrelin, while prolactin, ACTH, and cortisol are elevated (44,62,63). It has also been shown that ghrelin has potent GH-releasing effects (62).

iv. Pathologies [see Table 4]

Ghrelin levels are low in states of decreased insulin sensitivity, such as obesity and gestational diabetes mellitus (16,62,63). In pregnancy-induced hypertension and IUGR, ghrelin levels are elevated (16,62).

6) hCT, PTH-rP

In the 1970s, some research was conducted into human chorionic thyrotropin (hCT), a placental form of TSH. This hormone was believed to be secreted in small quantities and to stimulate the thyroid gland and exert certain effects on maternal metabolism (43). However, this research was not pursued in the following decades and hCT has since disappeared from current publications on placental endocrine function.

Another placental hormone not receiving much attention currently is PTH-rP, parathyroid hormone-related peptide. This polypeptide hormone influences maternal calcium metabolism during pregnancy, increasing gastrointestinal calcium absorption, stimulating placental calcium transport, thereby regulating fetal calcium levels (1). Synergistically with hPL, PTH-rP increases the replication and inhibits apoptosis of pancreatic β-cells (1). Furthermore, PTH-rP promotes breast development and liberates calcium for breast milk synthesis (1).

	GDM	PE	IUGR
hPL	↑	↓	↓
Placental GH	?	↑?	↓
CRH			↑
Ghrelin	↓		↑

Table 4: Changes in peptide hormone levels in pregnancy-related pathologies (1,6,9,38,58,60,62). A question mark represents unclear or conflicting data while a blank space indicates a lack of data on the topic.

C. Adipokines

1) Leptin

There is a plethora of information and research concerning this adipokine. Originally, leptin was identified as the product of the ob gene in 1994 by Zhang et al. and considered to be an adipocyte-derived regulator of appetite and weight (19,23,36,45,64). However, as more research was conducted into this hormone, it was discovered to fulfill many other functions, including regulatory effects on angiogenesis, reproduction, hematopoiesis, and bone mass (65). It was then discovered that the adipocyte is not the only source of leptin, but that the gastric epithelium, brain, and placenta can also synthesize this hormone (36,40,66,67). Placental leptin is identical to adipose cell-derived leptin in size, structure, and immunoreactivity and is secreted in large quantities during gestation by the syncytiotrophoblast, chorionic villi, chorion laeve, and amnion (19,24,30,33,66,68). 95-98% of placental leptin is secreted into the maternal, 2-5% into the fetal circulation (57,66). Leptin does not cross the placenta (69).

There are two forms of the leptin receptor, a long and a short one, the long one being of greater importance in regulating body weight (5,65). Receptors for leptin are abundant in the human body and can be found in the hypothalamus, arcuate nucleus, liver, pancreatic β-cells, adipose tissue, and skeletal muscle (5,65,70). Leptin receptors are also present in the placenta, amnion, and chorion (71).

i. Levels during pregnancy

In non-pregnant individuals, leptin concentrations are proportional to fat mass (7,19,33,40,45,72). During pregnancy, both fat mass and leptin concentrations increase; however, the major site of leptin production during pregnancy is not the adipose tissue, but rather the placenta (66,73). This is evidenced by the fact that adipose tissue leptin mRNA expression does not significantly change during pregnancy, while placental tissue shows high amounts of leptin mRNA (66). Furthermore, leptin concentrations rise before a significant change in fat mass is observed in early pregnancy, and they decrease immediately after delivery of the placenta (40,73). Maternal leptin concentrations do not show a correlation with placental mass, unlike those of other placental hormones (30).

However, it has been suggested that female fetuses present with higher maternal leptin concentrations than male fetuses (74).

There is a consensus that leptin concentrations rise rapidly in early gestation to peak in the second trimester and then decline somewhat in the third trimester, remaining high until term [see Figure 11] (23,24,36,68). Placental leptin gene expression is at its highest in early pregnancy (30,52). Different authors have reported leptin concentrations to rise up to 2-50 times the normal level during gestation (66,68,70,75). The leptin peak occurs at 22-27 weeks of pregnancy and shows levels between 19-30 µg/l (7,40,76,77). Third trimester leptin levels have been measured at 20.4-35 µg/l (7,70,74), while at term another study found a leptin concentration of 17.0 µg/l (57).

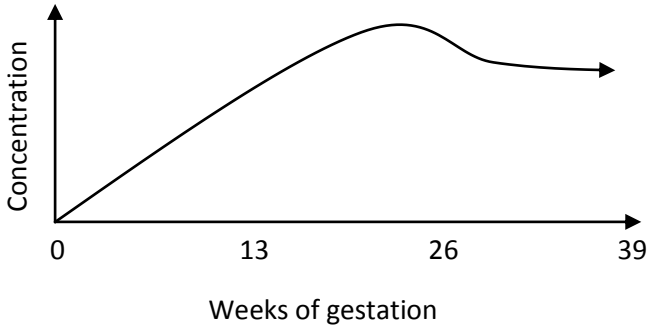

Figure 11: Time course of placental leptin concentrations during pregnancy (7,24,36,40)

ii. Functions [see Table 5]

In healthy non-pregnant individuals, leptin acts as a regulator of food intake and as an appetite suppressant by binding to receptors in the hypothalamus (5,29,33,40,45,66). However, pregnancy is associated with weight gain although leptin levels are high. This suggests that the mechanism of leptin action is different in pregnant than in non-pregnant individuals.

There is evidence that pregnant women develop a leptin resistance in the second trimester of pregnancy, blunting the anorexigenic effects of leptin in the central nervous system (5). There are many theories as to the cause of this leptin resistance [see Figure 12]. Leptin levels are not sufficiently high in early pregnancy to justify the development of a down-regulation of leptin receptors during this time (5). Ladyman et al. state that some but not all CNS leptin receptors are down-regulated in late pregnancy (5).

However, leptin-responsive neurons may become resistant without being down-regulated (5). Another explanation may be the decreased transport of leptin across the blood brain barrier, as well as increased binding of leptin to soluble plasma receptors and thus a decreased bioavailability to the hypothalamus (4,5,30,68). It is likely that leptin resistance develops as a combination of a down-regulation of the leptin receptor, impaired leptin signaling, and decreased availability of bioactive leptin. Leptin resistance is not only present in the CNS, it also develops in peripheral organs such as pancreatic β-cells (65).

The causes of these changes are not fully elucidated, though several gestational hormones are thought to be involved [see Figure 12]. The most likely candidates seem to be prolactin and hPL, but progesterone and estradiol have also been suggested. Leptin resistance can be induced in non-pregnant rats through infusions of hPL (5). Ladyman et al. state that chronic activation of the prolactin receptor, as is the case in mid- to late pregnancy, can cause leptin resistance (5). Other authors believe that the loss of the pre-conception cyclic pattern of estradiol secretion, in addition to elevated progesterone and subsequent changes in feeding behavior in the first trimester account for changes in leptin responsiveness (4). Estradiol and progesterone are able to exert substantial effects on leptin-responsive tissues as they are not regulated by maternal feed-back mechanisms during pregnancy and reach very high concentrations (5).

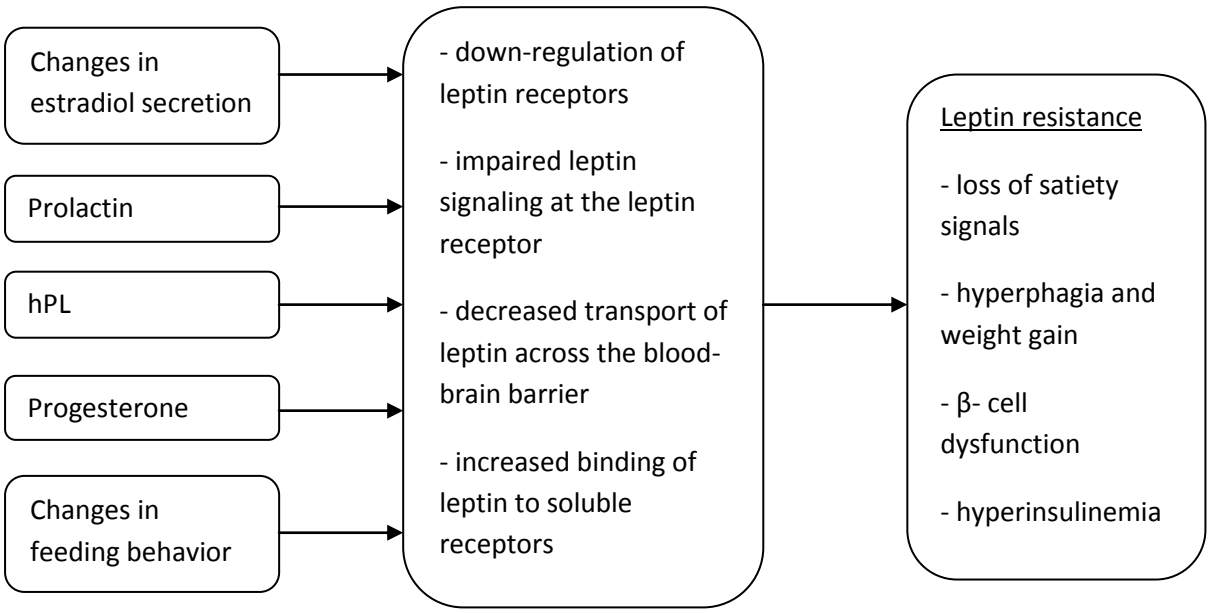

Figure 12: Factors leading to the development of leptin resistance in mid- to late pregnancy (4,5,65)

Due to leptin resistance, leptin actions during pregnancy differ from its physiological actions in non-pregnant humans. In pregnancy, leptin contributes to the increase in body weight and fat stores in early and mid-pregnancy by helping to induce hyperphagia, while enhancing the mobilization of fat stores in the catabolic phase of late pregnancy (4,45,66). Unlike conventional weight loss, weight loss due to leptin only involves adipose tissue while sparing lean mass (66).

There are some contradictions as to the effect of leptin on insulin sensitivity. While many authors believe that leptin is an insulin-sensitizing hormone, others claim it decreases insulin sensitivity and inhibits insulin signaling (11,51,52,72,75,78). Possibly, leptin has different effects on insulin sensitivity at different concentrations and at different times during pregnancy depending on the severity of leptin resistance. It has been observed that leptin increases skeletal muscle glucose uptake while reducing hepatic glucose production, indicating insulin-mimetic properties (79). According to some authors, the secretion of insulin by pancreatic β-cells is reduced in the presence of leptin, while others have found an increase (33,65,73). Seufert describes an adipo-insular feedback loop by which leptin from adipose tissue inhibits pancreatic insulin secretion, maintaining glucose homeostasis [see Figure 13] (65). In leptin resistance, this feedback loop is broken, leading to uncontrolled insulin secretion and eventually to β-cell failure and diabetes (65).

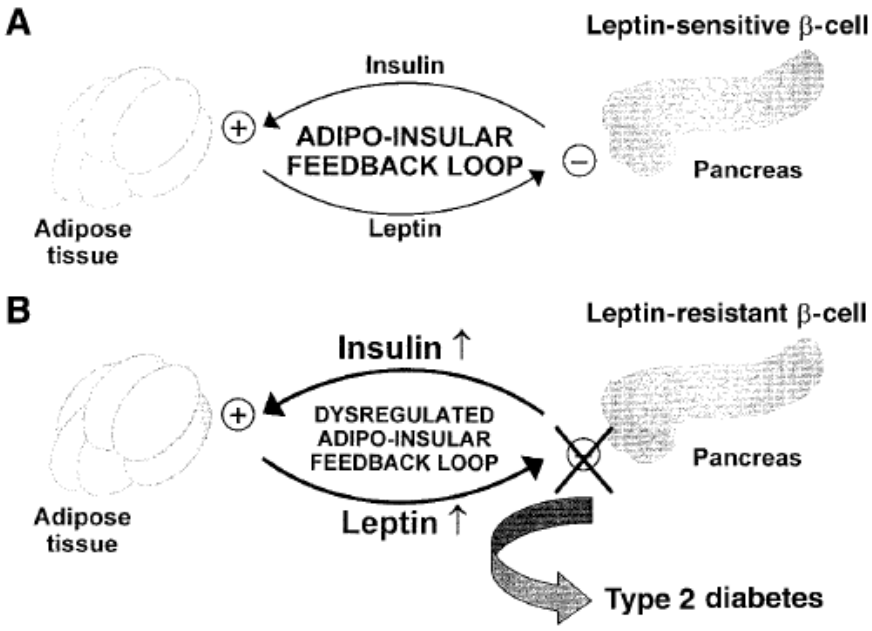

Figure 13: Dysregulation of the adipo-insular axis and pathogenesis of type 2 diabetes. Adapted from Seufert (65)

In addition to its endocrine properties, leptin also exerts autocrine and paracrine effects (30,35,36,40,66). Leptin is one of the hormones which promote trophoblast differentiation and placental growth (40,80). It may also be a local immunomodulator, counteracting the effects of pro-inflammatory cytokines at the maternal-fetal interface (68).

iii. Regulation and interactions with other hormones

Although placental leptin is structurally identical to leptin from adipose tissue, the mechanisms regulating its synthesis and release seem to be unique, although they are not exactly known (19,33,66). However, several factors have been consistently shown to up-regulate placental leptin production by different research teams. These are estrogen, insulin, TNF-α, and hypoxia (19,23,24,29-31,33,40,64-66,71,72,68,81,82). A stimulation on leptin release was also observed after administration of hCG, cortisol, IL-1, IL-6, and forskolin (24,30,33,40,68,71). Factors thought to down-regulate leptin are hPL, progesterone, androgens, and ghrelin (24,30,63). Although it has been suggested that leptin is regulated by placental GH, several studies have yielded contradictory results (57,81). GnRH does not regulate placental leptin production (81).

On the other hand, leptin positively influences the secretion of GnRH, LH, and FSH from the hypothalamus and pituitary gland (45). Leptin also stimulates a rise in the number of hCG pulses and pulse amplitude and up-regulates placental GH, CRH, and various inflammatory cytokines such as IL-1, IL-6, and TNF-α (30,36,40,45,57,66,67). Interestingly, leptin is up-regulated by TNF-α and IL-1 and IL-6 while also up-regulating these cytokines. This mechanism can be observed in preeclampsia or diabetes mellitus, where an excess of inflammatory products is produced in response to a systemic pathological change in the mother. Regardless of which hormone or cytokine is elevated first, these pathologies lead to chronically high levels of leptin, IL-1, IL-6, and other cytokines, which continue to potentiate each other's effects and further promote inflammation (66).

Similarly, hCG up-regulates leptin and leptin up-regulates hCG. Due to the vastly different peaks of these two hormones in pregnancy, it is unlikely that hCG can have an effect on leptin in late pregnancy. On the other hand, leptin levels are comparatively low at the time of the hCG peak in early pregnancy, so a stimulation at this point also seems

unlikely. However, it is possible that at certain times during pregnancy, these two hormones stimulate each other, but this probably does not occur simultaneously.

Finally, leptin acts directly at the maternal-fetal interface with TNF-α to increase the expression of placental endothelial lipase and placental phospholipase, thereby aiding the transport of fatty acids and cholesterol across the placenta (69).

iv. Pathologies [see Table 6]

As has already been mentioned, leptin is elevated in pathologies associated with chronic inflammation, such as preeclampsia and diabetes mellitus (25,30,31,33,40, 51,63,66,68,70,71,80,83,84). In preeclampsia, elevated leptin levels have been observed prior to the onset of all other symptoms (71,82,85,86). This could make leptin a useful screening tool if levels were measured at different times throughout the pregnancy. There have been some reports of unchanged or even decreased leptin levels associated with preeclampsia, but the majority of studies have found that levels significantly increase (71). The same is true for leptin concentrations in gestational diabetes mellitus. In GDM, different studies show increased, unchanged, or decreased leptin levels (12,25,29,70,71). However, most authors have found an increase and it has even been suggested that high leptin levels in early gestation predict the risk for developing GDM later on (76,80). One explanation for the various observations on leptin with GDM has been postulated by Lappas et al., who found increased levels of adipose tissue leptin and decreased placental leptin in GDM, with total leptin being increased (33,80). Other conditions associated with increased leptin concentrations are pregnancy-induced hypertension, hydatidiform mole, choriocarcinoma, and obesity (25,36,66,70,72, 83,84).

According to Hauguel-de Mouzon, there is no condition associated with a down-regulation of placental leptin gene expression (66). However, several authors have described decreased leptin concentrations in pregnancies with IUGR fetuses, which they saw as a consequence of impaired placental function due to insufficient perfusion (30,40,71,80,68). Other studies have found increased leptin concentrations with this condition (70,74,80). Briana et al. provide an explanation by suggesting that the pregnancies that showed increased leptin levels may have additionally been complicated by other gestational pathologies such as preeclampsia, and that maternal characteristics like BMI and smoking had not been taken into account, leading to falsely high

measurements (71). Alternatively, leptin levels may relate directly to the severity of the disorder, appearing lower in mild IUGR and higher in severe IUGR (71). One study found decreased leptin levels in pregnancies with macrosomic fetuses (29). Lastly, leptin levels may be abnormally low in a state of extreme fasting or starvation (67).

2) TNF-α

Tumor necrosis factor-α is in inflammatory cytokine which is mainly produced in monocytes, macrophages, T-cells, and neutrophils, as well as in fibroblasts and adipocytes, which is why it is also termed an adipokine (29,50). Generally speaking, TNF-α is correlated with fat mass and is increased in obesity and insulin resistant states (37). During pregnancy, TNF-α can be found in the placental syncytiotrophoblast, decidua, and amniotic fluid (37,87). In non-pregnant individuals, TNF-α production is greater in omental than subcutaneous adipose tissue, while in pregnancy placental TNF-α production exceeds that of omental and subcutaneous adipose tissue (37). Thus, the placenta is most likely responsible for the increased TNF-α concentrations that can be observed during normal human pregnancy (25).

There are two types of receptors for TNF-α, named TNFR1 and TNFR2. TNFR1 is constitutively expressed throughout many tissues, including adipocytes, liver, endothelial cells, granulocytes, and the placenta, while TNFR2 is localized to immune cells (64,87). There is also a soluble form of the TNF-α receptor (64). TNF-α does not cross the placenta (69).

i. Levels during pregnancy

TNF-α levels are closely related to the level of insulin resistance and have a negative correlation with whole body insulin sensitivity (14,37,50,72,88). By many authors, TNF-α is heralded as the best predictor of peripheral insulin resistance during pregnancy (11,14,89). Thus, TNF-α can decrease briefly in early pregnancy when insulin sensitivity is augmented (14). After 30 weeks, parallel to the development of insulin resistance, TNF-α and TNF-α receptor concentrations begin to rise and continue to do so until term [see Figure 14] (1,14,37,83). The onset of labor is associated with a further increase in TNF-α (90). After delivery, maternal TNF-α levels fall rapidly, indicating both a

significant contribution of the placenta to total TNF-α and a return of insulin sensitivity (14).

Many authors have measured TNF-α levels in healthy pregnant women during the various stages of pregnancy. In the first trimester, levels of 1.56 pg/ml have been reported and the third trimester measurements ranged from 0.9-65 pg/ml (14,25,69, 77,87,91). 94% of placental TNF-α is secreted into the maternal circulation, while the remaining 6% are secreted into the fetal circulation (14).

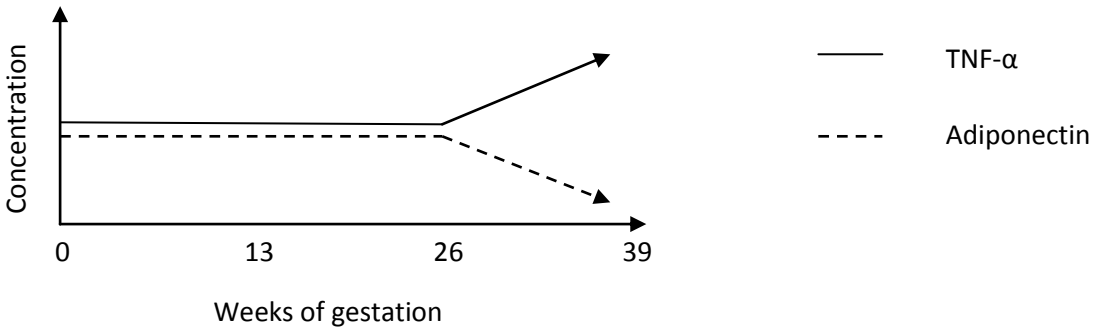

Figure 14: Time course of TNF-α and adiponectin concentrations during pregnancy (1,6)

ii. Functions [see Table 5]

Because TNF-α is not a pregnancy-specific cytokine, many of its effects during pregnancy are similar to those in non-pregnant individuals. These include immune surveillance, cell differentiation and renewal, and inflammation (87). However, TNF-α also has some additional functions during pregnancy. In the early phase of implantation and trophoblast invasion, TNF-α acts as an inhibitor of syncytialization and induces trophoblast apoptosis as a means of maintaining trophoblast turnover and renewal (87). TNF-α is also believed to cause apoptosis of vascular smooth muscle cells in spiral arteries, contributing to the remodeling of these arteries during trophoblast invasion (87).

Another very important function of TNF-α during pregnancy is the modulation of maternal metabolism. Like leptin, TNF-α traditionally causes an decrease in food intake and body weight while increasing metabolism (72). Also like leptin, the overall effect of TNF-α in combination with other hormones of pregnancy paradoxically leads to impaired glucose tolerance and the development of insulin resistance (72). However, TNF-α is much more closely correlated with insulin resistance than leptin, leading to the hypothesis that it is in fact its major cause (50,88). TNF-α contributes to skeletal muscle

insulin resistance by causing a decrease in insulin receptor tyrosine phosphorylation and GLUT-4 gene expression, leading to impaired insulin signaling and glucose disposal (1,15,29,37,50,71,72,88). In the presence of TNF-α, insulin signaling is also decreased in adipose and hepatic tissues and hepatic lipogenesis, cholesterol synthesis, and VLDL production are increased (14,15,72). Furthermore, TNF-α inhibits lipoprotein lipase in adipocytes, stimulates lipolysis, and impairs pancreatic β-cell function, resulting in hyperglycemia and hyperlipidemia (1,15,25,37,53,71,72).

iii. Regulation and interactions with other hormones

Not much is known about the regulation of placental TNF-α production. Coughlan et al. conducted a study with placental explants in which high glucose concentrations stimulated TNF-α release (37). Other stimuli for placental TNF-α production are hypoxia and infection (71). Finally, adiponectin down-regulates TNF-α (83,92,93).

On the other hand, TNF-α exerts many regulating effects on other hormones. It increases concentrations of leptin, placental endothelial lipase and phospholipase, IL-6, IL-8, and CRH (33,64,68,69,72,87,94). Resistin, adiponectin, and visfatin are down-regulated in the presence of TNF-α (1,15,29,33,50,79,85,88,95,96). Contrary results have been published regarding the effect of TNF-α on β-hCG production, with increases as well as decreases being reported (23,87).

iv. Pathologies [see Table 6]

Since TNF-α is strongly associated with insulin resistance, elevated levels can be observed in pregnancies with type 2 diabetes mellitus, gestational diabetes, and obesity (12,14,25,29,37,63,64,71,88). Due to its properties as an inflammatory cytokine, elevated TNF-α concentrations can also be observed in pregnancies complicated by preeclampsia (14,71,82,83,87). According to Haider et al., TNF-α can be used as a marker for the severity of preeclampsia, as concentrations are higher in more severe cases (87). There have been several studies which have observed higher levels of TNF-α in pregnancy-induced hypertension and placental insufficiency in combination with IUGR (71,83,87). An increase can also be seen in chorioamnionitis and preterm labor as a result of ascending bacteria (87). Finally, 40-70% of recurrent spontaneous abortions are associated with high TNF-α levels (87). In this case, elevated TNF-α can either be a consequence of amniotic

infection leading to abortion, or the abortion can be caused by an excess of TNF-α itself due to its cytotoxic effect on trophoblast cells (87).

3) Adiponectin

Adiponectin is a polypeptide hormone which is released exclusively from white adipose tissue and, during pregnancy, the placenta (29,97). It is found more abundantly in subcutaneous than in omental adipose tissue (95). Plasma adiponectin concentrations are higher than those of any other adipokine (11,24). Although concentrations can vary greatly amongst individuals, women exhibit higher adiponectin levels than men (98). Adiponectin levels are negatively correlated with intraabdominal fat mass and BMI and positively correlated with whole body insulin sensitivity, an observation which is consistent with the anti-atherogenic and insulin-sensitizing properties of this hormone (11,29,33,50,95,97,99,100). Adiponectin receptors are located in skeletal muscle, liver, pancreatic β-cells, adipose tissue, and the placenta (71,101,102).

i. Levels during pregnancy [see Figure 14]

As with many adipokines, there is some controversy as to the changes in adiponectin concentrations during pregnancy. Many authors have reported a decrease in adiponectin levels as pregnancy progressed, while others observed no change or even an increase (25,50, 84,103). Naruse et al. saw a 30% decrease in adiponectin concentrations during pregnancy, which they attributed to hemodilution (83). Thus, adiponectin production during pregnancy may be increased while plasma adiponectin concentrations remain stable or decrease. To summarize the results of many studies, non-pregnant women showed adiponectin levels between 0.4 ng/ml to 17 μg/ml (15,103,104). First trimester levels have been reported at 5.2-12.3 μg/ml, second trimester levels at 5.1-11.8 μg/ml, and third trimester levels at 4.7-14.7 μg/ml (11,25,33,74,76,77,83-86, 92,96,97,99,100, 103,105-107).

ii. Functions [see Table 5]

As has been mentioned above, adiponectin has anti-atherogenic, anti-inflammatory, and insulin-sensitizing properties (29,71,74,83,85,86,95,97,99,103). Adiponectin improves insulin signaling by increasing insulin-induced tyrosine

phosphorylation of the insulin receptor in skeletal muscle and other insulin-sensitive tissues while decreasing hepatic gluconeogenesis (25,29,33,50,71,85,88,95,101,108). In skeletal muscle and liver, adiponectin increases the oxidation of free fatty acids, leading to decreased triglyceride levels, further benefiting insulin sensitivity (15,92,97,98,105). Additionally, adiponectin improves hepatic lipoprotein metabolism in response to insulin and induces lipoprotein lipase gene expression (95,98,101). There is some evidence that adiponectin may improve β-cell function during pregnancy (76). Overall, adiponectin combats the effects of TNF-α and other diabetogenic hormones to reverse insulin resistance by decreasing plasma free fatty acids, triglycerides, and glucose, even reducing body weight (25,29,93,101,105).

iii. Regulation and interactions with other hormones

Adiponectin is regulated by feeding and fasting, decreasing as a response to insulin secretion (95,99). Adiponectin concentrations are down-regulated in the face of increased fat mass and obesity (11). Furthermore, this hormone is down-regulated by placental and pituitary growth hormone, prolactin, IL-6, glucocorticoids, and catecholamines (1,11,95,101).

A complicated relationship exists between adiponectin and TNF-α. These two hormones are considered antagonists and an inverse correlation exists between them (96,102). TNF-α is able to down-regulate adiponectin; however, adiponectin can also inhibit TNF-α signaling and down-regulate its release from macrophages (1,15,25,29,33, 50,83,92,93,95,96,100). It seems that these two hormones do not coexist well, but it is unclear which is the more dominant player. Adiponectin is able to reverse insulin resistance to a certain degree in the first and second trimester, but as pregnancy progresses and the hormonal cocktail leading to insulin resistance grows stronger TNF-α emerges as the leading hormone.

iv. Pathologies [see Table 6]

Due to its insulin-sensitizing effects it could be speculated that adiponectin would be up-regulated in insulin-resistant states such as diabetes mellitus or gestational diabetes. However, observations by many different authors have shown that these pathologies show decreased adiponectin levels (6,12,15,29,50,63,71,76,84,88,92,95,99,

102,105). Because many women who develop gestational diabetes during pregnancy have a predisposition for this condition, it is possible that the protective mechanism of action of adiponectin is inherently weak. Thus, impaired insulin sensitivity during pregnancy may be a result of inadequate adiponectin production prior to conception. In fact, adiponectin concentrations may be a useful diagnostic tool for predicting the risk for gestational diabetes early on. Several authors have found that adiponectin concentrations are low months before gestational diabetes manifests itself (71,76,100). Williams et al. go so far as to claim that low adiponectin levels are a dose-dependent risk factor for gestational diabetes, where lower adiponectin levels indicate a higher risk (100). In accordance with these results, pregnant women with macrosomic fetuses had lower adiponectin levels than controls in one study (29).

In preeclamptic pregnancies, adiponectin concentrations can be increased, decreased, or unchanged (51,71,75,83-85,86,103,106). The majority of authors have reported elevated adiponectin concentrations with this condition, possibly as a compensatory mechanism to combat the inflammation (97). In pregnancies with IUGR fetuses, maternal adiponectin concentrations were decreased in two studies, but more research needs to be done in the field (71,74). In contradiction to this, one author measured higher adiponectin levels in pregnancies with pathological uterine perfusion (85).

4) Visfatin

Previously known as pre-B cell colony enhancing factor (PBEF), this adipokine was first identified as the product of lymphocytes (90,94). Later, it was also found in skeletal muscle, bone marrow, hepatic tissue, and visceral fat, hence the name change (79,90,109,110). Visfatin levels show a negative correlation with visceral, but not subcutaneous fat, and omental secretion has been observed to be elevated during pregnancy (79,88,94). The placental syncytiotrophoblast, chorionic cytotrophoblast, amniotic epithelium, mesenchymal cells, parietal decidua, and fetal capillary endothelium have been identified as additional sites of visfatin production (71,79,94,109,110). Visfatin binds to the insulin receptor in a non-competitive way, exerting insulin-mimetic effects (75,94,110).

i. Levels during pregnancy

Because visfatin expression is up-regulated to up to seven times the normal level in omental adipose tissue during pregnancy, it is not clear how large the contribution of the placenta is to maternal visfatin levels (94). Some authors have reported no increase of visfatin concentrations during pregnancy, while others have observed a rise throughout gestation and other groups measured decreasing visfatin concentrations as pregnancy progressed (71,75,90,94,110). As with many other placental hormones, there seems to be great individual variability. In early to mid-gestation, concentrations have been reported from 26-67.5 ng/ml while at term the measurements range from 6.2-695.9 ng/ml (75,79,84,85,91,94,109). Morgan et al. state that in late pregnancy visfatin levels are elevated by 20-50 times compared to the luteal phase of the menstrual cycle (94). A further elevation of visfatin concentrations can be observed with the onset of labor, possibly in response to subclinical infection (90). Briana et al. found comparable visfatin concentrations in maternal and fetal blood, suggesting a passive transplacental transfer of this adipokine (109).

ii. Functions [see Table 5]

The majority of authors agree that visfatin acts as an insulin-mimetic of equal potency as insulin (84,85,88,94,109,110). Because it does not utilize the same binding site on the insulin receptor, visfatin acts in concert with insulin to lower blood glucose, stimulate muscle and adipocyte glucose transport, inhibit hepatic gluconeogenesis, and promote adipogenesis (75,79,94,110). There is some evidence that visfatin can improve insulin sensitivity as chronic exposure lowers insulin levels (79). Visfatin gene and protein expression increase with decreasing β-cell function, suggesting a compensatory mechanism to mitigate insulin resistance (84). A regulatory role of visfatin on HDL-cholesterol has also been suggested (84). In recent years, several authors have suggested that visfatin may not act as a hormone in the classical sense, but rather operate in a paracrine or autocrine manner without any systemic effects (94). This hypothesis resulted from the observation that visfatin concentrations are greatly increased locally in omental adipose tissue during pregnancy, while only slightly increasing in serum (94).

Visfatin also has pro-inflammatory and immunomodulating properties and acts as a local growth regulator to accommodate membrane distension due to amniotic infection and thereby protect against membrane tissue apoptosis (84,90,91).

iii. Regulation and interactions with other hormones

Visfatin secretion is up-regulated by glucocorticoids (88,110). There are conflicting results as to the effect of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 on visfatin secretion, with positive and negative effects being reported (71,79,85,88,90,110). One might expect visfatin, a pro-inflammatory cytokine, to be increased in the presence of other pro-inflammatory cytokines. On the other hand, visfatin may be secreted to counteract the impaired insulin signaling caused by an inflammatory milieu. More research needs to be done on this topic to elucidate how visfatin concentrations change in the face of inflammation. Briana et al. state that only placental and not adipose tissue visfatin production is elevated by pro-inflammatory cytokines, while Fasshauer et al. found decreased visfatin secretion in response to inflammation only in adipose tissue (71,85). Perhaps the contradictory results were achieved due to differences in study design and in the type of tissue that was investigated.

Visfatin levels are decreased in the presence of pituitary growth hormone, possibly due to the negative effect of GH on insulin sensitivity (88,110). Unlike with insulin, visfatin secretion is not regulated by fasting or feeding (110). Rather, it is constitutively expressed in pregnant and non-pregnant individuals alike (90,110). Mechanical stimuli such as membrane distension may trigger visfatin secretion (90). There may also be a role for glucose and insulin in the regulation of visfatin, but this is not yet proven (84).

iv. Pathologies [see Table 6]

Most of the pathologies associated with changes in visfatin concentrations are related to its insulin-mimetic effects. There have been many investigations into visfatin levels in diabetes mellitus, gestational diabetes, and obesity with contradictory results. Visfatin levels have been reported increased, decreased, and unchanged in each of these pathologies (71,75,79,84,85,91,94,109). Visfatin has also been suggested as a predictive

factor for gestational diabetes (84,94). Mastorakos et al. claim that first trimester visfatin levels predict insulin sensitivity in the second trimester (84).

Preeclampsia presents another contradiction. Elevated as well as decreased visfatin levels have been measured in preeclamptic women and several studies found increased visfatin concentrations in pathological placental perfusion and IUGR (71,75,77,85). As has been mentioned earlier, visfatin secretion is increased in chorioamnionitis and imminent birth (90,110).

	Hyperphagia	Fat storage	Insulin sensitivity	Insulin production	Plasma lipids
Leptin	↑	↑ in early, ↓ in late gestation	?	?	
TNF-α			↓	↓	↑
Adiponectin			↑	↑?	↓
Visfatin			↑	↓	
Resistin			↓		

Table 5: Effects of placenta-derived adipokines on the maternal metabolism during pregnancy (4,45,50,51,66,71-73,78,79,88). A question mark represents unclear or conflicting data while a blank space indicates a lack of data on the topic.

5) Resistin

This relatively novel cytokine is produced mainly by monocytes and macrophages and to a much lesser extent by adipose tissue, skeletal muscle, and pancreatic islet cells (63,71). In non-pregnant individuals, resistin synthesis is higher in abdominal than thigh fat (89). During pregnancy, resistin concentrations are elevated and there is evidence that the placenta is a source of resistin (12). The main production site of placental resistin is the syncytiotrophoblast, but resistin can also be found in the extravillous cytotrophoblast, decidua, and amnion (12,52,63). During pregnancy, resistin gene and protein expression is higher in the placenta than in adipose tissue (52). Although associated with the development of insulin resistance, resistin concentrations are independent of BMI during gestation (12).

i. Levels during pregnancy

Resistin levels are elevated during pregnancy (75,103). While most authors claim that resistin concentrations rise continually until term, others state that while concentrations are elevated in early gestation, they then decline progressively until term (12,51,52,71,75,89,103). Yet another author observed elevated resistin concentrations in the first and third, but not the second trimester (63). The change in resistin concentrations is most likely due to placental production, as no change is observed in adipose tissue resistin synthesis during gestation (70,89).

Resistin measurements in non-pregnant women show concentrations of 6.3-18.1 ng/ml (52,103). In early pregnancy, concentrations were measured between 5.0 and 17.9 ng/ml and late pregnancy values were between 2 and 68.2 ng/ml (33,51,103,106). The wide spectrum indicates that resistin concentrations probably vary greatly within the population like those of most other adipokines.

ii. Functions [see Table 5]

Resistin has been associated with the development of insulin resistance, but less research is available on this adipokine than on many other hormones of pregnancy (12). It has been observed that insulin sensitivity declines as a response to elevated resistin concentrations (51,52,71,103). Experiments with mice have shown that hepatic insulin resistance develops in the presence of high concentrations of resistin (63,71). In this respect, resistin works like many other diabetogenic hormones, impairing glucose uptake and thereby increasing plasma glucose and decreasing insulin sensitivity (51,70,88). *In vitro* experiments have shown a decrease in GLUT-4 activity, indicating a possible involvement of resistin in skeletal muscle insulin resistance (63,71). However, this observation calls for further research. At this time, resistin is believed to induce only hepatic, but not peripheral insulin resistance (33,63).

iii. Regulation and interactions with other hormones

Because resistin has not been extensively studied, not much is known about its regulation. Estrogens, progesterone, TNF-α, corticosteroids, and ghrelin lead to decreased resistin secretion (33,63). There seems to be a regulatory effect of insulin on resistin

secretion, but whether it is a positive or negative one is unclear (33,71). It is not known if and how resistin is involved in the regulation of other hormones.

iv. Pathologies [see Table 6]

Resistin levels can be expected to be elevated in insulin resistant states, such as obesity, diabetes mellitus, or gestational diabetes and this has been observed by some authors (63). However, other studies have found a decrease or no change in resistin levels in women with GDM (71). The same is true for preeclampsia, where increased, decreased, and unchanged resistin levels have been reported (71,75,106). The majority of authors believe resistin to be elevated in pregnancies complicated by preeclampsia as a consequence of impaired placental hormone production (51,103). Again, more research is required to make definitive statements on this subject.

6) Apelin

Apelin is a peptide hormone which is described as the endogenous ligand for the G-protein coupled APJ receptor (71,104,111). Both apelin and its receptor are widely distributed in the human body, occurring in lung, kidney, white and brown adipose tissue, hypothalamus, GI-tract, the pregnant and lactating breast, vascular endothelial cells, and the placenta (71,104,107,111). During pregnancy, the placenta is said to produce ten times more apelin than adipose tissue (104). Like resistin, it is a relatively novel adipokine and has not been studied extensively.

i. Levels during pregnancy

Preliminary observations on the changes in apelin gene and protein expression during pregnancy are ambiguous. Several authors have reported a decrease of plasma apelin concentrations from the first to the third trimester, while others observed an increase in adipose tissue and placental apelin in the pregnant state (71,104,107). Malamitsi-Puchner et al. reported that apelin concentrations decline rapidly after parturition in both maternal and fetal plasma, pointing to a significant placental production of this adipokine during pregnancy (112). The same authors also observed higher fetal than maternal apelin levels during pregnancy, suggesting a mode of passive transplacental transfer from mother to fetus (112). Kourtis et al. measured an apelin

concentration of 4.45 µg/ml in women during mid-pregnancy and a concentration of 5.0 µg/ml in non-pregnant control women (104).

ii. Functions

The functions of apelin cover a wide spectrum. It has a regulatory role on the immune system, cardiovascular system, angiogenesis, brain signaling of hunger and thirst, fat storage, and glucose homeostasis (71,107,111). During pregnancy, apelin is assumed to have a role in the regulation of placenta formation and fetal development, largely through the promotion of angiogenesis (112). It is also a local vasoconstrictor (107). In a study with mice, apelin increased glucose utilization and showed a negative correlation with oxidized LDL-cholesterol, perhaps indicating a positive effect on insulin sensitivity and atherosclerosis (104). However, the same study showed no correlation between apelin and markers of insulin sensitivity (104).

iii. Regulation and interactions with other hormones

Based on the research available at this time, the strongest factors regulating apelin release are fasting and feeding (71,104,111,112). Apelin is strongly up-regulated by insulin and therefore by feeding, while fasting strongly decreases apelin secretion (71,104,111,112). There is a negative correlation between apelin and adiponectin levels, but the significance of this remains to be explained (104). Finally, there may be a regulatory role for TNF-α on apelin secretion, but once again more research is required to make any concise statements (71).

iv. Pathologies [see Table 6]

*S*ince there are no long-term studies with apelin, it is difficult to say how it reflects on pregnancy-related pathologies. In a few studies, apelin levels were elevated in pregnant women who were obese or had diabetes (104,111). However, this elevation could only be observed if the women were hyperinsulinemic (111). Pregnancy-induced hypertension and preeclampsia may show elevated or decreased apelin levels (71,107). Due to its effect as a vasoconstrictor, changes in apelin concentrations may play a part in the development of preeclampsia (107). This is definitely an interesting point which should be the focus of more research in the future.

7) Chemerin

This relatively new adipokine was first described in 2003 as the ligand for the G-protein-coupled chemokine-like-receptor 1 and joined the group of adipokines in 2007 (76,77,113). Originally, chemerin was of interest due to its pro-inflammatory properties, but in recent years it has been investigated regarding its role as a regulator of glucose and lipid metabolism (113). So far, adipose tissue, the liver, and the placenta have been identified as sources of chemerin production (77). During pregnancy, the placenta produces more chemerin than omental or subcutaneous adipose tissue (113).

i. Levels during pregnancy

Because most of the research concerning chemerin is being done in the fields of obesity and diabetes mellitus, there is a relative paucity of papers regarding chemerin in pregnancy. However, there have been a few publications which mention chemerin levels in the third trimester ranging from 124.2-217.6 µg/l (76,77,113). These authors agree that chemerin levels are increased during pregnancy compared to non-pregnant control women (76,76,113). Pfau et al. state that chemerin concentrations are higher in the third than in the first trimester (76).

ii. Functions

There have been contradictory publications concerning the properties of chemerin as an adipokine. While Pfau et al. claim that chemerin has insulin-sensitizing properties and increases glucose uptake in adipocytes, other authors state the exact opposite, namely that chemerin impairs glucose tolerance, lowers serum insulin, stimulates lipolysis, and reduces insulin resistance (76,77,113). Since most of these results come from studies with mice, it is unclear how the situation is in humans. All the above authors agree that chemerin has an important role in the differentiation of adipocytes and the expression of adipocyte genes involved in glucose and lipid homeostasis (76,77,113).

iii. Regulation and interactions with other hormones

Chemerin secretion is up-regulated by IL-1β (113). There exists a significant positive correlation between chemerin and leptin, plasma triglycerides, and fasting insulin (77,113). However, it is not known whether these factors influence chemerin secretion.

iv. Pathologies [see Table 6]

Some authors have suggested that chemerin production is augmented as body mass index (BMI) increases, while others found no correlation (113). One publication shows that chemerin concentrations are unchanged in the plasma of obese pregnant women, but increased in the cord blood of the fetuses of the same women (113). Pfau et al. investigated chemerin concentrations in women with gestational diabetes mellitus and found no significant change (76). However, the authors attributed this to the fact that all women were matched to controls for fasting insulin and hypothesize that chemerin concentrations are higher in women with hyperinsulinemia. The authors conjecture that this elevation may either be a compensatory mechanism utilizing the insulin-sensitizing properties of chemerin to counteract insulin resistance, or a manifestation of chemerin resistance requiring more chemerin to maintain its physiological effects (76).

Finally, one study showed elevated chemerin concentrations in preeclamptic women in the third trimester and six months after delivery, compared to healthy control women (113).

	GDM	PE	IUGR
Leptin	↑	↑	?
TNF-α	↑	↑	↑
Adiponectin	↓	↑?	↓?
Visfatin	?	?	
Resistin	?	?	
Apelin	↑?		
Chemerin	↑?	↑?	

Table 6: Changes in adipokine levels in pregnancy-related pathologies (6,71,85,113). A question mark represents unclear or conflicting data while a blank space indicates a lack of data on the topic.

D. Placental Hormones in the Fetus

Although most placental hormones have an effect on fetal growth, not all are detectable in the fetal circulation. Aside from one, all publications on placental growth hormone have been unable to detect this hormone in the fetal circulation, meaning it does not cross the placenta (1,6,9,44,47,53,54,56,58,114,). Other placental hormones that do not cross the placenta are progesterone, hPL, CRH, leptin, and TNF-α; however, these hormones are directly secreted into the fetal circulation by the placenta and can therefore be detected in umbilical cord blood (6,9,14,33,38,43,66,69,115). For leptin and TNF-α, it has been determined that the fraction of hormone secreted into the fetal circulation is quite small in comparison to the total amount produced by the placenta, while it is not known in what amounts progesterone, hPL, and CRH enter the fetus (14,66,69). Visfatin and apelin are able to pass the placenta passively, leading to fetal concentrations equal to or higher than those in the mother (109,112).

As the fetus grows and its organs mature, it begins to produce some of these hormones itself, which complicates the matter as it is difficult to differentiate between hormones of placental and fetal origin in some cases. There is evidence for fetal production of leptin, resistin, adiponectin, and possibly ghrelin, all of which can be detected in cord blood (16,66,103).

Some placental hormones have been investigated as to their effects in the fetus. Human CG has a role in fetal development through its regulation of the 11β-hydroxysteroid-dehydrogenase type 2, a hormone which inactivates cortisol by converting it to cortisone (42). By up-regulating 11β-HSD 2, hCG creates a "glucocorticoid barrier", protecting the fetus from high levels of cortisol, which is of utmost importance in early pregnancy (42). Human CG also stimulates dehydroepiandrosterone synthesis in the fetal adrenal glands (42).

Human PL also has a function in fetal development, promoting the synthesis of insulin-like growth factors, insulin, adrenocortical hormones, and surfactant, regulating fetal metabolism, and possibly promoting fetal angiogenesis (9,43). Furthermore, hPL levels correlate positively with fetal weight in the second and third trimester (38,60). Like hPL, CRH stimulates the fetal adrenal glands, but also the pituitary gland and the

production of ACTH (38,60). Placental growth hormone cannot be detected in the fetal circulation, yet a correlation exists with birth weight, suggesting an indirect effect on fetal growth (38,60).

Although only 2-5% of placental leptin is secreted into the fetal circulation, it is one of the most abundantly found placental hormones in the fetus (66). The abundance of leptin receptors in fetal tissues such as cartilage, lung, bone, kidney, testes, and hypothalamus, suggests an important role of this adipokine in fetal development and growth (66,70). Leptin is involved in fetal vasculogenesis, erythropoiesis, lymphopoiesis, and the regulation of fetal fat stores (66,70,116). Because fetal adipose tissue also produces leptin, its concentration is thought to reflect the metabolic state of the fetus and can be elevated in gestational diabetes or diabetes mellitus in response to hyperinsulinemia (116). Likewise, IUGR fetuses have lower leptin levels because there is less adipose tissue to produce it (66). Apelin receptors are present in the fetus, suggesting a role for this adipokine in the promotion of fetal growth and possibly on angiogenesis (112).

Hormone	Transfer into the fetal circulation	Functions in the fetus	Fetal production
Progesterone	Direct secretion by the placenta		Yes
hCG		Regulation of 11β-HSD, steroidogenesis	
hPL	Direct secretion by the placenta	Synthesis of IGF, insulin, adrenocortical hormones, surfactant Regulation of metabolism, angiogenesis	
PGH	No	Regulation of fetal growth?	No
CRH	Direct secretion by the placenta	Stimulation of adrenal and pituitary glands	
Ghrelin			Yes?
Leptin	Direct secretion by the placenta	Vasculogenesis, erythropoiesis, lymphopoiesis, regulation of fat stores	Yes
TNF-α	Direct secretion by the placenta		
Adiponectin			Yes
Visfatin	Diffusion		
Resistin			Yes
Apelin	Diffusion	Promotion of fetal growth, possibly angiogenesis	

Table 7: Placental hormones and their functions in the fetus (6,9,14,16,33, 38,42,43,60,66,70,103,109,112). A question mark represents unclear or conflicting data while a blank space indicates a lack of data on the topic.

IV. Discussion

The purpose of this paper is to review the hormones that are produced by the placenta during pregnancy which have an effect on the maternal metabolism. While many reviews already exist regarding this topic, most of these focus on one or several placental hormones and do not offer a comprehensive overview of all relevant hormones and cytokines. Also, many of these reviews focus on one portion of maternal metabolism, such as glucose or lipid homeostasis, while others address more areas rather superficially. The goal of this paper is to provide a global overview of the metabolic changes that occur in pregnancy and the actions and interactions of the hormones responsible for these changes. Although the scope of this paper is quite wide, each hormone was thoroughly researched and analyzed as to its history, functions, physiological concentrations, regulation, influence on other hormones, and role in common pathologies of pregnancy. The most important metabolic changes of pregnancy, such as hyperphagia, insulin resistance, leptin resistance, facilitated anabolism, and accelerated starvation were also discussed.

It has long been known that the placenta secretes certain factors which cause metabolic changes in the mother during pregnancy. Initially, the steroid hormones estrogen and progesterone were the focus of research, followed by placental GH and hPL. The discovery of leptin in 1994 brought attention to adipose tissue as an endocrine organ with potent effects on glucose and lipid metabolism. When it was discovered that many other tissues including the placenta produce leptin, this led to an explosion of studies on leptin during pregnancy. Since then, many other adipokines have been discovered, including TNF-α, adiponectin, visfatin, resistin, apelin, and chemerin, all of which are secreted by the placenta. Thus, research on the effects of adipokines on maternal metabolism in pregnancy has been booming in recent years. While it was previously thought that the steroid hormones, placental GH, and the lactogens were the main predictors of weight gain and insulin resistance during pregnancy, these hormones are now assigned a minor role by many authors, with the adipokines taking the lead. While leptin, TNF-α, and adiponectin are well researched, the role of other adipokines is still unclear.

In this paper, the "old" placental hormones estrogen, progesterone, hCG, hPL, placental growth hormone, CRH, and PTH-rP have been revisited and the current opinions regarding their functions and importance have been stated. Furthermore, the "new" placental hormones, ghrelin, leptin, TNF-α, adiponectin, visfatin, resistin, apelin, and chemerin have been discussed. The time course graphs of the concentrations of these hormones allow for an interpretation of their relative significance in the different phases of gestation. The first trimester is dominated by hCG, estrogen, progesterone, and leptin, while concentrations of hPL and PGH are relatively low. The result of this hormonal mix is hyperphagia and weight gain, but not yet insulin resistance. Because of the early peak and subsequent low concentrations of hCG, it is likely not a major factor in this process, albeit having a key role in the implantation of the blastocyst and the continuation of estrogen and progesterone secretion in the first trimester. In the second trimester, concentrations of estrogen, progesterone, leptin, hPL, and PGH continue to increase and are joined by ghrelin and CRH. While the anabolic quality of the first trimester is maintained, insulin sensitivity begins to decline. The early third trimester is characterized by very high levels of estrogen, progesterone, leptin, hPL, PGH, and TNF-α, while adiponectin concentrations decrease. Here, insulin resistance is very pronounced and the maternal metabolism shifts to a catabolic state. Shortly before term, leptin and hPL decrease slightly, while CRH increases rapidly, ushering in parturition. It can be inferred that the steroid hormones and leptin play a major role in the changes occurring in the early first trimester and that these changes become more pronounced as the concentrations of these hormones rise and are joined by increasing concentrations of hPL and PGH. It is likely that these five hormones are responsible for the development of insulin resistance in mid-pregnancy. CRH is present in low concentrations throughout gestation, increasing only in the last weeks before parturition. Though this hormone has a role in the induction of labor, its metabolic effects are likely not very significant. Although it has been suggested by many authors that TNF-α is a major predictor of insulin resistance in pregnancy, this statement is not congruent with the fact that TNF-α concentrations begin to rise quite late in gestation when insulin resistance is already apparent. It can, however, be assumed that TNF-α adds to and perhaps exacerbates insulin resistance in the third trimester.

Since it is not clear how the concentrations of visfatin, apelin, and chemerin change throughout gestation, it is difficult to hypothesize when and how strongly they

affect the maternal metabolism. While it is likely that these hormones affect insulin sensitivity, glucose metabolism, and lipid metabolism, the lack of a definite pattern of secretion suggests that this effect is probably not very pronounced.

The subject of this paper is of importance because an understanding of the physiological changes of pregnancy and their causes allows for improved medical care of pregnant women. Not only is it possible to give advice as to eating behavior, weight gain, and fat mass to ensure an uncomplicated pregnancy, it may also be possible to detect and manage pregnancy-related pathologies. Certain hormones or adipokines could be used as screening parameters, with measurements in early, mid-, and late gestation. A baseline value measured at the beginning of a pregnancy could serve as a reference point for future measurements as well as a risk assessment for developing GDM or preeclampsia. Even more ideal would be measurements taken before conception, but this would be very difficult to achieve. Possibly, adipokines with insulin-sensitizing properties such as adiponectin and visfatin could be used to treat gestational diabetes.

This paper has some limitations. Although the topic was thoroughly researched, it is impossible to include all available literature. Research into the placenta as an endocrine organ has been conducted for decades, resulting in many publications that are no longer pertinent. Sources that were published before the year 2000 were viewed critically as to their merit and relevance and it was attempted to include more recent literature to maintain the relevance of this paper. Another issue that arose during the research process was the fact that many authors quote each other, resulting in a multitude of publications ultimately stemming from one original study. As the information is passed along, it may be misinterpreted. Also, if many authors make the same claim it is tempting to assume that this claim is true, when it may have only been one author's original claim that was taken up in subsequent publications. Therefore, the original papers were identified and considered wherever possible.

There are some discrepancies in the results of studies conducted by different research teams. This is particularly evident in the regulation of the hormones studied and their concentrations in gestational diabetes, preeclampsia, and IUGR. There are many reasons for these contradictory results. Firstly, not all studies utilized the same material. Some studies investigated hormone concentrations in the serum of pregnant women at different times throughout the pregnancy, while other studies used placental explants

from the first, second, or third trimester, or cultured trophoblast cells. It is very difficult to compare these studies since the design is so different, although a general trend can be observed. It is not ethically feasible to subject pregnant women to invasive procedures or experiments, therefore it is necessary to make do with biopsies or cell lines to gain information, but these experiments occur in a tightly controlled setting with one or two variables, very unlike the complex hormonal interactions taking place in the maternal circulation during gestation. It is therefore questionable whether these studies give a realistic indication of what actually happens in the pregnant woman.

A second factor which contributes to the contradictory results is the nature of pregnancy and the development of pregnancy-related pathologies. Because pregnancy is a continuous, ever-changing, highly individual process, different results may be obtained at any given point. Obviously, studies using placentas or plasma from the first trimester cannot be compared to studies of the third trimester. Similarly, studies in women with a certain pregnancy-related pathology can yield highly dissimilar results because each woman is in a different stage of the disease. Thus, adiponectin may be increased in the early stage of preeclampsia as an attempt to alleviate the inflammation, and decreased in a later stage as a result of placental insufficiency. The same is true for GDM and IUGR.

Thirdly, not all studies on pregnant women had identical criteria for including or excluding subjects. Studies with very strict criteria can't be compared to studies which were more lax. Some of the results may have been influenced by factors such as smoking, BMI, or an additional pathology that was not accounted for.

Finally, many placental hormones exhibit a great individual variability in their concentrations. This makes it difficult to determine whether a woman has an elevated, decreased, or normal level of a certain hormone. Adipokines present some difficulty since they are not secreted only by the placenta, but also by adipose tissue and other organs. As there is usually not a difference in structure or function, it is not always possible to distinguish between a placental or other origin of an adipokine. The question therefore arises how much the placenta really contributes to the circulating hormone levels.

In the future, more research needs to be be done in the area of adipokines to determine physiological concentrations, the contribution of the placenta, and the relationship between increased or decreased concentrations and pathologies such as GMD, preeclampsia, and IUGR. Furthermore, an attempt should be made to characterize

adipokines that show a sufficient change in concentration during pregnancy and a significant association with pathologies of pregnancy to be of use as a diagnostic or screening parameter. Here, it would be beneficial to focus on areas that will be of practical use and may one day lead to the use of adipokines as a diagnostic tool or even as a treatment. Furthermore, researchers should strive to better standardize their research protocol, using similar criteria for inclusion and exclusion and eliminating confounding factors such as BMI and smoking. In studies on pregnant women, certain dates within a pregnancy could be identified and measurements could be taken only on these dates to achieve more comparable results.

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Appendix

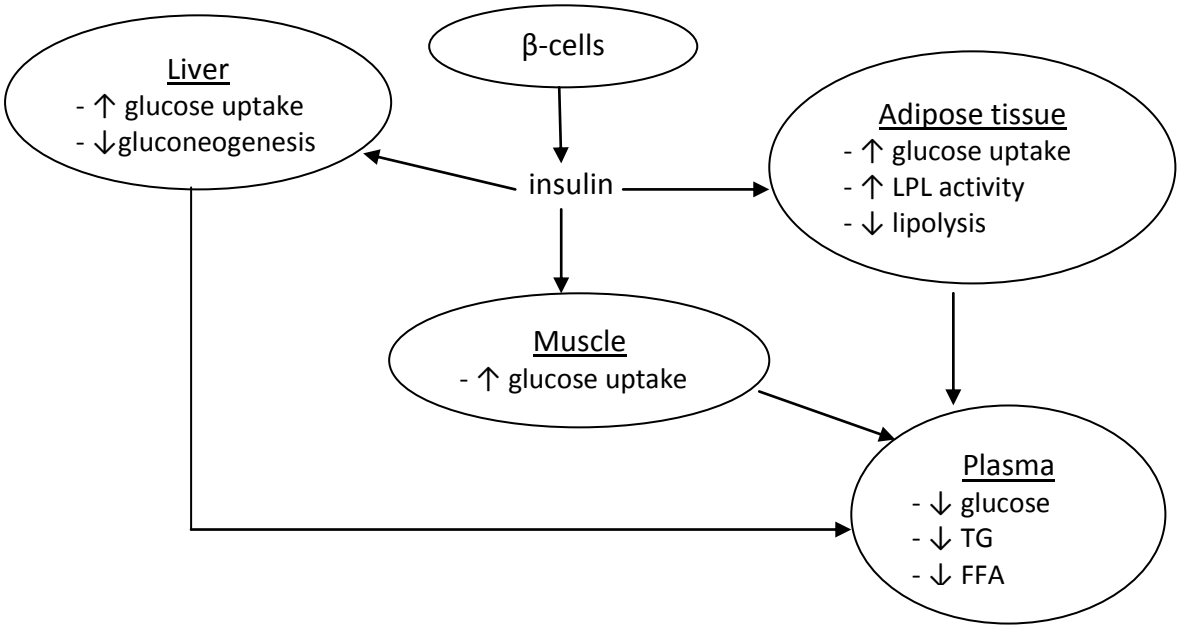

Figure 2: Physiological response of muscle, liver, and adipose tissue to insulin after feeding (15). LPL = lipoprotein lipase, TG = triglycerides, FFA = free fatty acids

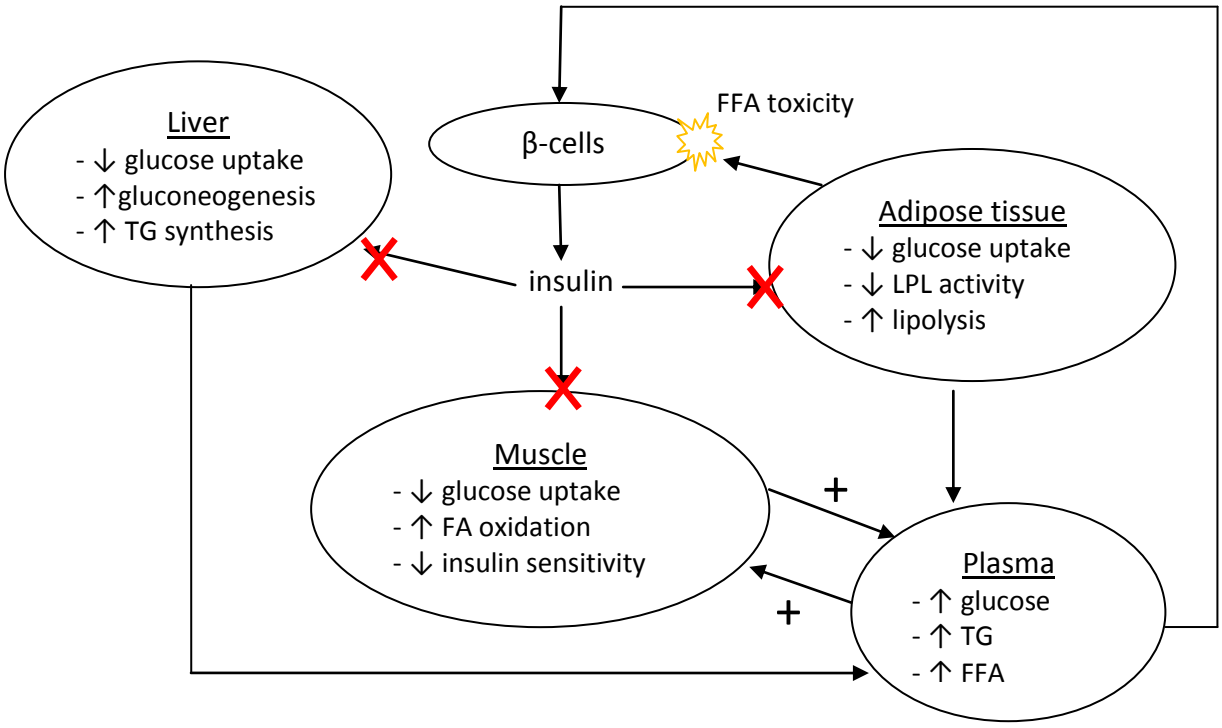

Figure 2: Effects of insulin resistance on maternal metabolism during the second half of pregnancy (15). LPL = lipoprotein lipase, TG = triglycerides, FFA = free fatty acids

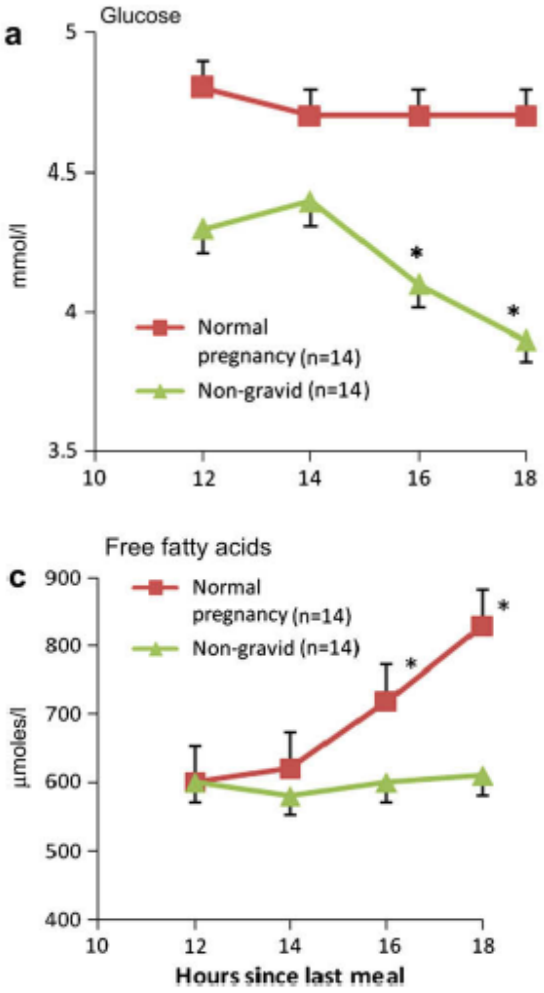

Figure 3: Changes in plasma concentrations of glucose and free fatty acids in non-gravid (n=14, triangles) and healthy pregnant (n=14, squares) women between 12 h fasting and 18 h fasting during the third trimester. Adapted from Hadden and McLaughlin (3)

	First trimester	Second trimester	Third trimester
Food intake	↑	↑↑	↑↑
Fat mass	↑	↑↑	↑↑
Insulin production	↑	↑↑	↑↑↑
Glucose tolerance	↔ or ↑	↓	↓↓
Insulin sensitivity	↔ or ↑	↓	↓↓
Free fatty acids	↓ then ↑	↑↑	↑↑↑
Triglycerides	↓ then ↑	↑↑	↑↑↑
Cholesterol	↔	↑	↑↑
Amino acids	↓	↓	↓

Table 1: Maternal metabolic changes during early, mid-, and late pregnancy (1,3,7,8,18)

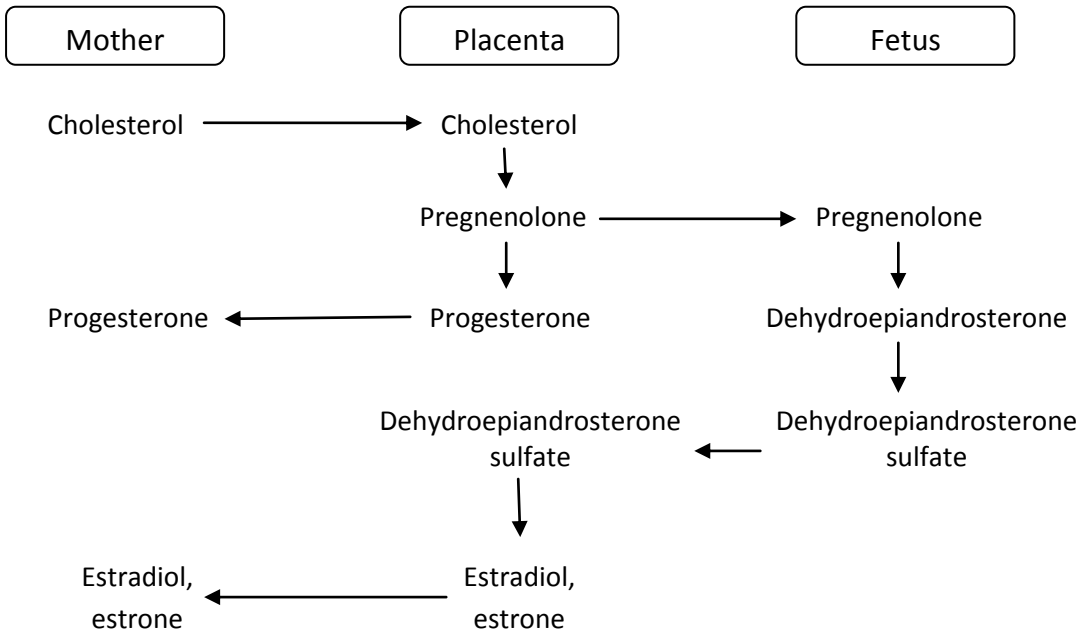

Figure 4: Synthesis of estradiol and estrone by the fetoplacental unit, placental progesterone synthesis (8,19,21)

	GDM	PE	IUGR
Estrogen	?	↓	↓
Progesterone	↑		
hPL	↑	↓	↓
Placental GH	?	↑?	↓
CRH			↑
Ghrelin	↓		↑
Leptin	↑	↑	?
TNF-α	↑	↑	↑
Adiponectin	↓	↑?	↓?
Visfatin	?	?	
Resistin	?	?	
Apelin	↑?		
Chemerin	↑?	↑?	

Compilation of tables 2,4,6: Changes in placental hormone levels in pregnancy-related pathologies (1,6,9,19,34,37,38,58,60,62,71,85,113). A question mark represents unclear or conflicting data while a blank space indicates a lack of data on the topic.

	Hyperphagia	Fat storage	Insulin sensitivity	Insulin production	Plasma lipids
Estrogen		?	↑ in early, ↓ in late gestation		↑
Progesterone	↑	↑	↓		↑
hPL	↑	↑	↓	↑	↑
PGH		↑ in early, ↓ in late gestation	↓		↑
Leptin	↑	↑ in early, ↓ in late gestation	?	?	
TNF-α			↓	↓	↑
Adiponectin			↑	↑?	↓
Visfatin			↑	↓	
Resistin			↓		

Compilation of tables 3 and 5: Effects of placental hormones on maternal metabolism during pregnancy (1,4,6,9,13,26,45,50,51,56,66,71-73,79,88). A question mark represents unclear or conflicting data while a blank space indicates a lack of data on the topic.

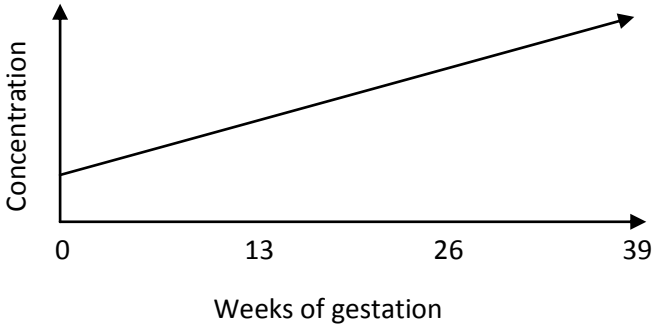

Figure 5: Time course of estrogen and progesterone concentrations during pregnancy (1)

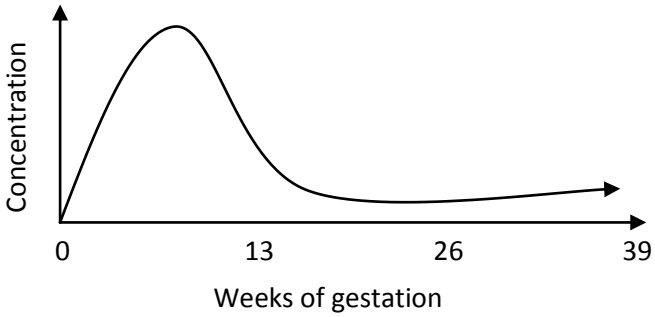

Figure 6: Time course of hCG concentrations during pregnancy (13,27,39,42,43)

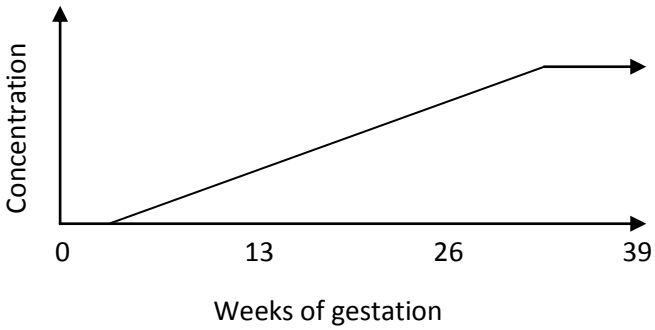

Figure 7: Time course of hPL concentrations during pregnancy (1,6,9)

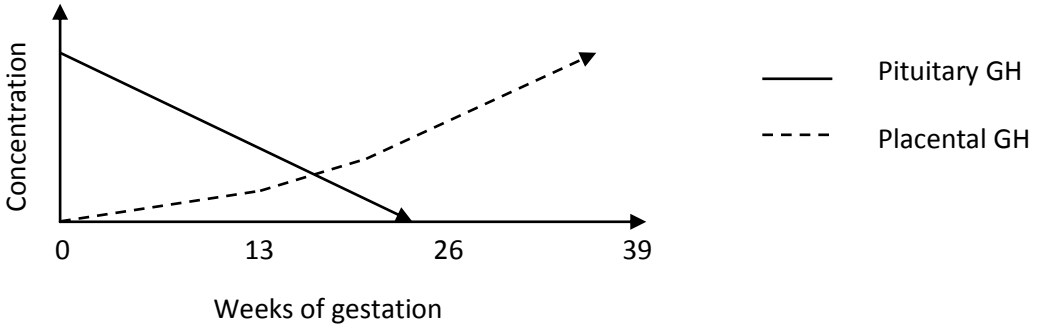

Figure 8: Time course of placental GH and pituitary GH concentrations during pregnancy (1,6,47)

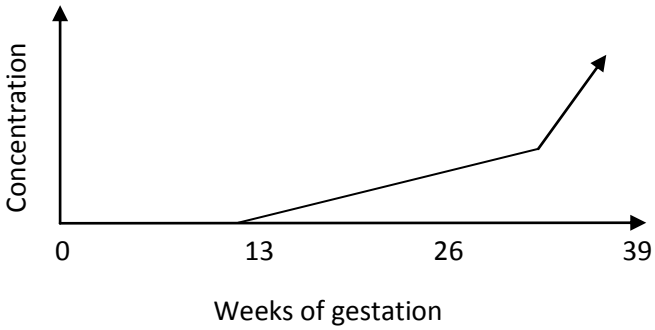

Figure 9: Time course of CRH concentrations during pregnancy (32,59)

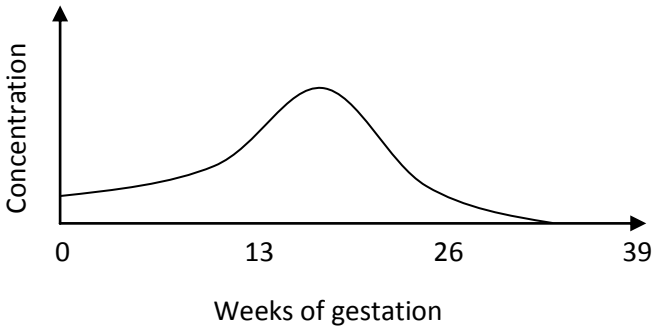

Figure 10: Time course of ghrelin concentrations during pregnancy (1,16,62)

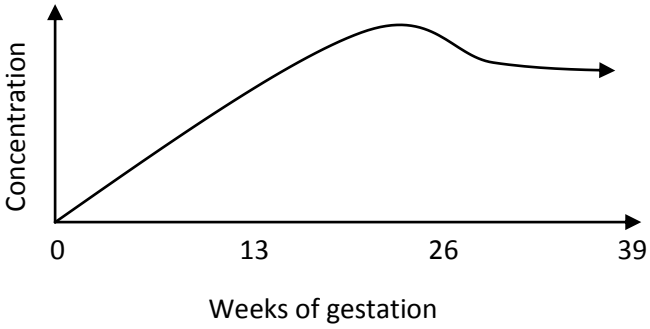

Figure 11: Time course of placental leptin concentrations during pregnancy (7,24,36,40)

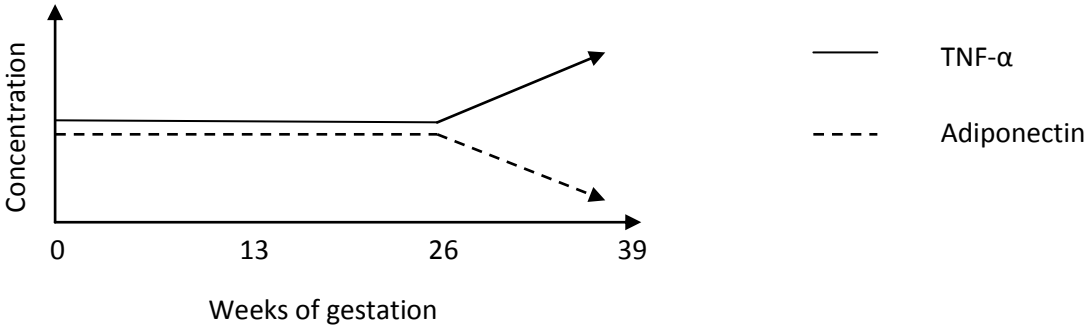

Figure 14: Time course of TNF-α and adiponectin concentrations during pregnancy (1,6)

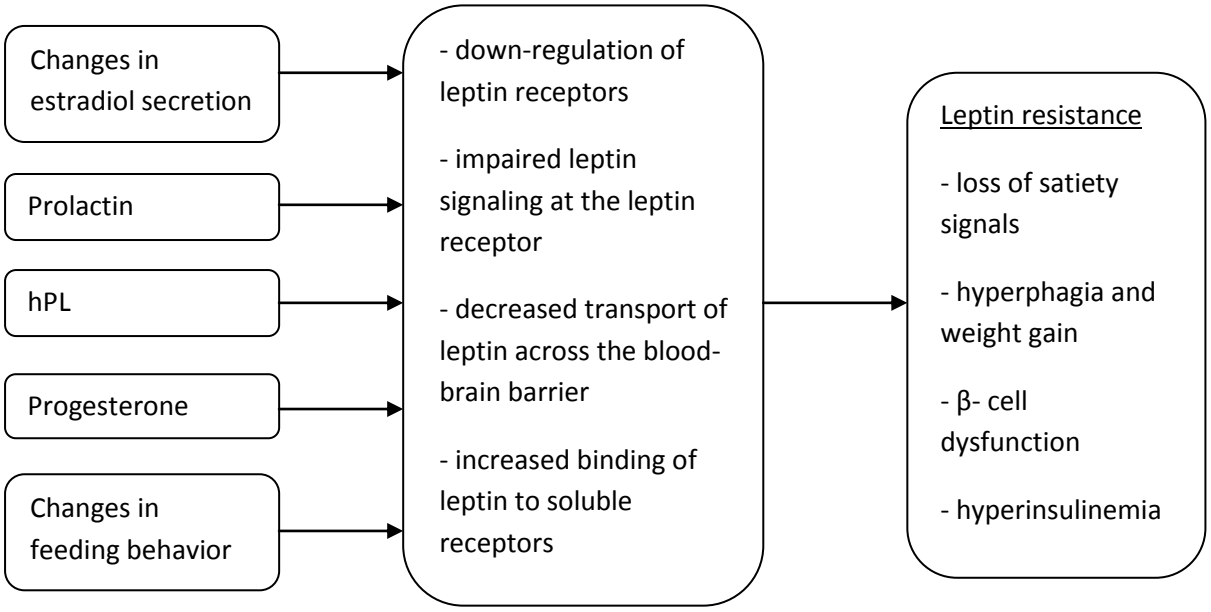

Figure 12: Factors leading to the development of leptin resistance in mid- to late pregnancy (4,5,65)

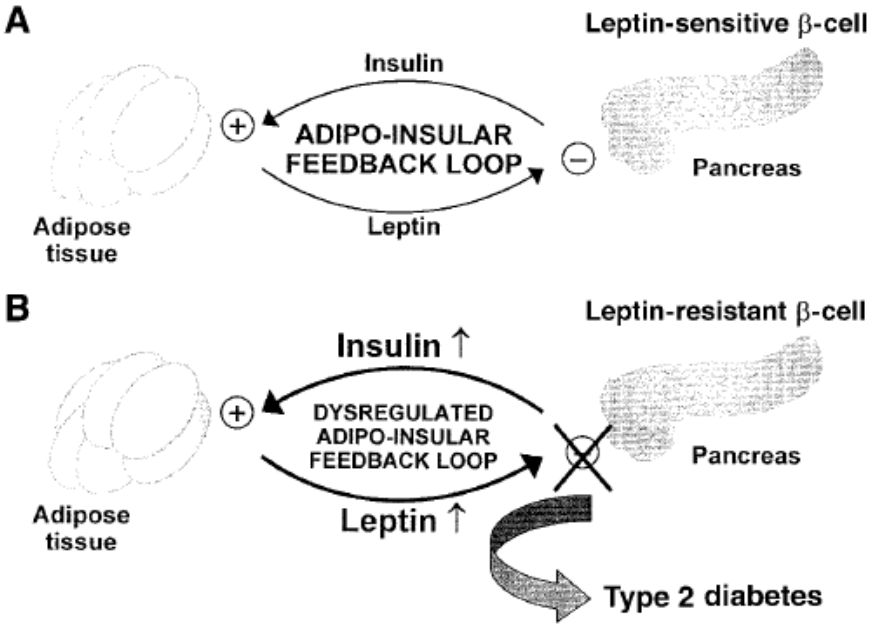

Figure 13: Dysregulation of the adipo-insular axis and pathogenesis of type 2 diabetes. Adapted from Seufert (65)

Hormone	Transfer into the fetal circulation	Functions in the fetus	Fetal production
Progesterone	Direct secretion by the placenta		Yes
hCG		Regulation of 11β-HSD, steroidogenesis	
hPL	Direct secretion by the placenta	Synthesis of IGF, insulin, adrenocortical hormones, surfactant Regulation of metabolism, angiogenesis	
PGH	No	Regulation of fetal growth?	No
CRH	Direct secretion by the placenta	Stimulation of adrenal and pituitary glands	
Ghrelin			Yes?
Leptin	Direct secretion by the placenta	Vasculogenesis, erythropoiesis, lymphopoiesis, regulation of fat stores	Yes
TNF-α	Direct secretion by the placenta		
Adiponectin			Yes
Visfatin	Diffusion		
Resistin			Yes
Apelin	Diffusion	Promotion of fetal growth, possibly angiogenesis	

Table 7: Placental hormones and their functions in the fetus (6,9,14,16,33, 38,42,43,60,66,70,103,109,112). A question mark represents unclear or conflicting data while a blank space indicates a lack of data on the topic.