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Gestational diabetes mellitus (GDM) and macrosomia: a controversial story

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Summary. - Increased perinatal morbidity-mortality are associated with gestational diabetes mellitus (GDM). We studied 69 non-diabetic pregnancies (age 30 ± 5 years) by repeating oral glucose tolerance test (OGTT, 100 g; area under glycemic, AUGC as g min/dl, and insulinemic, AUIC as mU min/ml, curves were calculated) and HbA1c measurement at 14, 24 and 33 weeks. In the 3rd trimester, 7 women had abnormal OGTT, but none of the 12 mothers of large babies (> 3.9 kg) had GDM. Among 15 pregnants with basal body mass index (BMI) > 25 kg/m^2, 2 developed GDM, 5 had babies > 3.9 kg, 8 had normal birthweight babies. Those pregnants who showed after-load hyperglycemia despite normal insulin secretory response (insulin resistance) developed GDM, but delivered normal birthweight babies. Large neonates were delivered from women with the greatest both gestational weight gain and insulin sensitivity, but normal glucose tolerance. The heaviest pregnants with normal both glucose tolerance and insulin sensitivity had normal weight gain and normal birthweight infants. Neonatal body weight was correlated with maternal gestational weight gain, placental weight, 3rd trimester AUIC/AUGC ratio and 1st-2nd trimester HbA1c.

Key words: gestational diabetes, macrosomia, insulin sensitivity.

Riassunto *(Diabete gestazionale mellito (GDM) e macrosomia: una storia controversa).* - Una ridotta tolleranza glucidica materna si associa ad una maggiore morbilità e mortalità perinatale. Abbiamo studiato 69 gravide non diabetiche (30 ± 5 anni) ripetendo la curva da carico glucidico *per os* (OGTT, 100 g; le aree sotto la curva glicemica, AUGC in g min/dl, e quella insulinemica, AUIC in mU min/ml, sono state calcolate) e l'emoglobina glicosilata (HbA1c) a 14 ± 3, 24 ± 2 e 33 ± 1 settimane di gestazione. Nel terzo trimestre, 7 donne presentavano OGTT patologico (GDM), ma nessuna delle 12 madri di macrosomi (> 3,9 kg) aveva GDM; di 15 gravide con BMI pregravidico > 25 kg/m^2, 2 sviluppavano GDM, 5 partorivano macrosomi, 8 avevano neonati normopeso. Sviluppavano GDM le gravide con iperglicemia post-carico, ma risposta insulinemica normale (insulino-resistenza), che partorivano bambini normopeso. Nascevano macrosomi alle gravide con maggiore incremento ponderale gravidico e maggiore sensibilità all'insulina, ma normale tolleranza glucidica. Le gravide obese, con normale tolleranza al glucosio e normale sensibilità all'insulina, presentavano regolare incremento ponderale e partorivano neonati normopeso. Il peso neonatale era correlato con l'incremento ponderale materno durante la gestazione, il peso placentare, il rapporto AUIC/AUGC al 3° trimestre ed i livelli di HbA1c al 1° e 2° trimestre.

Key words: diabete gestazionale, macrosomia, insulino-sensibilità.

Introduction

As far back as 1909 Williams described the effect of maternal glucose intolerance on pregnancy and fetus [1]. So far, however, until now consensus is lacking about the pathogenetic mechanisms of macrosomia. Fetal macrosomia is defined as an infant birth weight greater than 4.0 kg or the 90th percentile for gestational age, race, and sex [2]. Preexisting diabetes mellitus is one of the strongest risk factors for macrosomia and macrosomic infants of diabetic mothers are at higher risk for perinatal morbidity and mortality [3]. Maternal hyperglycemia has been supposed to stimulate fetal hyperinsulinemia associated with increased growth and fat deposition in insulin-sensitive tissues [4]. A number of the problems reported in diabetic pregnancies, macrosomia included, may be present in gestational diabetic pregnancies too, where an abnormal glycemia is firstly evidenced during pregnancy. Controversial results among clinical studies probably ensue from the circumstances of diagnosing gestational diabetes mellitus (GDM): many heterogeneous hyperglycemic states may be labelled as GDM, yet greatly differring upon their genesis. So, GDM could be an unidentified preexisting diabetes (either type 1, insulin-dependent diabetes mellitus, or type 2, non insulin-dependent), or a previous state of reduced glucose tolerance unmasked by gestational metabolic stress, or a direct effect of the maternal hormonal environment [5]. Since infant birth weight is dependent on several genetic, maternal, and intrauterine factors, macrosomia can develop despite normal glucose tolerance [6]. *Genetic* factors include gender, ethnicity, parental height; *maternal* predisposing factors may be age, parity, birth weight, prepregnancy weight, gestational weight gain, socioeconomic status; among *intrauterine* factors, the available maternal fetal

fuels, mainly amino acid and glucose surely play a crucial role [7].

The relationship between glucose tolerance and complications of pregnancy in nondiabetic women is a conflictual matter since it has been often accepted [8-15], more than once denied [16-22]. In some macrosomic infants born to nondiabetic mothers, increased cord blood insulin [21] and proinsulin [7] levels have been documented. According to Ratner [5], in view of really understanding the pathogenesis of fetal macrosomia, it seems advisable to consider all the aspects of maternal fuel metabolism (insulin secretion, insulin sensitivity as well as carbohydrate, fat, and amino acid metabolism) instead of focusing on blood glucose levels only.

In 1966, O'Sullivan *et al.* [8] reported data from 5534 prenatal patients who had performed a glucose challenge test (1 h 50 g GCT) and delivered at the hospital with a single birth. Age resulted the only significant maternal factor associated with 1 h glycemia. There was no glycemia-birth weight correlation in the general population, whereas that relationship did exist among "potentially diabetic" women: overweight subjects who had delivered large babies presented mean blood glucose levels higher than both overweight women with a normal weight infant as well as normal weight women with a large baby. The authors concluded that the glycemia-birth weight relation postulated for diabetics could be operating even in the prediabetics. However, lean mothers of macrosomes had significantly lower glycemia, implying alternative mechanisms (genetic?) to play a role.

As for the extent of the relation between infant birthweight and maternal fuels and hormones, in 1985 Knopp *et al.* [10], by screening 283 women, found infant birthweight to be positively correlated with mother's age, prepregnancy weight and pregnancy weight gain, maternal blood glucose, insulin, placental lactogen, estriol, apoprotein A1.

That patients with minor abnormalities of carbohydrate metabolism during pregnancy are at risk for fetal macrosomia has been suggested by several studies [11-14]. Nevertheless, just in 1989, Ales and Santini [18], reviewing literature, concluded that scientific data supporting an universal screening program for GDM were limited, thus advising a more restrained approach. Unfortunately, either the retrospective studies are uncontrolled and most prospective studies involve active intervention, conceivably changing pregnancy outcome.

In 1989, Langer *et al.* [23] closely examined the relationship between the level of glycemic control and the neonatal weight in 334 gestational diabetic women and 334 matched controls: overtreatment and undertreatment could result in small for gestational age *vs* large for gestational age infants, respectively. The rate of large infants was significantly higher in the high mean glycemia category regardless of maternal obesity. No difference was observed as for mean maternal weight gain and primary cesarean section between the control and the gestational diabetic subjects. These results should support the efficacy of stringent metabolic control for the reduction of the incidence of macrosomia, yet warning of the risk of intrauterine growth retardation in case of too low mean glycemia.

Phillipou [22] found that 1 h 50 g GCT glycemia had no predictive power as for the birth of large baby in 368 Europid women who had no preexisting medical condition and experienced no pregnancy complications. On the contrary, the 1 h glycemia was correlated to maternal height, weight and age. As important determinants of large for gestational age infants resulted only parity, maternal height and weight, neonate sex.

Green *et al.* [24], who had studied 2069 black, Latina, Chinese, and white mother-infant pairs, reported a modest association between glucose level and increased birth weight when maternal body mass index (BMI) was controlled and indicated maternal body habitus as a major confounder in studies of the relationship between maternal glucose tolerance and infant birth weight.

Cogswell *et al.* [25] observed that the association between maternal gestational weight gain and neonate birthweight varied by mother's prepregnancy BMI. Risk for infant low birth weight decreased with increasing maternal weight gain for average-weight women. There was no reduction in risk beyond weight gains of 14-15 kg for overweight women.

However, risk for high birth weight did increase with increasing weight gain in all groups of mothers. Any supposed risk associated with GDM seems sufficiently small to require large study populations to provide reliable statistical significance. The greater morbidity of gestational diabetic pregnancies, consisting essentially of a higher frequency of macrosomia and cesarean section, might be in part due to the association of gestational diabetes with obesity, on the one hand, and to patterns of obstetrician decision making if GDM is the case, on the other hand [20]. The correlation of glycemia to birth weight is lost by adjusting for maternal age and weight [8]. Also the efficacy of diet or insulin treatment in reducing the incidence of macrosomia is questionable [5, 18, 20, 23].

Little *et al.* [16] evaluated 287 pregnant women by 3 h 100 g OGTT at about 28 weeks and stratified them based on 2 h glycemia into three groups: there was a trend toward higher birth weights but no difference in perinatal complications or infant morbidity or mortality among groups.

Lucas *et al.* [17] reported that class A1 gestational diabetes was not significantly associated with obstetric and perinatal morbidity and doubted that dietary counseling could be an explanation for the lack of differences in outcome. On the contrary, maternal obesity

resulted a potent and independent risk factor for large infants than was glucose intolerance. Also Goldman *et al.* [26] assessed obstetric complications in 305 control subjects and 150 women with GDM, intensively treated by diet only or insulin. They observed that abnormalities of labor, birth trauma, and fetal macrosomia were not more common in GDM; despite this, the cesarean section rate remained higher than in controls.

Supplemental tests for GDM screening have been also checked. The use of glycated proteins such as glycated hemoglobin and glycated albumin have been discussed at length. Phelps *et al.* [27] first reported a biphasic excursion of glycated hemoglobin in normal pregnancy with nadir levels at 24 weeks' gestation followed by peak levels near term. This change could reflect fluctuations in the mean blood glucose occurring about 4 weeks earlier.

The lack of sensitivity and the delay in reflecting blood glucose changes discourages glycated hemoglobin as the first choice measurement to diagnose GDM. However, some data support its useful role as additional assay for detection and control of abnormal glucose tolerance [28-32], yet other reports do not [33-37].

Preliminary results from our prospective study

In 69 young non diabetic pregnancies we repeated the oral glucose tolerance test (OGTT, 100 g) and HbA1c measurement at each of the three trimesters of gestation.

In the 3rd trimester, 7 women had abnormal OGTT, but none of the 12 mothers of large babies (> 3.9 kg) had GDM. Among fifteen pregnants with basal BMI > 25 kg/m^2, 2 developed GDM, 5 had babies > 3.9 kg, 8 had normal birthweight babies. In normal pregnancies (no. 42), both AUGC (area under glycemic curve) and AUIC (area under insulinemic curve) increased significantly from the 1st to the 3rd trimester, AUGC (g min/dl) still remaining lower that AUIC (mU min/ml). In mothers of large babies (no. 12), both AUGC and AUIC increased to a lesser extent: a low AUGC corresponded to a low AUIC. In mothers with GDM (no. 7), AUGC became greater than AUIC, although AUIC apparently increased as much as in normal pregnant women. In obese mothers of normal birthweight infants (no. 8), changes in AUGC and AUIC resulted in a normal range.

Mothers of macrosomes differed from obese mothers of normal birthweight babies as for the higher gestational weight gain, gestational week at delivery, 1st trimester HbA1c, yet lower 1st trimester AUGC. Neonatal body weight was correlated with maternal gestational weight gain, placental weight, AUIC/AUGC ratio at the 3rd trimester and HbA1c levels at the 1st-2nd trimesters. Thus, developed GDM those pregnants who showed after-load hyperglycemia despite normal insulin secretory response (insulin resistance), but delivered normal birthweight babies. *Large neonates* were delivered from women with the greatest both gestational weight gain and insulin sensitivity, but *normal glucose tolerance*. The heaviest pregnants with normal both glucose tolerance and insulin sensitivity had normal weight gain and normal birthweight infants.

Our findings confirm the link between maternal metabolic milieu and foetal development, but the main determinant of infant birth weight seems to be mother insulin sensitivity, apart from glucose tolerance or the absolute level of serum insulin.

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