Research in Obstetrics and Gynecology 2013, 2(4): 37-47
DOI: 10.5923/j.rog.20130204.01

Metabolic Adaptations in Pregnancy in Lean and Obese Women – A Literature Review

Sklempe Kokic Iva[1,2]

[1]Department of Physiotherapy, Polytechnic «L. Ruzicka», Vukovar, 32000, Croatia
[2]Faculty of Mathematics, Natural Sciences and Information Technologies, University of Primorska, Koper, 6000, Slovenia

Abstract Adaptation to pregnancy involves substantial metabolic changes in order to satisfy the increasing demands of the fetus. This article provides an insight into the recent findings on metabolic adaptations during normal pregnancy, with an overview of metabolic adaptations in obese women and possible effects of obesity on pregnancy outcomes. A comprehensive search was conducted during January, 2013 within the Pubmed and OvidSP databases. Early gestation can be viewed as an anabolic stage with an increase in maternal fat deposits, changes in insulin sensitivity and protein metabolism. Late pregnancy, may be described as a catabolic state with decreased insulin sensitivity, resulting in the increase in maternal glucose and free fatty acid concentration. Due to metabolic changes in pregnancy, decreased insulin sensitivity in particular, overweight pregnant women face higher risk of metabolic disorder during pregnancy, as well as short and long-term adverse pregnancy outcomes. Children of obese women also face higher risk of metabolic dysfunction. Increased obesity among women of reproductive age stress the need for better knowledge and understanding of metabolic occurrences during pregnancy and their effects on child's growth, development and long-term health, as well as mother's health after the pregnancy.

Keywords Metabolic Adaptation, Pregnancy, Obesity

1. Introduction

Pregnancy is accompanied by a series of anatomical, physiological and biochemical adaptations and any of these changes begin soon after conception and continue throughout the pregnancy[1]. Most of the changes are a response to the physiological stimuli of the fetus and placenta. During normal pregnancy, changes occur in nearly every organ system. Metabolic changes occur due to increased demands of the growing fetus and placenta, and are numerous and intensive. No other physiological condition causes such major changes in the functioning of metabolism. By the third trimester, maternal basal metabolic rate increase by 10-20% when compared to the pre-gravid period, with an additional 10% increase for twin pregnancies[2]. Total energy requirements estimate 80000 kcal, respectively 300 extra kcal a day[1].

Pregnancy is a dynamic, anabolic state. Physiological adaptations can be classified according to gestational periods, e.g. the first and the second half, three trimesters or four quarters. The first half of pregnancy is primarily a preparation stage for the demands of rapid fetal growth in late pregnancy. Although over 90% of fetal growth occurs during the second half of gestation, adaptations of nutrient metabolism are visible from the first weeks of pregnancy. Within a few weeks following conception, a new endocrine organ, the placenta, develops and secretes hormones and cytokines affecting the metabolism of all nutrients. These adaptations support fetal growth and development, and at the same time maintain homeostasis in the mother and prepare her for lactation. Depending on the nutrient, one or more adaptations take place: 1. growth of new tissue or deposition of nutrients in maternal reserves, 2. redistribution between tissues, and 3. increased turnover or metabolism of substances[3].

Circulating concentrations of most nutrients decline by the end of the first ten weeks of pregnancy, before the increase of plasma volume. The concentration of serum albumin decreases by 8-10% in the first ten weeks of pregnancy, and since albumin is the carrier for many nutrients, its significant decrease can explain the abrupt decrease of circulating nutrient concentrations[3].

Rapid fetal growth during the second half of pregnancy dictates the changes in basal metabolism, proteins and deposition of minerals. Changes in glucose metabolism, and probably in fatty acids as well, occur simultaneously with mother and child's increased energy demands, whereas adaptation of protein metabolism appears to occur in anticipation of maternal and fetal demands[4]. Glucose is the primary energy source for the fetus, whereas nitrogen accretion and protein deposition are essential components of

* Corresponding author:
iskokic@vevu.hr (Sklempe Kokic Iva)
Published online at http://journal.sapub.org/rog

fetal growth and the synthesis of new fetal and maternal tissue.

Utilization of nutrients can be changed either by increased intestinal absorption, or decreased renal or gastrointestinal secretion. Changes in nutrient metabolism can be described by several general statements: 1. they are caused by hormonal changes, fetal demands and maternal nutrient supply, 2. there is more than one potential adaptation for each nutrient, 3. changes in mother's behaviour affect physiological adaptations and 4. physiological capacity of nutrient metabolism adaptation has a limitation which, if exceeded, causes impaired fetal growth and development[3].

The purpose of this article is to provide an overview of recent findings on metabolic adaptations during pregnancy. The article focuses primarily on the metabolism of all main nutrients during normal pregnancy. It contains the descriptions of basal metabolism, changes in body composition and weight gain, as well as the metabolism of water, minerals and electrolytes. There are also description of characteristics of metabolic adaptations in obese women and the possible effects of obesity on pregnancy outcomes.

2. Methods

A comprehensive database search was performed during January, 2013 within PubMed and OvidSP with the purpose of finding trials on metabolic adaptations in pregnancy. There were no limitations with respect to trial design or the time when articles were published, apart from including exclusively papers in English dealing with the pregnant population. The search was concluded on January 31st 2013. The key terms and their combinations used for the search were: "pregnancy", "metabolism", "metabolic", "adaptation", "weight gain", "insulin resistance", "obesity", "fetus", "lipid", "carbohydrate" and "protein". The procedure was concluded by using references found in all relevant papers.

3. Results

3.1. Basal Metabolism and Weight Gain

Average weight gain in pregnancy is approximately 12.5 kg[1]. Around 40% of the total weight gain is related to the weight of the fetus, placenta and amniotic fluid, whereas the remaining 60% represents the increased mass of maternal tissue, including the uterus, breasts, blood, adipose tissue and extracellular fluid[5]. Some other organs also increase in size, e.g. the liver, kidneys and heart[4]. The weight of the fetus, supporting tissues (uterus, placenta and amniotic fluid), and tissues preparing for lactation (mammary glands) account for approximately 6.5 kg, whereas the rest is related to increased water retention and adipose tissue in the pregnant woman's organism.

There are one or more adaptations for the preservation of energy: 1. decreasing lipid synthesis and the deposition of maternal adipose tissue, 2. changing the intensity of physical activity and 3. increasing food and energy intake[3]. The total resting energy expenditure, and adipose and lean tissue gained during pregnancy, range from 60000 to 170000 kcal, whereas in theory, estimated energy needs are 80000 kcal[6]. Additional energy needs during normal pregnancy, reported in 10 healthy pregnant women, ranged between 210 and 570 kcal/a day, whereas most women ingested more than the extra 300 kcal recommended for pregnant women[6]. A higher cumulative increase in basal metabolic rate is related to increased birth weights and the tendency to deposit less adipose tissue. Energy metabolism and fetal growth depend on the pre-pregnancy energy status and the quality of living conditions during pregnancy[7]. Increase in pregnancy-related energy expenditure is a fairly flexible value, because some women consume a lot less, and some considerably more energy than recommended.

By the third trimester, maternal basal metabolic rate increase by 10-20% in comparison to the pre-gravid period, with an additional 10% increase for twin pregnancies[2]. Basal metabolic rates are 20% higher in pregnant obese women, as opposed to non-gravid obese women[8]. These women enter pregnancy with large fat deposits, causing a boost in their basal metabolism, in order to level out further deposition of adipose tissue.

Increase in adipose tissue deposits correlates positively with gestational weight gain and indicates that women with higher weight gain also deposit more fat. There is also an inverse relation between maternal fat deposits before pregnancy and adipose tissue gain during pregnancy, which is consistent with the observation that obese women gain less weight during pregnancy. Deposition of fat occurs primarily during the second and third quarter of pregnancy i.e. between the 13th and 35th week and is assumed to represent the energy deposits to be used in the final quarter, when fetal energy demands are the highest. The total estimated adipose tissue gain is 3.35 kg, but can range from -2 to 10 kg in healthy women[7], i.e. from 1.9 to 5.8 kg[9]. High amounts of gained adipose tissue increase the risk of obesity after birth. In women with normal body weight, energy intake and fat deposits are not related, which is in contrast with the expectations that larger fat deposits are related to higher energy intakes[7].

In underweight women basal metabolism is reduced in early pregnancy, as opposed to women with normal weight, who show quite opposite tendencies. Maternal energy status, i.e. fat deposits at the moment of conception, is the main determinant of basal metabolic rate trends during pregnancy.

Excessive fat deposits can have adverse effects on the health of both fetus and mother. Maternal obesity is related to a linear risk increase for a large number of complications during pregnancy[9]. Fat is mainly deposited centrally i.e. combined in the subcutaneous truncal and visceral adipose tissue. Visceral adipose tissue is related to metabolic disorders. Excessive levels of central adipose tissue are related to cardiovascular diseases and diabetes in adults, as

well as glucose intolerance/gestational diabetes and gestational hypertension/preeclampsia during pregnancy. In obese pregnant women, there are elevated levels of circulating leptin concentrations, as well as elevated levels of inflammatory mediators, including IL-6. Considering the known relation between the inflammatory state and preeclampsia, this contributes to increased risks in obese pregnant women.

Due to the variability of energy expenditure during pregnancy, it is difficult to set nutrition standards. For women with normal body weight and obese women living in developed countries, estimated additional energy needs are less than 300 kcal/a day, especially in case of decreased physical activity. Food intake above these recommended values results in excessive adipose tissue deposition, due to a generally anabolic state during pregnancy. In undernourished women and women performing strenuous physical activities, consumption of nutritional supplements, however brief, during 90 days of pregnancy is beneficial for fetal growth[10].

In 1990 new standards were proposed on weight gain during pregnancy[11], acknowledging the fact that weight gain varies significantly among women who have given birth to healthy infants of optimal body weight. New guidelines set different standards for undernourished, well-nourished and obese pregnant women, giving a wide range of weight-gain recommendations for each of the three groups.

3.2. Carbohydrate Metabolism

Normal pregnancy is characterised by mild fasting hypoglycaemia, postprandial hyperglycaemia and hyperinsulinemia. After oral glucose ingestion in pregnant women, there is prolonged hyperglycaemia and hyperinsulinemia, as well as increased suppression of glucagon secretion[12]. This response is related to the induced state of peripheral insulin resistance, whose purpose is probably to maintain a postprandial supply of glucose to the fetus. The fetus is estimated to utilize 20-25 g of glucose a day in late pregnancy[13]. In early pregnancy, basal glucose and insulin concentrations do not differ significantly from pre-gravid values. Until the third trimester, the basal glucose concentration is 10-15 mg/dL (0.56-0.83 mmol/L) lower, whereas insulin concentration is almost double when compared to non-gravid women[13]. Postprandial glucose concentration is significantly elevated, whereas peak glucose concentration is retained longer. Basal endogenous hepatic glucose production is increased by 16-30%[13].

Fasting glucose levels decrease progressively as pregnancy advances. These levels decrease even further in case of prolonged fasting. The mechanism is complex, whereas potential contributing factors include: 1. effects of dilution (elevated plasma volume in early pregnancy), 2. elevated glucose consumption (or increased fetoplacental glucose consumption, or increased maternal glucose deposition, due to elevated β-cell function) and/or 3. insufficient glucose production (limited hepatic production in relation to circulating glucose concentrations)[14].

Despite decreased fasting glucose and elevated fasting insulin concentrations, hepatic glucose production (normally suppressed by insulin) is elevated. This contributes to decreased insulin sensitivity and results in decreased suppression of hepatic glucose production in women with normal glucose tolerance. Additionally, in obese pregnant women with abnormal glucose tolerance, occurs a decreased ability to completely suppress hepatic glucose production in late pregnancy after administering intravenous insulin, when compared to measurements before and during early pregnancy. These findings indicate a further decrease in insulin sensitivity in obese women.

There are significant changes in insulin sensitivity during pregnancy. It is characterised as a postreceptor defect resulting in decreased insulin ability to stimulate GLUT4 mobilisation from the interior to the surface of the cell[15]. Although until now the human placental lactogen has mainly been mentioned as the source of decreased insulin sensitivity (HPL)[16], recent research draws attention to the role of cytokines and elevated lipid concentrations during pregnancy, which correlate positively with longitudinal changes in insulin sensitivity, in both non-gravid[17] and pregnant women[18, 19].

In early pregnancy, insulin sensitivity varies and depends on maternal pre-gravid insulin sensitivity, as well as other speculative mechanisms. Changes in late pregnancy are accompanied by significantly decreased insulin sensitivity, whereas the stimulus for the decrease of insulin sensitivity in muscles and adipose tissue stems probably from hormone and cytokine production in the placenta. In pregnant women with little adipose tissue there is a 10% decrease, and in obese pregnant women a 15% increase in insulin sensitivity during early pregnancy, as opposed to the pre-gravid period[20]. Decreased need for insulin in early pregnancy observed in some women may be the result of a relative insulin sensitivity increase. This is particularly prominent in obese women with decreased insulin sensitivity prior to conception. Peripheral insulin sensitivity further decreases in late pregnancy, with the decrease ranging from 33-78%. Women with less adipose tissue have a lower overall decrease in insulin sensitivity.

A normal β-cell response to insulin resistance is an increase in insulin secretion, i.e. a decrease of the effects of insulin resistance on circulating glucose levels. Increased insulin secretion (or increased β-cell function) during pregnancy is most likely compensation for progressive insulin resistance, and not the other way around, because insulin resistance occurs even if endogenous insulin secretion is absent. Taking into consideration, however, that insulin secretion increases as much as 50% early in the second trimester, before the manifestation of insulin resistance, hormonal characteristics of pregnancy may prove to be responsible for increased insulin secretion, regardless of insulin resistance. The mechanisms leading to increased insulin secretion in pregnancy, primary or compensatory to

resistance, are not entirely known. They are partly related to metabolic effects of several hormones and cytokines which are elevated in maternal circulation during pregnancy. There is a confirmed parallel between the pattern of insulin resistance during pregnancy and the simultaneous growth of the fetoplacental unit, and the increase of the concentration of placental hormones. An elevated concentration of circulating free fatty acids can also increase tissues' resistance to insulin[21].

Likewise, circulating concentrations of TNF-α are inversely correlated with insulin sensitivity. Together with leptin, cortisol, HPL, HCG, estradiol, progesterone and prolactin, TNF-α is the only relevant predictor of insulin sensitivity change, from the pre-gravid state, to late gestation [14]. Elevated TNF-α concentrations can suppress the insulin signalling pathway and result in observed decreased insulin sensitivity. The source of elevated TNF-α is probably placental.

In late pregnancy, there is increased carbohydrate contribution to the oxidative metabolism. Using respiratory calorimetry, the measured 24-hour respiratory quotient is significantly higher in late pregnancy than postpartum; carbohydrate oxidation expressed as a percentage of the consumption of non-protein energy sources decreases from 66% in late pregnancy, to 58% six months postpartum, whereas absolute carbohydrate oxidation values are significantly higher during pregnancy (282 g a day) than postpartum (210 g a day)[13].

The effects of obesity on these adaptations are significant and there is a particular decrease in fasting glucose during early pregnancy. There is also a significant peripheral and hepatic insulin resistance, manifested as decreased insulin-mediated deposition of glucose, decreased insulin-stimulated carbohydrate oxidation, and decreased insulin suppression of endogenous glucose production. In a postprandial state, obesity-related insulin resistance increases the circulating nutrient levels, e.g. glucose, lipids and amino acids. Consequently, this leads to impaired glucose uptake and fetal exposure to hyperglycaemia; the inability to suppress lipolysis leads to increased levels of free fatty acids to be transferred in the placenta; a decreased insulin ability to suppress amino acid turnover causes elevated maternal concentrations of branched-chain amino acids and facilitates the transfer of excessive amounts of nutrients to the fetus. All these factors contribute to fetal macrosomia.

Although precise mechanisms of regulating insulin sensitivity are not yet known with certainty, it does appear that fat mass plays the principal role. Women with less adipose tissue have an inverse correlation between the changes in insulin sensitivity and fat mass. Obese women show a negative relation between decreased insulin sensitivity and increased fat mass, from the pre-gravid stage, to late pregnancy. Additionally, although changes in insulin sensitivity in late pregnancy are mediated on the peripheral level primarily, and on the hepatic level secondarily, elevated levels of non-esterified free fatty acids in late pregnancy also contribute to peripheral and hepatic insulin resistance, with estrogen facilitating further lipid increase.

3.3. Lipid Metabolism

Although changes in glucose metabolism are often regarded as the primary metabolic adaptations during pregnancy, significant changes also occur in lipid metabolism. Non-obese women deposit approximately 3.5 kg of fat during normal pregnancy, however, with significant individual variations[7]. Subcutaneous fat mass, primarily centrally distributed, increases significantly during pregnancy. Additionally, the ratio of preperitoneal and subcutaneous adipose tissue changes, indicating an increase in intra-abdominal adipose tissue, whereas an increase in visceral adipose tissue may be related to decreased insulin sensitivity[14].

Lipid, lipoprotein and apolipoprotein concentrations in the plasma significantly increase during pregnancy. Total triglyceride concentrations increase 2-4 times, total cholesterol by 25-50%, LDL by 50%, whereas HDL increases by 30% by mid pregnancy, after which it declines as term approaches[14].

Maternal hyperlipidemia is one of the most consistent and most prominent changes in lipid metabolism during pregnancy. This increase is most prominent in pregnant women suffering from gestational diabetes[22]. The mechanisms responsible for these changes include increased lipolytic activity and decreased activity of lipoprotein lipase in adipose tissue[23]. The effects of estradiol and progesterone on the liver also play an important role[24]. After birth, the concentrations of lipids, lipoproteins and apolipoproteins decrease, which is even more accelerated by lactation[25].

Decreased insulin sensitivity during pregnancy is not limited merely to glucose metabolism, but is also related to lipid metabolism[22]. Increased concentrations of free fatty acids are related to decreased insulin ability to suppress lipolysis in late pregnancy. Freinkel[26] uses the term «accelerated starvation in pregnancy» to describe the increased risk of ketosis in pregnant women. Elevated levels of free fatty acids are a useful energy source for maternal needs in late pregnancy, when energy demands are the highest. This is also related to higher birth weight rates[27]. Recent trials conducted by Di Cianni and associates[28] and Schaefer-Graf and associates[29] show a significantly positive correlation between maternal triglyceride concentrations in late pregnancy, and fetal growth/adiposity. Increased concentrations of fatty acids and glycerol in the plasma are consistent with the mobilisation of fat deposits. This shift from an anabolic towards a catabolic state stimulates the use of lipids as maternal energy sources, while preserving glucose and amino acids for the fetus.

Changes in lipid metabolism stimulate the accumulation of maternal fat reserves in early and mid pregnancy, and improve adipose tissue mobilisation in late pregnancy.

Adipose tissue is deposited primarily mid-pregnancy[30, 31], with more deposits centrally than peripherally. Adipose tissue is available for transfer to the placenta during the last trimester, when fetal growth is at its maximum and there are high demands for essential fatty acids[23, 32].

Lipid metabolism differs among women with little adipose tissue and obese women. Lean women experience the predominance of lipogenesis in the first stage of pregnancy, and lipolysis in the late stage. In obese women, on the other hand, lipogenesis occurs only in the pre-gravid period, whereas lipolysis predominates in both stages of pregnancy[14]. These data confirm insulin's inability to suppress lipolysis in all women as pregnancy advances, and offer further evidence of increased insulin resistance in obese women, as opposed to women with normal weight in earlier stages of pregnancy[14].

In obese pregnant women, hyperlipidemia is even more prominent. Total and VLDL triglycerides tend to be even more elevated, whereas plasma HDL is even lower, as opposed to LDL, which remains unchanged. Relative insulin inability to suppress lipolysis in the entire body leads to a significant increase of free fatty acids in the plasma. Oxidative susceptibility of LDL, related to endothelial dysfunction, atherosclerosis and cytotoxicity, further increases with maternal obesity.

Dyslipidemia can contribute to vascular complications, including preeclampsia – maternal hypertriglyceridemia is characteristic in women who develop preeclampsia. Observed triglyceride changes in preeclampsia were accompanied by an almost triple increase of VLDL1 and a double increase of VLDL2 levels, a significant increase of fatty acids and a triple increase of LDL levels. Low-density LDL particles, which are enlarged in both preeclampsia and obesity, are highly atherogenic and capable of inducing the formation of fatty foam cells and endothelial dysfunction, causing further damage to endothelial function, due to increased free fatty acids[9]. Obese women or women with excessive weight gain, with previously diagnosed or recently developed cases of dyslipidemia, are more susceptible to the development of acute placental atherosis and preeclampsia. Furthermore, this relation, in addition to inflammation, potentially provides an explanation for the strong epidemiological connection between preeclampsia and pre-pregnancy BMI and excessive weight gain in non-obese women[9].

However, Saarlainen and associates[33] have discovered that endothelium-dependent vasodilator responses actually improve during pregnancy. This improvement is partly the result of elevated HDL cholesterol concentrations that are most likely inhibiting the oxidation of low-density lipoprotein, thus protecting the endothelium. Their findings indicate that the cause of increased risk of cardiovascular diseases in multiparous women should be sought among the factors not related to maternal hypercholesterolemia.

One must not forget that, recently, understanding the role of adipocytes has improved immensely. Adipose tissue is not only a source of maternal calories, but rather an active metabolic tissue with a key role in one's metabolism. Adipocytes and adipose stromal cells are a rich source of cytokines and inflammatory mediators, which can either increase insulin resistance (TNF-α), or reduce it (adiponectin). Their role in the modulation of metabolic changes in pregnancy is not entirely known. The interaction between the cytokines in maternal adipose and placental tissue could play a much larger role in maternal metabolism than previously believed.

3.4. Leptin and Ghrelin

Leptin is a peptide hormone secreted primarily by adipose tissue and plays a key role in the regulation of body fat and energy reserve expenditure. Leptin levels increase in pregnancy and reach their peak in the second trimester, whereas until birth they remain in a 2-4-fold higher concentration than in non-pregnant women[34]. Serum leptin levels continuously increase from the 6^{th}-8^{th} week to the 38^{th}-40^{th} week of pregnancy, with a drastic decline after birth[35].

This increase is only partly a result of weight gain, because substantial amounts of leptin are also produced by the placenta. The production of leptin is observed in the placental trophoblast and amniotic cells, as well as syncytiotrophoblast cells. In fact, the mass of the placenta positively correlates with leptin levels[36]. Hauguel-de Mouzon and associates[37] established a hypothesis that increased leptin production is critical for the regulation of increased energy demands in pregnant women. Leptin could also play a role in the regulation of fetal growth, the incidence of macrosomia, as well as fetal growth restriction [38-41]. There is more and more evidence that leptin serves as a detector of long-term energy source availability, as well as a signal of sufficient maternal reserves of adipose tissue for the initiation of reproduction[13].

It is presumed that low leptin concentrations in women with extremely low amounts of adipose tissue disable reproduction, due to insufficient secretion of gonadotropins [42]. Elevated leptin concentrations in obese women do not have adverse effects on gonadotropin concentrations, but can, however, directly inhibit estrogen production, thus contributing to fertility problems. Decreased leptin levels are indicative of pregnancy termination, either through birth, or a pathological process.

In pregnant women, differences in appetite, thermogenesis and lipid metabolism could partly be leptin-regulated. It is know that leptin inhibits the release of neuropeptide Y, a strong appetite stimulant. Elevated leptin concentrations during pregnancy may appear to be a paradox, due to an assumed increase in food intake, which practically causes resistance to leptin. The role of leptin in pregnancy must be examined in more detail.

Ghrelin is another hormone related to adipose tissue and probably plays a role in fetal growth and cell proliferation. It is likewise produced in placental tissue and regulates the

secretion of growth hormone. Maternal levels of serum ghrelin increase and reach their peak mid-pregnancy, after which they begin declining until term[43]. It is known that ghrelin levels also decrease in other conditions related to insulin resistance, such as the metabolic syndrome[44].

3.5. Protein Metabolism

During pregnancy, significant adaptations also take place in protein metabolism, in order to satisfy the increasing needs of the fetus. These adaptations are complex and change gradually during the course of the pregnancy. While the adaptations of glucose and fatty acids metabolism occur simultaneously with increased energy demands of mother and fetus, changes in protein metabolism are anticipatory of those demands. There is a decrease in the overall α-amino nitrogen, a decrease in urea synthesis and in the rates of transamination of branched-chain amino acids[4]. Adaptation responses of nitrogen metabolism in pregnancy are directed towards the deposition of nitrogen and protein, initially in the mother's organism, and later in the fetus, as well. The exact mechanism of this adaptation is unknown, but is probably related to pregnancy-induced insulin resistance[4].

At the end of pregnancy, the fetus and placenta reach the mass of approximately 4 kg and contain approximately 500 g of protein, i.e. around half of the total protein growth in pregnancy, estimated at 925 g[45]. The remaining amount is deposited in the uterus in the form of contractile proteins, in the mammary glands and in the blood[34].

Hypoaminoacidemia and a reduced response of amino acids to protein intake occur during pregnancy, indicating an increased uptake of amino acids in visceral organs. Hypoaminoacidemia during fasting, which occurs in early pregnancy and persists throughout pregnancy, can be related to the effects of pregnancy-related hormones. Moreover, during fasting, there is a much larger decrease in glucogenic amino acids – alanine, serine, threonine, glutamine and glutamate, which can indicate that they are responsible for fasting hypoglycaemia, although there is no direct evidence to corroborate this assumption[4]. The concentration of amino acids is higher in the fetus than the mother[46, 47].

The increase of amino acid concentration in the fetus is regulated by the placenta, which is not only responsible for the concentration of amino acids in fetal circulation, but also for the synthesis of proteins, oxidation and transamination of certain amino acids[48]. There is a positive correlation between the total concentration of amino acids, the concentration of serine, lysine, proline, ornithine, arginine, and neonatal birth weight[49]. These correlations do not necessarily mean that the mentioned amino acids play a key role in fetal growth, because some of them (e.g. serine) are not transported to the fetus in substantial amounts. Thus, changes in the concentrations of certain amino acids can reflect other metabolic processes that in turn can modify the metabolism of these specific amino acids.

During pregnancy, most amino acids are used for protein synthesis, with a decrease in their oxidation by approximately 10%[45]. Although, contrary to expectations, there is no increase in measured protein synthesis in the first trimester, there is a 15% increase in the second and a 25% increase in the third trimester[45]. These changes are not proportionate to the highly active protein synthesis in the fetus and placenta, thus indicating a general increase in protein synthesis in maternal tissues. The effects of the turnover of maternal proteins on the fetus are considerable, with higher levels of maternal synthesis in the second trimester, related to increased birth length and also affecting birth weight.

King[50] concluded a while ago that nitrogen retention in a pregnant woman's organism is greater than the estimated protein uptake in pregnancy. Nitrogen retention reaches its full potential during the final quarter of pregnancy, whereas adaptations of maternal nitrogen metabolism occur in early gestation, before significant increases of nitrogen supply to the fetus. Calloway[51] calculated that between the 20th and 40th week there is nitrogen retention of approximately 1.3 g/a day. Measuring nitrogen balance proves that a more efficient utilisation of proteins from food does occur, and that nitrogen retention levels are on average 0.2 g/a day before pregnancy, -0.4 g/a day in the 12th week of pregnancy, 0.5 g/a day in the 23rd week and 1.2 g/a day in the 34th week, which are somewhat lower values than those previously estimated[52]. The same authors also measured the urinary excretion of 3-methylhistidine and came to the conclusion that in order to cater to the metabolic demands, it is not necessary to use maternal muscle proteins. Additional confirmation to the thesis on maternal nitrogen retention is provided by Kalhan and associates[53], who have discovered a decrease in the production of non-essential serine.

Increased nitrogen retention in late pregnancy occurs due to reduced urinary excretion of nitrogen, with the reduction amounting to approximately 1.5 g/a day[3]. Reduced urinary excretion of nitrogen occurs due to reduced excretion of urea, which is in turn caused by the reduced synthesis of urea. It is approximately 30% lower during the first trimester, and 45% lower by the third trimester[3]. Lower concentrations of blood urea are visible in early gestational stages and are attributed to increased renal clearance. Decreased urea synthesis can also be attributed to a reduced supply of necessary substrates to the liver. Excretion of other nitrogen compounds (e.g. ammonia, creatinine and uric acid) is elevated during pregnancy, especially in the late stages. Increased excretion of these substances is probably caused by increased glomerular filtration. Insulin clearance is increased by approximately 50% in the 16th week of pregnancy, and 80% by term[1].

Requirements for food proteins during pregnancy are inconsistent, and based on the factor approach, the estimated requirements from the first to the fourth quarter are 0.64 g, 1.84 g, 4.76 g and 6.10 g respectively. Current nutrition recommendations propose an intake of 6 to 10 g of protein a day[45]. However, there is no simple connection between

protein intake through food and fetus size[45].

At present, the effects of obesity on amino acid metabolism are unknown. In obese non-gravid women, however, protein synthesis is less stimulated in hyperinsulinemia, as opposed to women without much adipose tissue, although there are no differences with respect to protein oxidation. Visceral lean tissue correlates positively with maternal protein turnover. Overall, this could indicate that in obese women there is a possibility of impaired anabolic response to pregnancy, as well as the possibility of a mechanism limiting fetal growth in case of hyperinsulinemia.

3.6. Water, Electrolytes and Minerals Metabolism

Increased water retention is a normal physiological occurrence during pregnancy and appears in the early stages. It is partly caused by decreased plasma osmolality of approximately 10mOsm/kg, induced by changes in osmotic threshold for thirst and vasopressin secretion[54, 55]. Until term, the amount of water in the fetus, placenta and amniotic fluid is approximately 3.5 L. Additional three litres of water are accumulated due to increased blood volume, uterus and breast size. Thus, the minimal amount of additionally accumulated fluid in normal pregnancy is approximately 6.5 L. There is visible peripheral and tibial oedema, especially at the end of the day. This fluid build up, which amounts to approximately one litre, is caused by increased venous pressure below the level of the uterus and is a result of partial vena cava occlusion. Oedema is also facilitated by the decrease of interstitial colloid osmotic pressure[56].

During normal pregnancy a woman retains approximately 1000 mEq of sodium and 300 mEq of potassium[57]. Despite elevated glomerular filtration of sodium and potassium, excretion of these electrolytes does not change during pregnancy due to tubular reabsorption[5, 59], whereas despite the increase in their overall accumulation, their serum concentrations are mildly reduced, due to expanded plasma volume. The concentrations do, however, remain very close to the normal values for non-gravid women[60].

Pregnancy is related to substantial changes in calcium and bone metabolism, as well as changes in bone-mineral status. The overall level of serum calcium concentration decreases during pregnancy, thus reflecting decreased plasma albumin concentration, as well as the consequential decrease in calcium-binding proteins. The levels of serum ionized calcium remain the same[61]. A developing fetus has a considerable effect on maternal calcium homeostasis. For instance, fetal skeleton accumulates approximately 30 g of calcium by term, 80% of which is accumulated during the third trimester. Most of the accumulated calcium is taken over from maternal calcium deposits. The mother satisfies the increased fetal calcium demands by doubling intestinal calcium absorption, partly mediated by 1.25-dihydroxyvitamin D3[62]. Pregnancy is a state of hyperestrogenemia and weight gain, both of which produce protective effects for bones. Additionally, later stages of pregnancy are characterised by increased levels of active vitamin D and increased calcium absorption, thus protecting skeletal integrity. The effects of pregnancy on the skeletal-mineral status are difficult to determine due to a lack of adequate methods, as well as the fact that postpartum measurements can be influenced by lactation.

Breastfeeding is also accompanied by decreased skeletal-mineral status, as well as increased skeletal remodelling, and decreased excretion of calcium in urine. During the first four months, maternal calcium loss is approximately 150 mg a day[63]. These effects are reversible, whereas after weaning, several skeletal regions have higher levels of skeletal minerals than after birth. These changes do not depend on calcium intake through food. The change patterns support the hypothesis that there are physiological mechanisms which provide sufficient supplies of calcium for fetal growth and milk production, without relying on calcium from food. There is, however, evidence that pregnant women with normally low calcium intake could benefit from calcium supplements during pregnancy. In addition, low calcium intake is related to a higher risk of pregnancy-induced hypertension and other related obstetric complications, whereas calcium supplementation has been proven to reduce blood pressure in pregnant women[64].

Serum magnesium levels also decline during pregnancy. Bardicef and associates[65] have come to the conclusion that pregnancy is in fact a state of extracellular depletion of magnesium deposits. When compared to non-pregnant women, pregnant women have considerably lower levels of total and ionised magnesium[66]. Serum phosphate levels remain the same in both pregnant and non-pregnant women. The renal threshold for inorganic phosphate excretion is increased during pregnancy, due to elevated calcitonin levels[67]. Pregnancy does not affect the metabolism of other minerals and elements, except for their retention in amounts necessary for fetal growth. The only exception is the increased need for iron.

4. Discussion

Due to metabolic changes during pregnancy, especially because of decreased insulin sensitivity, overweight pregnant women face a higher risk of metabolic dysregulation during pregnancy. This particularly refers to gestational diabetes, preeclampsia and fetal macrosomia. Pregnancy can, thus, be considered a state of metabolic stress and a risk factor for metabolic syndrome in the future. Knowing and understanding this risk opens a possibility for prevention. For instance, pregnancy planning provides an opportunity to regulate body weight before the actual conception. Avoiding excess weight gain during pregnancy enables the prevention of obesity after pregnancy. Likewise, on the basis of the «in utero programming» concept, life-style regulation can produce short and long-term benefits for the health of both mother and child. Increased infant adiposity at birth presents a risk factor for childhood obesity

and long-term metabolic dysfunction[68].

Obese women face a higher risk of many unwanted pregnancy outcomes. The metabolic syndrome in pregnancy includes a higher risk of hypertension, impaired nutrient metabolism and increased inflammatory parameters. Although there is normally a clinical remission of this condition after birth, affected women do retain a latent subclinical metabolic disorder and face an increased risk of metabolic syndrome later in life, especially if gaining weight postpartum[69]. Much like the increase in persons with impaired fasting glucose levels (33.8%), or impaired glucose tolerance (15.4)[70], there could also be an increase in women with gestational diabetes. Pathophysiology of gestational diabetes results in a 50-60% increase in type II diabetes, ten years after being diagnosed with gestational diabetes[71].

The risk of premature cardiovascular diseases is closely related to the severity of metabolic disorders during pregnancy[72]. Although there are massive amounts of data relating metabolic complications in pregnancy to future cardiovascular diseases, obstetric medical history has not yet been included in everyday medical practices or in the latest guidelines for the prevention of cardiovascular diseases in women[73]. Hypertensive disorders in pregnancy double the risk of developing hypertension and cardiovascular diseases later in life[74]. The assumption is that normal pregnancy in itself stimulates the inflammatory response, which in preeclampsia is excessive, and triggers endothelial dysfunction in uterine circulation, thus probably making the placenta the ultimate source of inflammatory stimulus[75].

There is substantial evidence that intrauterine impairment of growth and development is related to a higher risk of cardiovascular and metabolic diseases in adulthood. The perinatal environment plays an important role in the programming of the regulation of metabolic axes in adulthood. A strong inverse relation has been discovered between birth weight and the risk of developing the metabolic syndrome in adulthood[76]. Persons who suffered from intrauterine growth restriction and have experienced "catch-up" growth in the postnatal period, have an increased amount of visceral fat and a resistance to insulin[77]. It is presumed that the reset of the HPA axis in intrauterine growth restriction participates in the pathophysiology of obesity and metabolic syndrome[78]. In fact, cortisol acts as a pathophysiological mediator for central obesity due to excess glucocorticoids, which, when related with hyperinsulinemia, contributes to increased lipogenesis and decreased lipolysis on the visceral level, in a combination with the stimulation of hepatic gluconeogenesis and the inhibition of peripheral glucose uptake[79]. Neonates with extremely low birth weight and cardiovascular risk factors have increased basal and stimulated cortisol secretion levels, which occurs in early stages of life and can be a result of intrauterine programming of the HPA axis[76]. Moreover, it is known that the functioning of glucocorticoids in adipose tissue does not only depend on the circulating hormone concentrations, but rather its prereceptor and receptor metabolism, as well. One might suggest that nutritional changes responsible for intrauterine growth restriction and postnatal "catch-up" growth can program the visceral adipose tissue of glucocorticoid metabolism, as well as the accompanying metabolic disorders in adulthood[76]. High prevalence of maternal obesity and the epidemic of obesity among the very young population suggest that the risk of childhood obesity may be a direct result of shared «obesogenic» environment between the mother and child in utero, or in the early postnatal period.

The most consistent adverse outcome for mothers with excessive weight gain in pregnancy is increased postpartum weight retention, which persists until the third year after birth, regardless of the pre-gravid BMI. This can contribute to adverse outcomes of subsequent pregnancies, where gain of $3kg/m^2$ or more increases the risks of preeclampsia, gestational hypertension and gestational diabetes, caesarean delivery, fetal death and birth of infants too large for gestational age. The connection is linear to weight gain and is clearly expressed in women with normal BMI prior to both pregnancies[69].

Biochemical indicators indicate that pregnancy and breastfeeding are accompanied by the utilisation and release of skeletal calcium during pregnancy, and that the mobilisation of calcium continues during early months of lactation, whereas values return to their normal pre-gravid state during breastfeeding or after weaning. This would imply that changes must occur in mother's skeletal minerals. If these changes are of sufficient magnitude to increase or decrease mother's skeletal-mineral status, pregnancy and lactation could change the risk of osteoporosis later in life.

Metabolic changes and demands of pregnancy must be further examined, especially during unusual conditions and events during pregnancy (e.g. certain diseases or drug treatments), in order to produce detailed scientifically-based recommendations for nutrition during pregnancy. Comparing the pre-gravid and gravid state is very complicated. Ideally, trials would be conducted with the same women, examined before and during pregnancy, allowing participants to be their own control subjects. In most trials, women are observed during pregnancy and postpartum, or the control group consists of different non-gravid women. Neither method is ideal, so the best option is to combine cross-sectional and longitudinal approaches.

Increased number of obese women in their reproductive age and the existence of short and long-term complications for both mother and child due to obesity stimulate quick development of interventions for the improvement of pregnancy outcomes. Without a doubt, the most successful intervention for the prevention of obesity is the one conducted before the onset of a woman's reproductive age. Knowledge of the factors influencing fetal growth and development is important, in order to more easily solve the public health issues of our time.

5. Conclusions

Pregnancy consists of a series of continuous changes which affect the metabolism of all nutrients. Likewise, pregnancy is only one of the stages in the female reproductive cycle. There is increasing evidence that the best time to prepare for the demands of pregnancy is the period immediately before conception. It is necessary to establish public health measures to enable optimal nutrition during all stages of the reproductive cycle, while providing detailed scientifically-based guidelines for nutrition during pregnancy. The amount of nutrients necessary for positive pregnancy outcomes is not a fixed value, but rather varies largely among the population and depends on the nutritive status and health before pregnancy, fetus size, health and lifestyle during pregnancy, as well as genetic factors.

Obesity in pregnancy and insulin resistance represent significant short and long-term risk factors for both mother and child. To obese women, pregnancy represents a metabolic stress and an increased risk of gestational diabetes and preeclampsia, which are related to metabolic syndrome incidence later in life. Children of obese mothers also face a higher risk of metabolic dysfunction in childhood, which can potentially lead to obesity and insulin resistance, thus closing the circle towards metabolic syndrome in adulthood. In order to successfully solve public health issues of the modern age, it is necessary to improve understanding of the metabolic adaptations in pregnancy and the consequences of metabolic dysfunction. The epidemic of maternal obesity calls for the development of efficient interventions for the improvement of pregnancy outcomes. New interventions should include detailed understanding of maternal metabolic environment and its consequences for the health of both mother and child.

REFERENCES

[1] Hytten, F. E. (1991.). Weight gain in pregnancy. In: Hytten, F. E., Chamberlain, G. (Eds.). Clinical Physiology in Obstetrics, 2nd Ed. Oxford: Blackwell, p 173

[2] Shinigawa, S., Suzuki, S., Chihara, H. i sur. (2005.). Maternal basal metabolic rate in twin pregnancy. Gynecol Obstet Invest 60(3):145-8.

[3] King, J. C. (2000.). Physiology of pregnancy and nutrient metabolism. Am J Clin Nutr 71(5 Suppl):1218S-25S.

[4] Kalhan, S. C. (2000.). Protein metabolism in pregnancy. Am J Clin Nutr 71(5 Suppl):1249S-55S.

[5] Pitkin, R. M. (1977.). Components of weight gain during pregnancy. In: Schenider, H. A., Anderson, C. E., Coursin, D. B. B. (Eds.). Nutritional support of medicine practice. Hagerstown: Harper & Row, pp 407-21

[6] Kopp-Hoolihan, L., van Loan, M. D., Wong, W. W., King, J. C. (1994.). Longitudinal assessment of energy balance in well-nourished, pregnant women. Am J Clin Nutr 69(4):697-704.

[7] King, J. C., Butte, N. F., Bronstein, M. N., Kopp, L. E., Lindquist, S. A. (1994.). Energy metabolism during pregnancy: influence of maternal energy status. Am J Clin Nutr 59(2 Suppl):439S-445S.

[8] Bronstein, M. N., Mak, R. P., King, J. C. (1995.). Unexpected relationship between fat mass and basal metabolic rate in overweight pregnant women. Br J Nutr 75(5):659-68.

[9] Nelson, M. S., Matthews, P., Poston, L. (2010.). Maternal metabolism and obesity: modifiable determinants of pregnancy outcome. Hum Reprod Update 16(3):255-75.

[10] Kusin, J. A., Kardjati, S., Houtkooper, J. M., Renquist, U. H. (1992.). Energy supplementation during pregnancy and postnatal growth. Lancet 340(8820):623-6.

[11] Institute of Medicine, Food and Nutrition Bord, Commitee on Nutritional Status During Pregnancy and Lactation (1990.). Nutrition during pregnancy. Part I. Weight gain. Part II. Nutrient supplements. Washington: National Academy Press

[12] Phelps, R. L., Metzger, B. E., Freinkel, N. (1981.). Carbohydrate metabolism in pregnancy, 17. Diurnal profiles of plasma glucose, insulin, free fatty acids, triglycerides, cholesterol, and individual amino acids in late normal pregnancy. Am J Obstet Gynecol 140(7):730-6.

[13] Butte, N. F. (2000.). Carbohydrate and lipid metabolism in pregnancy: Normal compared with gestational diabetes mellitus. Am J Clin Nutr 71(5 Suppl):1256S-61S.

[14] Lain, K. Y., Catalano, P. M. (2007.). Metabolic changes in pregnancy. Clin Obstet Gynecol 50(4):938-48.

[15] Catalano, P. M. (2010.). Obesity, insulin resistance, and pregnancy outcome. Reproduction 140(3):365-71.

[16] Ryan, E. A., Enns, L. (1988.). Role of gestational hormones in the induction of insulin resistance. J Clin Endocrinol Metab 67(2):341-7.

[17] Hotamisligil, G. S., Murray, D. L., Choy, L. N. i sur. (1994.). Tumor necrosis factor alpha inhibits signaling from the insulin receptor. Proc Natl Acad Sci USA 91(11): 4854–4858.

[18] Xiang, A. H., Peters, R. K., Trigo E., Kjos, S. L., Lee, W. P., Buchanan, T. A. (1999.). Multiple metabolic defects during late pregnancy in women at high risk for type 2 diabetes. Diabetes 48(4):848-54.

[19] Kirwan, J. P., Hauguel-de Mouzon, S., Lepercq, J., Challier, J. C., Huston-Presley, L., Friedman, J. E., Kalhan, S. C., Catalano, P. M. (2002.). TNFα is a predictor of insulin resistance in human pregnancy. Diabetes 51(7):2207-13.

[20] Catalano, P. M., Huston, L., Amini, S. B., Kalhan, S. C. (1999.). Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. Am J Obstet Gynecol 180(4):903-16.

[21] Freemark. M. (2006.). Regulation of maternal metabolism by pituitary and placental hormones: Roles in fetal development and metabolic programming. Horm Res 65 Suppl 3:41-9.

[22] Catalano, P. M., Nizielski, S. E., Shao, J., Preston, L., Qiao, L., Friedman, J. E. (2002.). Downregulated IRS-1 nad PPARγ in obese women with gestational diabetes: relationship to free fatty acids during pregnancy. Am J Physiol Endocrinol Metab 282(3):E522-33.

[23] Herrera, E., Amusquivar, E., Lopez-Soldado, I., Ortega, H. (2006.). Maternal lipid metabolism and placental lipid transfer. Horm Res 65 Suppl 3:59-64.

[24] Desoye, G., Schweditsch, M. O., Pfeiffer, K. P., Zechner, R., Kostner, G. M. (1987.). Correlation of hormones with lipid and lipoprotein levels during normal pregnancy and postpartum. J Clin Endocrinol Metab 64(4):704-12.

[25] Darmady, J. M., Postle, A. D. (1982.). Lipid metabolism in pregnancy. Br J Obstet Gynaecol 89(3):211-5.

[26] Freinkel, N. (1980.). Banting lecture 1980: Of pregnancy and progeny. Diabetes 29(12):1023-35.

[27] Catalano, P. M. (2010.). Obesity, insulin resistance, and pregnancy outcome. Reproduction 140(3):365-71.

[28] Di Cianni, G., Miccoli, R., Volpe, L., Lencioni, C., Ghio, A., Giovannitti, M. G. et al (2005.). Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance. Diabet Med 22(1):21-5.

[29] Schaefer-Graf, U. M., Graf, K., Kulbacka, I., Kjos, S. L., Dudenhausen, J., Vetter, K., Herrera, E. (2008.). Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care 31(9):1858-63.

[30] Hytten, F. E., Thomson, A. M. (1968.). Maternal physiological adjustments. In: Assali, N. S. (Ed.). Biology of Gestation, Vol I. The Maternal Organism. New York: Academic Press

[31] Pipe. N. G. J., Smith, T., Halliday, D., Edmonds, C. J., Williams, C., Coltart, T. M. (1979.). Changes in fat, fat-free mass and body water in human normal pregnancy. Br J Obstet Gynecol 86(12):929-40.

[32] Innis, S. M. (2005.). Essential fatty acid transfer and fetal development. Placenta 26 Suppl A:S70-5.

[33] Saarelainen, H., Laitinen, T., Raitakari, O. T., Juonala, M., Heiskanen, N., Lyyra-Laitinen, T. et al (2006.). Pregnancy-related hyperlipidemia and endothelial function in healthy women. Circ J 70(6):768-72.

[34] Cunningham, F., Leveno, K., Bloom, S., Hauth, J., Rouse, D., Spong, C. (2010.). Williams Obstetrics, 23rd Ed. Chicago: McGraw-Hill Professional

[35] Schubring, C., Siebler, T., Kratzsch, J., Englaro, P., Blum, W. F., Triep, K. et al (1999.). Leptin serum concentrations in healthy neonates within the first week of life: relation to insulin and growth hormone levels, skinfold thickness, body mass index and weight. Clin Endocrinol 51(2):199-204.

[36] Pighetti, M., Tommaselli, G. A., D'Elia, A., Di Carlo, C., Mariano, A., Di Carlo, A. et al (2003.). Maternal serum and umbilical cord blood leptin concentrations with fetal growth restriction. Obstet Gynecol 102(3):535-43.

[37] Hauguel-de Mouzon, S., Lepercq, J., Catalano, P. (2006.). The known and unknown of leptin in pregnancy. Am J Obstet Gynecol 194(6):1537-45.

[38] Gohlke, B. C., Huber, A., Bartmann, P., Fimmers, R., Hecher, K., Bouret, S. G. et al (2006.). Cord blood leptin and IGF-I in relation to birth weight differences and head circumference in monozygotic twins. J Pediat Endocrin Metabol 19(1):3-9.

[39] Grisaru-Granovsky, S., Samueloff, A., Elstein, D. (2008.). The role of leptin in fetal growth: a short review from conception to delivery. Eur J Obstet Gynecol Reprod Biol 136(2):146-50.

[40] Henson, M. C., Castracane, V. D. (2006.). Leptin in pregnancy: An update. Biol Reprod 74(2):218-29.

[41] Lepercq, J., Guerre-Millo, M., Andre, J., Cauzac, M., Hauguel-de Mouzon, S. (2003.). Leptin: A potential marker of placental insufficiency. Gynecol Obstet Invest 55(3):151-5.

[42] Magoffin, D. A., Huang, C. T. F. (1998.). Leptin and reproduction. Endocrinologist 8(2):79-86

[43] Fuglsang, J. (2008.). Ghrelin in pregnancy and lactation. Vitam Horm 77:259-84.

[44] Riedl, M., Maier, C., Handisurya, A., Luger, A., Kautzky-Willer, A. (2007.). Insulin resistance has no impact on ghrelin suppression in pregnancy. Intern Med 262(4):458-65.

[45] Duggleby, S. L., Jackson, A. A. (2002.). Protein, amino acid and nitrogen metabolism during pregnancy: how might the mother meet the needs of her fetus? Curr Opin Clin Nutr Metab Care 5(5):503-9.

[46] Cetin, I., de Santis, M. S., Taricco, E., Radaelli, T., Teng, C., Ronzoni, S. et al (2005.). Maternal and fetal amino acid concentrations in normal pregnancies and in pregnancies with gestational diabetes mellitus. Am J Obstet Gynecol 192(2):610-7.

[47] van den Akker, C. H., Schierbeek, H., Dorst, K. Y., Schoonderwaldt, E. M., Vermes, A., Duvekot, J. J. et al (2009.). Human fetal amino acid metabolism at term gestation. Am J Clin Nutr 89(1):153-60.

[48] Galan, H. L., Marconi, A. M., Paolini, C. L., Cheung, A., Battaglia, F. C. (2009.). The transplacental transport of essential amino acids in uncomplicated human pregnancies. Am J Obstet Gynecol 200(1):91.e1-7.

[49] Kalkoff, R. K., Kadaraki, E., Morrow, P. G., Mitchell, T. H., Kelber, S., Borkowf, H. I. (1988.). Relationship between neonatal birth weight and maternal plasma amino acid profile in lean and obese nondiabetic women and in type I diabetic pregnant women. Metabolism 37(3):234-9.

[50] King, J. C. (1975.). Protein metabolism during pregnancy. Clin Perinatol 2(2):243-54.

[51] Calloway, D. H. (1974.). Nitrogen balance during pregnancy.In: Winick, M. (Ed.). Nutrition and fetal development. Philadelphia: Wiley & Sons pp 79-94

[52] Mojtahedi, M., de Groot, L. C., Boekholt, H. A., van Raijj, J. M. (2002.). Nitrogen balance of healthy Dutch women before and during pregnancy. Am J Clin Nutr 75(6):1078-83.

[53] Kalhan, S. C., Gruca, L. L., Parimi, P. S., O'Brien, A., Dierker, L., Burkett, E. (2003.). Serine metabolism in human pregnancy. Am J Physiol Endocrinol Metab 284(4):E733-40.

[54] Heenan, A. P., Wolfe, L. A., Davies, G. A. L., McGrath, M. J. (2003.). Effects of human pregnancy on fluid regulation responses to short-term exercise. J Appl Physiol 95(6):2321-7.

[55] Lindheimer, M. D., Davison, J. M. (1995.). Osmoregulation, the secretion of arginine vasopresin and its metabolism during pregnancy. Eur J Endocrinol 132(2):133-43.

[56] Øian, P., Maltau, J. M., Noddelaned, H., Fadnes, H. O. (1985.). Oedema-preventinve mechanisms in subcutaneous tissue of normal pregnant women. Br J Obstet Gynecol 9 92(11):1113-9.

[57] Lindheimer, M. D., Richardson, D. A., Ehrlich, E. N., Katz, A. I. (1987.). Potassium homeostasis in pregnancy. J Reprod Med 32(7):517-22.

[58] Brown, M. A., Gallery, E. D. M., Ross, M. R., Esber, R. P. (1988.). Sodium excretion in normal and hypertensive pregnancy: A prospective study. Am J Obstet Gynecol 159(2):297-307.

[59] Brown, M. A. , Sinosich, M. J., Saunders, D. M., Gallery, E. D. (1986.). Potassium regulation and progesterone–aldostero ne interrelationships in human pregnancy: A prospective study. Am J Obstet Gynecol 155(2):349-53.

[60] Kametas, N., McAuliffe, F., Krampl, E., Sherwood, R., Nicolaides, K. H. (2003.). Maternal electrolyte and liver function changes during pregnancy at high altitude. Clin Chim Acta 328(1-2):21-9.

[61] Power, M. L., Heaney, R. P., Kalkwarf, H. J., Pitkin, R. M., Repke, J. T. et al (1999.). The role of calcium in health and disease. Am J Obstet Gynecol 181(6):1560-9.

[62] Kovacs, C. S. Fuleihan, G. E. (2006.). Calcium and bone disorders during pregnancy and lactation. Endocrin Metab Clin North Am 40(4):795-826.

[63] Ilich, J. Z., Kerstetter, J. E. (2000.). Nutrition in bone helath revisited: a story beyond calcium. J Am Coll Nutr 19(6):715-37.

[64] Prentice, A. (2000.). Maternal calcium metabolism and bone mineral status. Am J Clin Nutr 71(5 Suppl):1312S-6S.

[65] Bardicef, M., Bardicef, O., Sorokin, Y., Altura, B. M., Altura, B. T., Cotton, D. B. et al (1995.). Extracellular and intracellular magnesium depletion in pregnancy and gestational diabetes. Am J Obstet Gynecol 172(3):1009-13.

[66] Kametas, N., McAuliffe, F., Krampl, E., Sherwood, R., Nicolaides, K. H. (2003.). Maternal electrolyte and liver function changes during pregnancy at high altitude. Clin Chim Acta 328(1-2):21-9.

[67] Weiss, M., Eisenstein, Z., Ramot, Y., Lipitz, S., Shulman, A., Frenkel, Y. (1998.). Renal reabsorption of inorganic phosphorus in pregnancy in relation to the calciotropic hormones. Br J Obstet Gynaecol 105(2):195-9.

[68] Catalano, P. M., Farrell, K., Thomas, A., Huston-Presley, L., Mencin, P., de Mouzon S. H. et al (2009.). Perinatal risk factors for childhood obesity and metabolic dysregulation. Am J Clin Nutr 90(5):1303-13.

[69] Villamor, E., Cnattingius, S. (2006.). Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet 368(9542):1164-70.

[70] Center for Disease Control and Prevention (2007.). National diabetes fact sheet. Atlanta: US Department for Health and Human Services, Centers for Disease Control and Prevention

[71] Kim, C., Neston, K. M., Knopp, R. H. (2002.). Gestational diabetes and the incidence of type 2 diabetes. Diabetes Care 25(10):1862-8.

[72] Ray, J. G., Vermuelen, M. J., Schull, M. J., Redelmeier, D. A. (2005.). Cardiovascuar health after maternal placental syndromes (CHAMPS): population-based reprospective cohort study. Lancet 366(9499):1797-803.

[73] Mosca, L., Banka, C. L., Benjamin, E. J., Berra, K., Bushnell, C., Dolor, R. J. (2007.). Evidence-based guidelines for cardiovascular disease prevention in women: 2007 Update. Circulation 115(11):1481-501.

[74] Maas, A. H. E. M., van't Hof, de Boer, M. J. (2007.). Cardiovascular risk in women after metabolic complications in pregnancy. Neth Heart J 15(12):415-7.

[75] Redman, C. W., Sacks, G. P., Sargent, I. L. (1999.). Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynaecol 180(2 Pt 1):499-506.

[76] Grino, M. (2005.). Prenatal nutritional programming of central obesity and the metabolic syndrome: role of adipose tissue glucocorticoid metabolism. Am J Physiol Regul Integr Comp Physiol 289(5):R1233-5.

[77] Ong, K. K. L., Ahmed, M. L., Emmet, P. M., Dunger, D. B. (2000.). Association between postnatal catch-up and obesity in childhood: prospective cohort study. Br Med J 320(7240):967-71.

[78] Phillips, D. I. W. (1998.). Birth weight and the future development of diabetes. A review of the evidence. Diabetes Care 21 Suppl 2:B150-5.

[79] Björntorp, P., Rosmond, R. (2000.). Obesity and cortisol. Nutrition 16(10):924-36.