MACROSOMIA. A SYSTEMATIC REVIEW OF RECENT LITERATURE

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Abstract

Background and aims: *The obesity and overweight rate among women of childbearing age and fetal macrosomia associated with different birth injuries are very frequent all over the world and with an increasing incidence. The huge amount of published literature on this topic in the last decade is putting the practioners in a very challenging position.* ***Material and method:*** *We have done a systematic review on the recent literature (last five years) based on science direct database.* ***Results:*** *A total of 5990 articles were identified and after successive exclusion of some of them, 48 were deeply analyzed. The results were grouped in following topics: risk factors for fetal macrosomia, the pathophysiology of macrosomia, prenatal clinical and lab diagnosis and prevention of macrosomia.* ***Conclusions:*** *Considering the maternal, fetal and neonatal complications of macrosomia, the counseling, and monitoring of the pregnant women risk group are of particular importance for adopting a low calorie / low glycemic diet and avoiding a sedentary behaviour. Long-term follow-up of the mother and the macrosomic baby is required because of the risk of obesity, diabetes, hypertension, and metabolic syndrome later in life.*

key words: *fetal macrosomia, large for gesational age, obesity, pregnacy outcome*

Background and aims

Among women of childbearing age, the overweight rate in the USA is 20.2%, and in the UK the obesity rate is around 20%. Accordingly, every year, all over the world, newborns with 4000g or more represent about 10%, and about 1.5% of them weigh 4500g or more [1]. Macrosomia is associated with birth injury: shoulder dystocia, fracture of the clavicle and perinatal asphyxia. The rate of stillbirth is almost double in macrosomic fetuses [2]. These children are later in life exposed at risk for obesity, cardiovascular problems, and metabolic syndrome [3].

The excessive fetal growth is defined in the medical literature by two terms: "macrosomia" and "large for gestational age". Several criteria were proposed for the diagnostic of fetal macrosomia: the weight at delivery bigger than 4000g (8lb, 13oz) [2,4], 4500 g (9lb, 15oz) [5,6], regardless of the gestational age, or weight at delivery exceeding the 90th percentile, or above 2 standard deviations, for gestational age, and ethnicity [7,8]. This definition was used to point the weight above which delivery complications

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appear, like shoulder dystocia. Although the risk for the mother and the baby is high when the baby weights between 4000-4500g, this risk is higher when the weight exceeds 4500g.
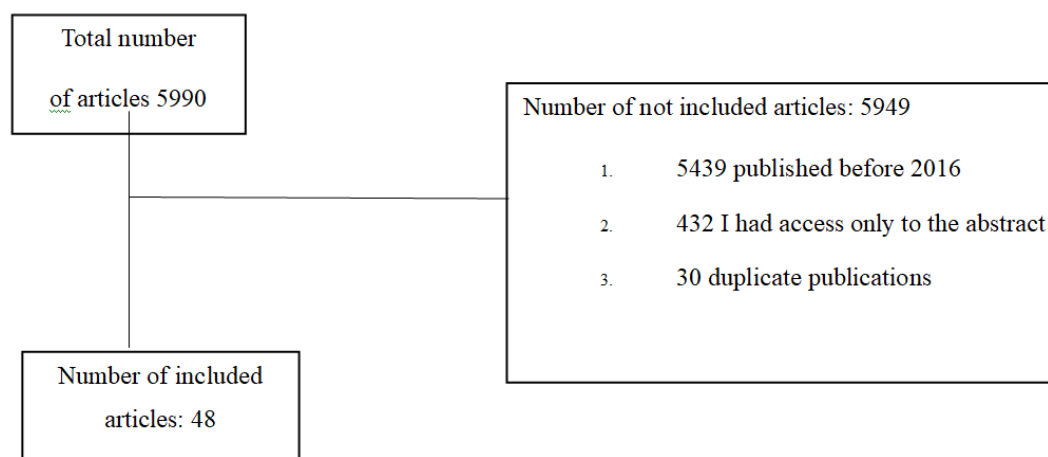
Materials and Method

We have done research on science direct database. (www.sciencedirect.com). The flowchart of our selection is in Figure 1.

Figure 1. *Study workflow diagram.*

Results

Data was extracted and grouped into following topics: risk factors and pathophysiology of fetal macrosomia, clinical and laboratory prenatal diagnosis of fetal macrosomia, prevention, maternal and fetal complications, and co-morbidities later in life.

Risk factors for fetal macrosomia

Although many risk factors can lead to fetal macrosomia, many women which present risk factors give birth to normal weight children. The cited risk factors are:

- The physical constitution of both parents, height and weight [2,9]; maternal overweight before pregnancy, body-mass index (BMI) over 30 [2,10,11]; father being overweight [5,12];
- Excessive weight gain throughout pregnancy [1,5,13-16], especially in the first trimester of pregnancy [17], and the overconsumption of sweets throughout pregnancy [9];
- Maternal macrosomia: women which were born with macrosomia tend to give birth to macrosomic children; Ahlsson et al. showed that pregnant women which weighed over 4000g as newborns have double risk to give birth to macrosomic babies [11];

- Women which gave birth to a bigger child than 4000 g have a bigger probability to deliver a macrosomic baby [18];
- Multiparity [5,11,16,19], with every newborn the weight increase with 100-150g [1];
- Male newborn [1,5]; newborn baby boys tend to weigh more than female babies [16];
- Post-term gestation (over 42 weeks) [5,10,11,13,16]; the fetus gain about 150-200g per week near term; macrosomic babies at term represent 1%, and post-term 3-10% of deliveries [2];
- Hispanic race; the frequency of gestational diabetes mellitus is higher among this ethnic group, but even after adjusting for diabetes, the newborn babies of Hispanic women tend to weigh more [16];
- Age: under 17 years old at pregnancy [2,5], or over 40 years old [5,11,12];
- Diabetes with onset before pregnancy and gestational diabetes are associated with fetal macrosomia [1,5,12,18];

- High blood pressure [19]
- Genetic diseases which lead to macrosomia, like Sotos Syndrome, in which appears a mutation at chromosome 5, and Wiedermann-Beckwith Syndrome [16] in which the chromosome 11 is affected;
- Idiopathic polyhydramnios [20].

No combination of these risk factors can anticipate macrosomia well enough to be used in medical practice. In most of the newborns over 4500 g, no risk factor was found.

The pathophysiology of fetal macrosomia

The fetal growth is a complex process of interaction between the mother, the placenta and the fetus, in which genetic, metabolic, and endocrine factors are involved [21].

The macrosomia can be either symmetric, in post-term pregnancy, or due by genetic factors, when the head circumference, the abdominal circumference and the weight exceed the 90th percentile for the gestational age; either asymmetric, in diabetic pregnancies, when abdominal and thigh diameters increase, compared with the head and the femoral dimensions which are according to the gestational age. Kurishita et al, showed that in normoglycemic, non-diabetic pregnancies, undetected hyperglycemic episodes influence the new born's ponderal status [22]. It was noticed that 80% of the macrosomic babies are delivered by undiagnosed mothers with hyperglycemia.

The excessive gestational weight gain, poorly controlled diabetes, and maternal obesity, all have in common intermittent periods of hyperglycemia and leads to fetal hyperglycemia, which triggers fetal insulin release, insulin-like growth factors, and other growth factors and growth hormones. Due to hyperinsulinemia, the fetal adipose tissue is more abundant, the liver has a bigger amount of glycogen, and the intrauterine growth is accelerated [2]. The excessive fetal growth is often a diabetes mellitus marker. A Swedish study on pregnant women with gestational diabetes mellitus showed that fetal macrosomia is especially associated with elevated capillary fasting glycemia [10].

Olmos showed that at overweight and obese pregnant women with gestational diabetes mellitus, the TG (triglycerides) are partially responsible for the fetal overgrowth [14], despite the good glycemic control throughout pregnancy [23]. Studies conducted on siblings of obese mothers, born before and after bariatric surgery, showed that the birth weight decreased with the decrease of the maternal BMI, and their genetic expression was different, showing improvement at newborns after surgery [17].

Prenatal diagnostic of macrosomia

The measurement of the height of the uterus, and Leopold maneuvers, in order to estimate fetal dimensions and presentation, can be influenced by the mother's height, amniotic fluid, bladder filling, pelvic tumor (cyst, fibroma), and fetal position.

Two-dimensional ultrasound investigation is the most common method of investigating pregnant women. The diagnosis of fetal macrosomia must be related to the clinical situation, using specific growth curves, indexes and formulas with different degrees of sensitivity and specificity. Unfortunately, errors are increasing with the fetal weight.

If after two consecutive scans at 3-4 weeks, estimated fetal weight (EFV), or abdominal circumference (AC) is bigger than 90% for gestational age, is useful to start monitoring the pregnant woman [5]. Monitoring of amniotic fluid and fetal growth is recommended every four weeks starting from 20 weeks of pregnancy, and every two weeks after 28 weeks, in diabetes before pregnancy, or gestational diabetes.

Polyhydramnios may indicate a poor glycemic control [5]. Abdominal circumference measurements 2 weeks before birth are sensitive, specific and predictive in about 90% of cases. In approximately 10% of the cases, errors may occur due to obesity of the mother, oligohydramnios, non-performing measuring instruments, or due to the examiner's lack of experience [5].

In the first trimester of pregnancy, is also useful to measure the placenta. The insulin growth factor II secreted by the obese pregnant women stimulates the placental growth [1]. A large size placenta in the first trimester of pregnancy allows a bigger nutrient transfer, and this rate of exchange remains throughout the whole pregnancy [3].

A study on nondiabetic pregnant women showed a correspondence between the fetal dimensions and his liver perfusion. Growth factors are synthesized in the fetal liver, and their production depends on the glucidic metabolism and the fetal liver venous irrigation. In macrosomic pregnancies, the liver irrigation is amplified at the end of pregnancy, compared with normal weight fetuses [21]. Is has been noticed a decrease of the pulsatility index (PI) of the umbilical artery in newborns larger than 4000g, versus normal weight [5].

Tridimensional ultrasound allows a better estimation of the fetal weight and is more accurate in soft tissue monitoring: shoulders, abdominal wall, thighs, and perioral region [5]. The soft tissue encounters the most changes in fetal growth disorders.

Magnetic resonance imaging (MRI) has the highest resolution and is more sensitive than the two-dimensional ultrasound [24]. In connection with maternal hyperglycemia, MRI scans show an increased fetal abdominal visceral adiposity. The shoulders width at examination was the same as in the measurement after birth. The

inconvenience is the high cost, therefore prior indication, preliminary examinations are required [5].

The counting of fetal movements is recommended in diabetic pregnancies from week 26-28. The perception of 10 movements within two hours is a good sign. It was shown that fetal activity is amplified when the blood sugar is high [5], in order to counteract the effects of maternal hyperglycemia. If a decrease in fetal movements is encountered, electronic monitoring and biophysical profile are recommended, in order to assess vitality [5].

Laboratory tests

In order to diagnose diabetes mellitus, a first-trimester pregnancy screening is performed at women with high risk (high glycemia: fasting, or occasional; history of delivery of macrosomic babies, or age over 40), and a universal screening between 24-28 weeks of pregnancy for gestational diabetes [25]. In a study on 25-32 weeks pregnant healthy women, without a history of diabetes mellitus, Mossayebi showed that fasting hyperglycemia and hypertriglyceridemia are independent variables that can predict a large for gestational age (LGA), or a macrosomic baby [26]. A Brazilian study on 199 pregnant women showed that LGA deliveries were associated with high BMI and higher levels of leptin in early pregnancy, higher glycemia in the second trimester, and lower adiponectin levels in the third trimester of pregnancy, compared to women with normal weight newborns. High BMI was associated as well with high maternal LDL (low-density lipoproteins) concentrations, and maternal HDL (high-density lipoproteins) concentrations were inversely correlated with the fetal weight [27].

Obesity is often associated with thyroid hormone dysfunction in both the mother and the fetus [28], and there is an inverse association of

maternal fT4 hormone in early pregnancy and the birth weight, especially in males; women with subclinical hypothyroidism have increased odds to deliver LGA babies [29]. TSH was slightly increased in newborns of obese women but didn't change at the mother [28]. Modi et al showed a link between the increase maternal BMI and the fetal abdominal fat content. The newborns of obese mothers have an increased insulin resistance from birth. It was shown that the altered function of the hypothalamic-pituitary-adrenal axis in obese pregnancy is correlated with prolonged pregnancy and macrosomia [30].

Intrahepatic cholestasis of pregnancy appears at some pregnant women after 30 weeks of gestation and is manifesting through pruritus (without any dermatological issue), elevated bile acids, elevated glutamic pyruvic transaminase (ALAT), and dyslipidemia (low level of HDL, high level of LDL, and high level of TG). Often, after cholestasis, gestational diabetes mellitus occurs, together with a postprandial hyperglycemia [31].

Pregnant women who delivered macrosomic babies also had in the first trimester of pregnancy high levels of PAPP-A (plasma protein A), and of beta-hCG (beta-chorionic gonadotropin) [3]. Neonatal evaluation for hypoglycemia, polycythemia, hyperbilirubin-emia, and ionogram is indicated for all macrosomic babies, due to maternal hyperglycemia which is sometimes not detected before delivery. Long-term follow-up is required for these children, because of the risk for obesity, cardiovascular problems, and metabolic syndrome [3]. Recent data show an association between childhood obesity and liver cancer later in life [17].

Prevention of fetal macrosomia

The diet, the physical activity, and the body/mass index need to be considered, as well as the familial history related to diabetes mellitus of the pregnant women in order to evaluate the risk for macrosomia [5]. The recommended weight to gain during pregnancy, is 28-40 lbs, for BMI <18.5, 25-35 lbs for BMI 18.5-24.9, 15-25 lbs for BMI 25.0-29.9, and 11-20 lbs for BMI >or=30.0 (Institute of Medicine, IOM, 2009) [2] Going through a low carbohydrate/ low calories diet in cases of overweight, and avoiding excessive weight gain during pregnancy, can prevent fetal macrosomia [3,32,33] in over 33% of the cases [30]. Daily physical exercise is associated with a low rate of large for gestational age babies [3]. Dietary and physical activity have to begin before pregnancy, or in early pregnancy [34].

In cases of hyperglycemia due to a heterozygous mutation of hexokinase, the fetal genotype is responsible for the baby's growth, showed Ali J Chakera et al. If the mutation is inherited by the baby, and hyperglycemia is not treated, its weight remains normal, while intensive treatment may reduce fetal growth [35].

Complications of fetal macrosomia

Morbidity and mortality linked to fetal macrosomia can be divided into: maternal, fetal and neonatal. A recent study of the effects of macrosomia on fetal mortality showed that higher fetal mortality rates are associated with a birth weight higher than 4250g for the newborns of nondiabetic mothers, and of 4000g for those of diabetic mothers [2].

Maternal

Macrosomia is associated with a double incidence of cesarean deliveries [2]. In the case of vaginal delivery, perineal laceration may

occur [2,5]. When the weight of the newborn is over 4500g, the incidence of postpartum hemorrhage is doubled [2]. The frequency of blood transfusion is five times higher when the baby is more than 4500g, compared to normal size babies [2].

Neonatal

Fetal macrosomia increases the number of instrumented deliveries and complications at birth. The incidence of neonatal injuries is much higher for vaginal delivery. Asymmetric macrosomia (diabetic pregnancies), with visceromegaly, excess muscle mass, abdominal and scapular fat, large shoulders, predispose to humeral dystocia, compared to macrosomic babies of nondiabetic mothers [5]. Humeral dystocia appears in approximately 0.2% of medium-sized newborns; between 4000-4500g, the risk increases up to 5%; and over 4500g, is around 30% [5]. Clavicular fracture and humeral fracture can appear in around 10% of shoulder dystocia cases, but the healing will be without consequences [5];

Brachial palsy (Erb-Duchenne palsy, due to C5-C8-T1 damage, more often on the right side) [9], occurs in 4% to 40% of cases, fortunately only in 10% of the cases the healing is not complete [5].

Hypoxia, respiratory distress syndrome, and cerebral ischemia can occur in 0.5-23% of the cases of humeral dystocia. The delivery interval between head and body is critical, the risk increase over 5 minutes. Intracerebral hemorrhage may appear, and 0.4% of the newborns die. If unlocking maneuvers fail [5], macrosomic newborns have a high need for oxygen, which leads to high erythropoiesis and polycythemia. After the destruction of these cells, hyperbilirubinemia and neonatal jaundice occur [5]. Metabolic complications and hypoglycemia may also occur. The need for intensive care services is greater when the weight of the newborn exceeds 4500 g.

Fetal

More often, the fetus of the diabetic mother develops metabolic disorders (anaerobic metabolism, with lactic acid accumulation) which leads to stillbirth [2]. Stillbirth rate is almost double in macrosomic babies [2]. In diabetic pregnancies, mortality occurs in about 8/1000 of the cases. Between 4500g and 5000g, the mortality rate is fewer than 2/1000; and between 5000g and 5500g, this rate is 5 to 18 deaths per 1000 deliveries in non-diabetic pregnancies and approximately 40 deaths per 1000 deliveries in diabetic pregnancies [2].

Co-morbidities later in life

Studies conducted in Sweden, Finland and Denmark showed that BMI at age of 18-26 was associated with birth weight [17,36]; 1 kg increase of birth weight was associated with a 50% risk for overweight at age of 9-14 years, showed an American study. The abdominal circumference reflects the visceral adiposity and is a good predictor of cardiovascular pathology and metabolic syndrome in adult life. It was shown that breastfeeding has a protective effect against developing overweight and obesity later in life, but unfortunately, obese women are able to breastfeed only for short time, or at all [17].

Conclusions

Considering maternal, fetal and neonatal complications of macrosomia, the counseling, and monitoring of the pregnant women risk group are of particular importance for adopting a low calorie / low glycemic diet and avoiding a sedentary behaviour. Long-term follow-up of the mother and the macrosomic baby is required because of the risk of obesity, diabetes, hypertension, and metabolic syndrome later in life.

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