Introduction

The term macrosomia is used to describe a newborn with excessive birth weight. Macrosomia defined as birth weight higher than 4000 g or more,it is encountered in up to 10% of deliveries***(Berkuset al.,1999).***

Apelin is a novel bioactive peptide,identified as the endogenous ligand of the orphan G protein-coupled receptor, APJ(putative receptor protein related to the angiotensin receptor AT1). It has a widespread pattern of expression in human tissues***(Falco et al.,2002)***.It is produced in several organs of the body, including brain, lung, lactating breast and gastrointestinal tract***(O'Carroll et al., 2000).***

Moreover the presence of apelin hasbeen documented in human placental tissue, indicating an important role ofthis peptidein fetal development, through a correct regulation of placenta formation during pregnancy ***(Cobellis et al.,2007).***

Recently, apelin has been identified as a novel adipokine, secreted in substantial amounts by adipose tissue in a regulated manner.In this respect, apelin is up regulated by obesity and hyperinsulinemia.Furthermore, insulin exerts a direct positive action on adipocyte apelin production both in vitro and in vivo and may influence plasma apelin levels in obese subjects ***(Boucher et al.,2005).***

Beside investigating the role of adipokines in whole body metabolism, many studies have explored their involvement in intrauterine growth***(Briana et al.,2009)***.

However, to our knowledge, there is no currently available information related to cord blood apelin concentration in full term macrosomic infants.

Aim of the Work

- To determine cord blood apelin concentrations in full term macrosomic neonates and to correlate it to insulin level.

- To study the relation between cord blood apelin concentrations and maternal diabetes, birth weight, gender and parity.

Macrosomia

Fetal macrosomia has been defined by some investigators as a birthweight of 4 kg or above.Some authors, however, consider a fetus withbirth weight 4.1 kg and aboveor 4.2 kg and above as fetal macrosomia. Otherstudies, utilising population specific growth curves, categories infantswith a birth weight above the 90th percentile as large for gestational age (LGA)***(Martin et al.,2006)***.

Epidemiology:

Among liveborn infants in the United States born in 2008, the incidence ofLGA based on theabove grades of macrosomia is 6.6, 0.9, and 0.1 percent for birth weights of 4000 to 4499 g, 4500 to 4999 g,and >5000 g, respectively.The birth rates for all three grades of LGA have declined in the United Statesfrom 1990 to 2008***(Martin et al.,2010)***.

However, in other countries (eg, Sweden and Australia), the reported incidence of LGAbirths has increased. In these countries, the rise in proportion of neonates born LGA was thought to bedue to a decrease exposure to prenatal smoking, and increases in maternal age and weight, and gestationaldiabetes***(Hadfield et al.,2009).***

Race and ethnicity

Racial and ethnic factors influence birth weight. In a study from the United States that included all term singleton live births

from 1995 to 1997, mothers who were white, American Indian, or Samoan were disproportionately overrepresented in the group with LGA offspring ***(Boulet et al.,2003).***

In contrast, black mothers were underrepresented. In another report of mothers with gestational diabetes, macrosomia occurred significantly more often in Latino than black infants (50 versus 19 percent) ***(Homko et al., 1995).***

Male infants weigh more than female infants throughout gestation; as a result, more macrosomic infants are male. In one report, males were more likely than females to have birth weights greater than 4500 g ***(Andrew et al.,1991).***

Risk factor:

Although the mechanisms that control fetal weight gain and growth arepoorly understood, excessive fetal growth appears to be due to increase delivery of nutrients to the fetus,which is influenced by genetic and intrauterine environmental factors, or a combination of the two***(*Gluckman& *Hanson,2004).***

Genetic factors:

Genetic syndromes

Several genetic disorders are characterized by early excessive growth resulting in an LGA infant***(Boulet et al.,2003)***. They include Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome, Sotos syndrome, Weaver syndrome, and Berardinelli lipodystrophia.

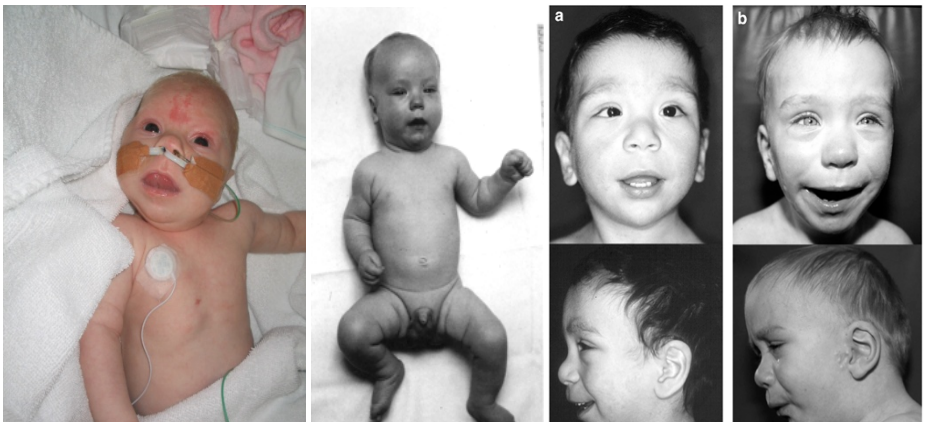

Figure (1): Beckwith-Wiedemann, Sotos syndrome and Weaver syndrome

Maternal factors:

A. Maternal Diabetes

Historically, infants born to mothers with diabetes have been at significantly greater risk for spontaneous abortion, stillbirth, congenital malformations, and perinatal morbidity and mortality. Fetal and neonatal mortality rates were as high as 65% before the development of specialized maternal and neonatal care. Over the past three decades, practitioners have sought to improve the outcome of diabetic pregnancies so that the results approach those of non-diabetic pregnancies ***(Potter et al., 2006).***

The Pedersen hypothesis and diabetic fetopathy:

Most, but not all, of the fetal and neonatal sequelae of diabetes during gestation are a function of maternal glycemic control. This concept had its ontogeny in the Pedersen hypothesis, which states that maternal hyperglycemia results in fetal hyperglycemia because glucose readily traverses the placenta.

Before 20 weeks' gestation, the fetal islet cells are not capable of responsive insulin secretion, and the main pathologic condition to which the embryo and early fetus are subjected is hyperglycemia. After 20 weeks' gestation, the fetus has a functioning pancreas and is responsible for its own glucose homeostasis, because maternal insulin does not cross the placenta in appreciable amounts.Unchecked fetal hyperglycemia results in hypertrophy of fetal pancreatic islets and hyperinsulinemia. The pathologic conditions in the late gestation fetus and newborn IDM are the result of fetal hyperglycemia, hyperinsulinemia, or the combined effects of the two***(Pedersen,1977).***

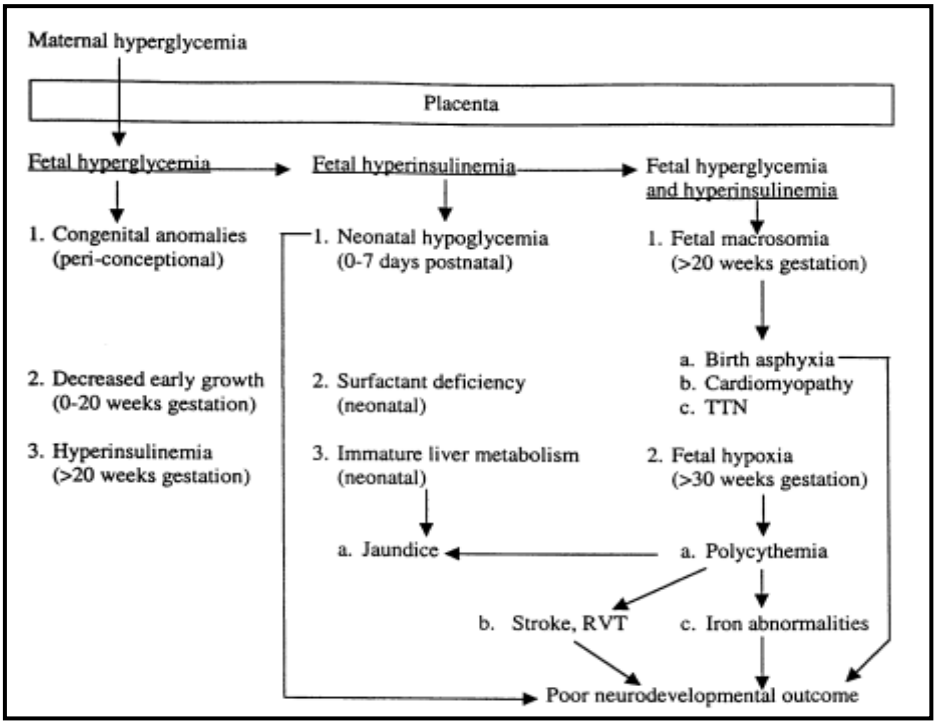

Figure (2): The fetal and neonatal evetns attributed to fetal hyperglycemia (column 1), fetal hyperinsulinemia (column 2), or both in synergy (column 3). Time of risk is denoted in parentheses ***(Joan et al.,2004)***

Diabetes in pregnancy is associated with an increased risk of complications in both the mother and fetus. Perinatal outcome is related to the onset and duration of glucose intolerance and to the severity of the disease. The White classification, which is based upon the age of onset and duration of maternal diabetes and the presence of vasculopathy, is used to estimate prognosis and risk factors for fetal compromise***(Diamond et al.,1987).***

Complications are minimal in infants of mothers with gestational diabetes. In contrast, hyperglycemia-induced teratogenicity occurs almost exclusively in pregestational diabetes. The most difficult pregnancies for the mother and fetus occur in diabetic women with renal, cardiac or retinal disease. Prognosis also is affected by complications of pregnancy. As an example, pre-eclampsia is twice as common in diabetic compared to normal pregnancies (9.9 percent versus 4.3 percent), and the incidence rises with increasing severity of diabetes***(Garner et al.,1990)***.

Pre-eclampsia frequently is associated with premature delivery, which also contributes to morbidity. In a report of 110 diabetic pregnancies delivered before 37 weeks gestation, one-third was delivered prematurely because of pre-eclampsia***(Greene et al.,1989).***

Anthropometric measurements differ between macrosomic IDMs and non-IDMs of similar weight and length at birth. IDMs have greater shoulder and extremity circumference, body

fat, and upper extremity skinfold, and decreased ratio of head-to-abdominal circumference. These alterations in body shape may contribute to the higher incidence of shoulder dystocia in IDMs***(McFarland et al.,1998)***.

B. Maternal obesity:

Macrosomia occurs more frequently with maternal obesity. In one report,theincidenceofbirthweightmorethan4500gwas1.4,2.0 and 3.6 percent in women with average overweight or very over weight pre-pregnancy size (BMI 19.8 to 26, >26 to 29, >29 kg/m2, respectively)***(Hedderson et al.,2006).***

C. Excessive maternal weight gain:

Maternal weight gain during pregnancy also influences birth weight; excessive weight gain is associated with macrosomia. In recent studies, 30 percent of women of average weight gained more than 40 pounds during pregnancy; this weight gain significantly increased the incidence of high birth. In another series, women with both higher body mass indices and weight gains delivered the largest infants***(Andrew et al.,1991).***

D.Prolonged gestation:

Macrosomia occurs more frequently as the duration of gestation increases, especially if pregnancy is prolonged. The incidence of macrosomia in a population-based study increased from 1.6 percent for term to 2.5 percent for greater than 42 weeks gestation***(Andrew et al.,1991).***

E.Previous delivery history:

Previous delivery of a large infant and high maternal birth weight increase the likelihood of subsequent macrosomic infants. In a case-control study, maternal factors, including previous history of macrosomia, were more powerful predictors of macrosomia than was mild maternal glucose intolerance***(Okun et al.,1997)***.In another report, women who have babies weighed more than 3600 g were more than twice as likely to have macrosomic infants compared to those with lower weight at the time of giving birth***(Klebanoff et al.,1987).***

Carbohydrate metabolismand its endocrinal controlin the fetus and newborn:

The maternal-fetal metabolic relationshipfor nutrientsand insulinhas become essential for our understanding of fetal, infant, and life longoutcomes in under and overgrown fetuses.Glucose is transportedacross the placentato the fetus by saturation-dependant carriers. The quantity of glucose delivered into the umbilicalcirculation is less than the quantity taken up from the uterine circulation because the placenta,also, utilizes glucose as a metabolic fuel***(Nold &Georgieff, 2004).***

In 1995,the subcellular distribution of mammalian passiveglucose transportersisoformsGLUT1, GLUT3,GLUT5, inhuman placenta, were investigated by(***Bell etal.,1990).*** They concluded that GLUT1 is the major isoform responsible for glucose transfer from the mother to the fetus. The absence

ofGLUT 4 isconsistent with the lack of insulin sensitive glucosetransport across the placenta (**Barrosa et al.,1995).**

Glucose crosses the placenta by facilitated diffusion and amino acids cross byactivetransport***(Freinkel et al.,1979)***.

Free fatty acids are transferred in limitedamounts for tissue synthesis, whileketones cross freely by diffusion. Enzymes necessary for ketonesoxidation are present in fetal brain and liver ***(Freinkel et al.,1979)***.

Maternal glycemic control during normal pregnancy:

The fetus exerts a significant impact on maternal metabolic adjustmentduringpregnancy,through continuous and totaldependence on maternal fuel in order to maintain growth***(Barker,1997)***.Both hyperglycemia and hypoglycemia are likely todevelop during pregnancy.

Maternal fasting blood glucose decreases during normal pregnancy reaching a normal value by 12 weeks of gestation ***(mills et al.,1998)***.That finding attributed to increased placental-fetal utilization of glucose ***(Hay et al., 1985),*** the hypoglycemic effect of insulin and the decrease of food intake due to nausea and vomiting, resulting from elevated levels of human chorionicgonadotrophin***(Soules et al.,1980).***

With gestation progress,a number of factors as human placental lactogen, progesterone,estrogen and insulin degrading enzymes in theplacenta counteractthe hypoglycemic effects of

insulin in the mother **(Hiden & desoye, 2010)**

This maternalglucose-insulinbalance that occurs during normal pregnancy favors hyperglycemia that facilitates the availability of fuel to the fetus***(Sizonenko, 1978)***.

The general insulin resistance during pregnancy makesit represent a severe diabetogenic stress in a mother with border line beta cell function.

The foregoingmetabolic changes of pregnancy result in gestational diabetes. In preexisting diabetic mother, the same changes will require an increased dosage of insulin ***(Lain & catalano, 2007))***.

Complications of fetal macrosomia and large for gestational age:

The likelihood of cesarean delivery of a macrosomic fetus is approximately twice that of a normally grown infant, primarily because of abnormalities of labor ***(Spellacy et al.,1985).***

Macrosomia also predisposes women to severe postpartum hemorrhage and vaginal lacerations.Birth weight greater than 4000 g approximately double the risk of maternal blood loss greater than one liter***(Sosaet al.,2009)***. Injuries related to macrosomia and the metabolic abnormalities associated with excessive growth.

Birth injury:

The incidence of shoulder dystocia in the general gravida population is reported to be between two and four per 1000 deliveries, although ***Acker et al.(1988)*** found the incidence in his series to be approximately one in 50 deliveries.The incidence of shoulder dystocia, perinatal mortality rate, and incidence of other injuries are increased gram for gram in macrosomic especially of diabetic mothers***(Langer et al.,2000).***

Fetal macrosomia even in a mother with a normal pelvis, can result in prolonged labor, cephalo-pelvic disproportion, shoulder dystocia and consequently birth injury during vaginal delivery ***(Mountain,1991)***.

McFarland et al.,(1988)also, found a strong relationship between the method of delivery and birth injuries, the risk being much greater in mid forceps and vacum extraction deliveries. Although most Erb's palsies recover completely within 6 to 8 weeks, the risk of permanent disability was reported to range from 22 to 44% depending on the severity of the initial injury and duration of follow up ***(Johnstone et al., 1998)***.

Hyperinsulinemia and Hypoglycemia:

LGA infants can develop hypoglycemia when the placental supply of glucose is interrupted at birth. In a report based upon data from the Netherlands Perinatal Registry from 1997 to 2002, the incidence of hypoglycemia in all LGA infants was about 19 percent and in LGA infants without maternal diabetes 15 percent***(Groenendaal et al.,2006)***. Seizures due to

hypoglycemia occurred in 0.3 percent of all LGA infants and in 0.2 percent of LGA infants without maternal diabetes.

Polycythemia:

Polycythemia occurs in more LGA than AGA infants. In one report, LGA infants were approximately three times more likely to have polycythemia than AGA infants (6 versus 2 percent at 38 to 42 weeks and 14 versus 4 percent at more than 42 weeks gestation)***(Wirthet al.,1979).***

The mechanism of polycythemia is thought to be increased erythropoietin production resulting from fetal hypoxia caused by the increased oxidative demands associated with hyperglycemia and hyperinsulinemia. Both IDM and non-IDM LGA infants have increased red blood cell volume compared to controls***(Dollberg et al.,2000).***

Congenital anomalies:

Minor congenital anomalies are more common in LGA than AGA infants. This was evaluated in a retrospective case-control study of more than two million births in Latin America, of which 1800 of 31,897 Infants with congenital anomalies were LGA ***(Lapunzina et al.,2002).***

The most common anomalies associated with macrosomia included:

- Talipes calcaneo-valgus and hip subluxation caused by intrauterine deformation.

- Hydrocephaly and combined angiomatosis resulting in increased body mass and fluid, and thus increased birth weight***(*Lapunzina*et al.,2002).***

Perinatal mortality:

Perinatal mortality is higher in LGA than in appropriate for gestational age (AGA) infants. In a study of more than two million births in California, fetal and neonatal mortality rates were 8.2 to 43 and 3.4 to 12 per 1000, respectively, in term infants more than 4500 g, compared to rates of 2 to 3.7 per 1000 in AGA infants***(Williams et al.,1982).***

A change in maternal BMI during pregnancy has an independent positive predictive value for fetal macrosomia. An increase in BMI ≥25% during pregnancy has a sensitivity of 86.2%, specificity of93.6%, positive predictive value of 71.4% and negative predictive value of 97.45% for macrosomia ***(Aye et al.,2010).***

Ultrasound measurements are reasonably accurate for estimating the weights of smaller fetuses, but precision drops off as fetal weight increases. Studies using abdominal palpation and fundal height to estimate the risk of macrosomia report sensitivities of 10% to 43% and positive predictive values of 28% to 53%***(Resnik et al.,2003).***