

## The Hormonal Pathophysiology of Fetal Macrosomia

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## 1. Summary

The pathophysiology of macrosomia is related to the associated maternal or fetal condition that accounts for its development. In general, poorly controlled diabetes, maternal obesity, and excessive maternal weight gain are all associated with macrosomia and have intermittent periods of hyperglycemia in common. Hyperglycemia in the fetus results in the stimulation of insulin, insulin-like growth factors, growth hormone, and other growth factors, which, in turn, stimulate fetal growth and deposition of fat and glycogen. Leptin and ghrelin also may play a role in enhanced fetal growth.

## 2. Introduction

As macrosomia is the fetus with birth weight over 4000 grams, higher than 90th percentile for gestational age (including race, socio-economic and geographic factors) or +2 SD of average birth weight according to gestational age. Maternal and neonatal morbidity is in these cases much higher and it increases, if the birth weight is over 4500 grams.

## 3. Risk Factors

- Diabetes mellitus
- Glucose intolerance of the mother
- Multiparity
- Macrosomic fetus in previous pregnancy
- Post-term delivery

- Obesity of mother
- Excessive weight gain during pregnancy
- Inherited height and weight from parents

Maternal mortality and morbidity is determined by higher number of caesarean sections, complications during birth per vias naturales in meaning of prolonged delivery, delivery ended surgically, larger injuries of birth canal, hemorrhage after delivery, rupture of uterus. Neonatal mortality and morbidity is associated with shoulder dystocia, which is 10-times higher in macrosomic fetuses than in fetuses with birth weight less than 4000 grams. Also injuries of brachial plexus are 20-times more often in fetuses with birth weight over 4500 grams [1]. The goal of this literature review article is to give a closer complex look of obstetrician on development of macrosomia, because macrosomic fetus and its mother are still at higher risk on intra-partial injuries and perinatal morbidity and mortality, despite the progress over the decades in this field.

## 4. Fetal Macrosomia

Main factors, which participate in pathophysiological mechanism in development of macrosomia, are substances influencing growth of fetus (growth-hormone – GH, insulin-like growth hormone – IGF), substances influencing nutrition of fetus (leptin, ghrelin), and development of diabetes (insulin).

## 5. Growth Hormone (GH) and Insulin-Like Growth Hormone (IGF)

Growth hormone (somatotropin) is a polypeptide synthesized, accumulated and released into the blood stream by somatotrophic cells of frontal lobe of hypophysis. It can be detected in serum of the fetus in the end of I. Trimester of gravidity. Studies in late decades confirmed, that key hormonal axis “GH – IGF” is playing crucial role in linear growth [2]. Concentration of placental growth hormone (PGH) and IGF-I in mother’s serum are relevantly corelating during the whole pregnancy, which can suppose, that placental growth hormone influences fetal growth by using IGF-I. Placental growth hormone is not detectable in fetal circulation. It is a product of GH-V gene, which is located in placenta. Receptors for growth hormone is located in villous trophoblast, as well as extra-villous trophoblast and they bind placental GH-receptors with similar affinity as hypophyseal GH. Activation of GH-receptors of placental growth hormone leads to the same intra-cellular signal as in hypophyseal growth hormone. That’s why the supposition, that placental GH acts as auto- or paracrine hormone of placental growth and affects placental function.

Chellakooty et al., [3] rated connection between levels of PGH and IGF-I in maternal serum and fetal growth in 89 women with single pregnancy, who gave birth between 37-40 gestational week. The levels of PGH were detected in all samples from 5th week of pregnancy and were increasing till 37th week of pregnancy, where they reached the peak with level 22 ng/ml (range 4, 6-69,2 ng/ml). Right after birth these levels decreased. The change in levels of PGH between 24,5th and 37, 5th gestational week positively correlated with rapid fetal growth, birth weight and levels of IGF-I. The study didn’t find any connection between size of placenta in birth and changes of placental GH levels, which can lead to supposing, that PGH is not a primary regulator of placental growth. Placental GH though regulates the transport of nutrition through placenta to fetus.

## 6. Leptin and Ghrelin

Important sight on mechanism of control of intrauterine growth can be evaluated by studies, which change the traditional idea, that fat tissue is the source of energy, into idea that it is very active endocrine organ, which excludes higher number of important metabolic hormones, energetic homeostasis and growth [4]. Indispensable factors of this control system are leptin and ghrelin, which signalize nutrition status and levels of energy stock of hypothalamic center [5].

Leptin is a proteohormone produced in adipose tissue but also in lower levels in muscles, liver and placenta. It plays important role in homeostatic regulation of body weight. It increases importance of intrauterine environment on development of obesity. Epidemiologic studies are trying to prove, that unfavorable intrauterine

environment caused by wrong nutrition of mother or placental insufficiency can “program” susceptibility of fetus to cardiovascular or metabolic diseases. Adipokines, and especially leptin, are in research for potential biomarkers, which can predict development of obesity, hypertension, insulin resistance or diabetes mellitus type 2 [6].

During pregnancy is leptin produced by three different tissues: maternal adipose tissue, fetal adipose tissue and placenta. Most of placental leptin is released into maternal circulation, while only small amount gets to the fetus. According to its high molecular weight is leptin not able to cross the placental barrier. This fact leads to independent levels of maternal and fetal leptin. Studies show, that leptin is highly concentrated in umbilical blood.

Karakosta et al. [7], in years 1994-2009 proved in 44 studies the positive correlation between levels of leptin in umbilical blood in fetuses with higher birth weight. Despite of that, leptin is not reliable index of fetal adiposity, it is though a regulator of fetal growth.

Wiznitzer et al. [8], in their studies tried to prove correlation between serum leptin, insulin-like growth factor I (IGF-I) and levels of insulin in macrosomic fetuses. In 52 women, who gave birth to macrosomic newborn in term and didn’t suffer diabetes, there were collected samples from maternal veins and umbilical arteries. Concentration of leptin in umbilical blood was evaluated as a risk factor of development of fetal macrosomia. Also there was proved statistically significant correlation between levels of leptin in umbilical blood, IGF-I and birth weight. Correlation between levels of insulin in umbilical blood and level of birth weight wasn’t statistically important.

Lepercq et al. [9], measured levels of insulin, IGF-I, IGFBP 3 and leptin from umbilical blood in 28 macrosomic fetuses and 21 fetuses of proper age-gestational weight. Macrosomic fetuses were divided into group of symmetric and asymmetric according to ponderal index. They proved, that middle levels of leptin concentration were significantly higher in asymmetric fetuses.

Ghrelin is a hormone responsible for feeling of hunger. First it was discovered in stomach of rats. It contains 28 amino acid residues and it is formed mostly by entero-endocrine cells of gastric and enteric mucosa. It influences also the growth of organism, because it stimulates feeling of hunger by mediating exclusion of growth hormone [10].

In latest findings there is supposition that levels of maternal and fetal ghrelin are increasing with increasing of length of pregnancy. Nakahara et al [11] proved, that placenta contributed to circulating level of maternal ghrelin in higher state of gestation. Maternal ghrelin rapidly and easily penetrates to fetus. They also proved that despite of fetal ghrelin comes from placenta and/or maternal blood, acyl- and des-acyl ghrelin are detected in maternal and fetal circulation in second period of pregnancy.

## 7. Insulin

The most important fetal growth factor in later gestational state is insulin [12]. Mechanism and pathophysiology of fetal nutrition in utero is not that clear and share of saccharides, lipids and proteins contributing to energetic income of fetus are not very well known. Endocrine changes during pregnancy are influencing adequate glucose support of fetus. In second part of pregnancy there are high levels of placental lactogen, cortisol and prolactin, which contribute to development of insulin resistance, which leads to post-prandial hyperinsulinemia. In women, who are not able to compensate hyperinsulinemia there can come to development of hyper-glycemia (gestational diabetes mellitus). Because the fact that glucose penetrates placenta by facilitated diffusion, the result is fetal hyper-glycemia. That leads to fetal hyper-insulinemia with transfer of glucose to fetal cells, which leads to fetal macrosomia. Fetal hyper-insulinemia causes macrosomia either directly or as anabolic consequence on nutrition income and supplementation, or indirectly through peptides as IGF I and II. In pregnant women with diabetes, although strict glycemic controls, is the fluctuation of maternal glucose concentrations higher than in women, who don't have diabetes. It is possible, that also a short period of hyper-glycemia can stimulate hyper-plastic fetal pancreas to react by disproportional release of high levels of insulin. Fetal hyper-insulinemia, which is connected with redundant transfer of nutrition to fetus has a key role in pathophysiology of diabetic fetopathy. It causes acceleration of its growth especially in last 10 weeks of gestation. Newborns of diabetic mothers are classified as high-risk babies with aggravated post-partial adaptation [13].

## 8. Conclusion

Number of newborns with higher birth weight is still increasing. This is according to the trend of mothers with bigger height, BMI (body mass index), weight growth during pregnancy and diabetes. These newborns with higher birth weight have higher risk of developing diabetes mellitus II. type in their lives, but also risk of occurrence of breast cancer in post-menopausal age. Management of delivery of these kinds of newborns is definitely a challenge for obstetrician and there isn't worldwide consensus for these cases. San San Aye, the consultant of North Devon District Hospital, noted, that excessive birth weight increases risk of shoulder dystocia and increases the number of caesarean sections. For clinical practice there is importance of knowing the risks of fetal macrosomia and also evaluate long-term consequences for mother and for child. In women, who already gave birth to macrosomic fetus there is higher likeliness that another child will have higher birth weight. Also the changes of maternal BMI during the pregnancy should point out the supposition of developing fetal macrosomia. Management of this situation should consider all mentioned circumstances [14].

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