Impact of Maternal GDM and Obesity on Mother and Fetus

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Over the last 2 decades, the incidence of obesity in reproductive-age women has increased significantly. The increase has been observed not only in developed areas of the world, but possibly more important in developing countries as well.[1] The increase in worldwide obesity is a harbinger of a shift of the global disease burden from acute infectious disease to chronic diseases such as diabetes and atherosclerotic vascular disease, with their associated increase in health care costs.

One of the primary metabolic abnormalities associated with obesity and diabetes is increased insulin resistance. During pregnancy, obese women are at increased risk of the "metabolic syndrome" of pregnancy, ie, gestational diabetes mellitus (GDM) and hypertensive disorders such as preeclampsia.[2] Women developing GDM have both increased insulin resistance and impaired beta cell function, whereas obese women often have increased insulin resistance but are able to compensate with increased beta cell response resulting in normoglycemia.[3] The insulin resistance of pregnancy not only affects glucose metabolism but also lipid and amino acid metabolism, ie, "fuel mediated teratogenesis" as described by Freinkel.[4]

In one study, we examined longitudinal changes in maternal insulin sensitivity with a hyperinsulinemic-euglycemic clamp in women with a pregravid body mass index (BMI) <25, 25–30, and >30. We found that obese women were significantly less insulin sensitive (ie, more insulin resistant) than lean women (P=0.0001) and overweight women (P=0.004), particularly pregravid and in early gestation (Figure).[5]

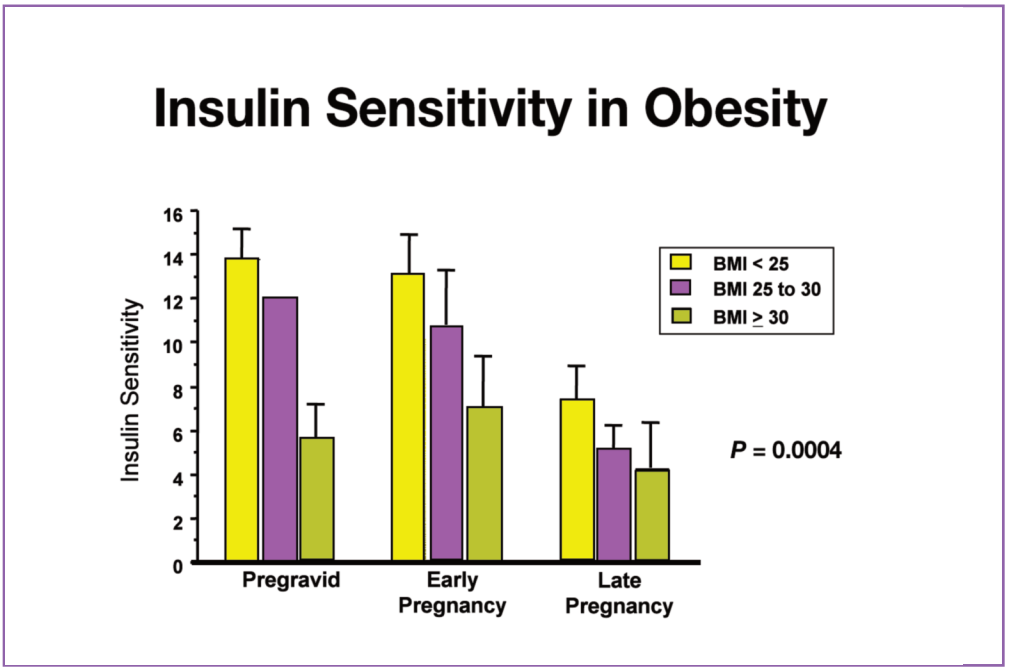

Figure. Longitudinal changes in insulin sensitivity in lean, overweight, and obese women, before conception (pregravid) and in early (12–14 weeks) and late (34–36 weeks) gestation.[5]

Source: Catalano P, Ehrenberg H. The short- and long-term implications of maternal obesity on the mother and her offspring. *BJOG*. 2006;113:1126–1133. Reproduced with permission of Blackwell Publishing Ltd.

Our research has focused on estimates of body composition to assess fetal growth, using anthropometrics, stable isotopes, total body electrical conductivity (TOBEC) and most recently air-displacement plethysmography (PEA POD®). At birth, infants of women with GDM often are larger than those of women with normal glucose tolerance because of increased fat and not lean body mass, even with the same weight.[6] Similarly, infants of obese women are larger at birth because of increased fat and not lean body mass.[7] Both GDM and maternal obesity are risk factors for later childhood obesity and related problems such as insulin resistance, glucose intolerance, and elevated blood pressure.[8]

Over 50 years ago, Jorgen Pedersen hypothesized that increased maternal glucose, which crosses the placenta in a concentration-dependent manner from mother to fetus (facilitated diffusion), results in increased fetal glucose concentrations and insulin response.[9] The combination of these two factors in women with diabetes results in fetal overgrowth, or macrosomia. More recently, investigators have

reported that maternal triglycerides are correlated with increased fetal growth and more specifically, adiposity.[10]

The increases in glucose and triglycerides during pregnancy are normal consequences of the physiology of pregnancy, ie, increased insulin resistance. However, when insulin resistance increases before conception, as seen in GDM and obesity, the physiologic changes in pregnancy are exaggerated. This results in greater nutrient availability to the fetus and subsequent fetal overgrowth. What then are the mechanisms by which insulin resistance increases progressively during pregnancy?

The insulin resistance of pregnancy improves significantly after delivery; therefore, placental factors are most likely responsible. Previously, placental hormones such as human placental lactogen (HPL) were assumed to be a factor. However, more recent research in both pregnant and nonpregnant women points to inflammation as the mechanism, resulting in dysfunction in postreceptor insulin signaling.[11-13] We studied 53 lean and 68 obese women who had a scheduled cesarean delivery to measure insulin resistance and inflammatory markers in the mothers and in umbilical cord blood.[14] Table 1 shows that obese women were significantly more insulin resistant and had significantly higher levels of several inflammatory markers than lean women.

Table 1. Maternal Systemic Inflammation in Obesity[14]

	Lean n=53	Obese n=68	*P* value
Pregravid BMI	22.0 ± 1.9	38.4 ± 6.3	0.0001
Plasma insulin (µU/mL)	11.8 ± 5.6	26.0 ± 14.6	0.006
Plasma glucose (mg/dL)	74 ± 7	79 ± 11	ns
Adiponectin (µg/mL)	10.7 ± 4.6	9.7 ± 4.0	0.0001
Leptin (ng/mL)	31.9 ± 20	72.1 ± 34.7	0.0001
IL-6 (ng/mL)	2.4 ± 1.4	4.6 ± 3.4	ns
TNF-alpha (pg/mL)	1.4 ± 0.9	1.3 ± 0.5	0.004
CRP (ng/mL)	8074 ± 6467	12433 ± 7918	

BMI=body mass index, IL-6=interleukin 6, ns=not sigificant, TNF-alpha=tumor necrosis factor alpha, CRP=C-reactive protein

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Evidence indicates that in obese nonpregnant individuals increased inflammatory cytokines derived from adipose tissue may play an important role in insulin resistance.[11] During pregnancy the placenta is another potential source for cytokine production.

Preliminary data have shown that maternal circulating monocytes may be the source of cytokine production. In the placenta, macrophages also may contribute to the inflammatory milieu of obese pregnancy.[15] In gene array studies of placenta from women with obesity/GDM and type 1 diabetes, there is a differential expression of genes related to lipid and glucose metabolism.[16] These data support our hypothesis that both maternal glucose and lipids can be the substrate source of adipose tissue in the developing fetus, depending on the mother's metabolic profile.

As noted previously, at birth infants of obese women have increased body fat. Fetal adiposity is strongly correlated with fetal insulin resistance, as estimated by umbilical cord blood measures of glucose and insulin in women undergoing scheduled cesarean delivery.[14] The increases in fetal adiposity and insulin resistance are related to the increase in obesity and insulin resistance in later childhood. In a regression analysis, maternal pregravid obesity was the strongest risk factor for fetal obesity at birth and in childhood, even in women with well-controlled GDM (Table 2).[8]

Table 2. Maternal Pregravid Obesity as a Predictor of Childhood Obesity[8]

Pregravid BMI >30

OR 5.45 (95% CI 1.62–18.4, *P*=0.0006)

Including gender and group (GDM)

OR 7.75 (95% CI 1.51–37.74, *P*=0.01)

Maternal obesity

Accounts for 17.6% of the variance in childhood obesity

Treated GDM appears to be less of a risk factor for childhood obesity than maternal pregravid obesity

BMI=body mass index, (weight [k]/height [m]^2), GDM=gestational diabetes mellitus, OR=odds ratio

However, more research is needed in the time between birth and childhood in order to understand the effect of the modifiable factors on the individual's growth and development.

Finally, is there anything we can do during pregnancy to interrupt the cycle of maternal obesity and GDM that begets childhood problems of obesity and related metabolic dysfunction? Recently, two randomized controlled trials in women with GDM have shown improved neonatal outcomes at birth.[17,18] There is evidence that treatment of mild GDM can decrease the risk of macrosomia, fetal adiposity, and other related perinatal outcomes. However, only short-term studies have been conducted in children up to 5 years of age, without evidence of long-term benefit.[19,20]

The treatment of maternal obesity during pregnancy is not as well defined. All would agree that avoidance of excessive gestational weight gain during pregnancy is important for both mother and fetus.[21] Although the Institute of Medicine has recently revised the guidelines for gestational weight gain, many feel the guidelines do not go far enough, particularly in the 30+% of pregnant women who are obese.[22] Much research needs to be done in this area to determine both the short-term and long-term benefits of limited weight gain or loss in overweight and obese pregnant women. In the interim, our research group and others are examining lifestyle and dietary factors relating to decreasing inflammation in pregnancy and thereby improving maternal insulin sensitivity and fetal growth. Because of the effects of maternal metabolism on placental growth and gene expression, prevention—which ideally should begin before a planned pregnancy—by necessity should be initiated as early in pregnancy as possible.

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Q & A

Q: Dr Catalano, you talked a bit about looking at the new recommendations for diagnosis of gestational diabetes mellitus (GDM). A lot of times women are diabetic before they become pregnant and the condition just manifests itself in pregnancy. And other women actually have gestation-induced diabetes. Is there any thought on looking at those two groups? You have stated often that what a woman is in late pregnancy is the same as what she was before, and we may manage those who actually have GDM differently than those we just see and realize they are diabetic.

Dr Catalano: I think you are right. The trouble is that we all use classification schemes that we are bound to. So up until the paper from the International Association of Diabetes and Pregnancy Study Groups (IADPSG) came out, we would call these women gestational diabetics. We would lump together women with gestational diabetes at 12 weeks with women with mild glucose intolerance at 34 weeks. This is like preeclampsia. Women can have mild preeclampsia or preeclampsia at 28 weeks, which is devastating. We call both conditions preeclampsia. With the IADPSG criteria, we can go forward calling glucose intolerance in early pregnancy overt diabetes. If these criteria are accepted, we will be able to differentiate between the women who had undiagnosed type II diabetes beforehand and those with the delayed effect of beta-cell dysfunction because of the insulin resistance in late pregnancy.

On the other hand, if these criteria are accepted, who is going to pay for the results? I have a diabetes clinic now in which I hardly ever see 5% of the patients. Who is going to pay for taking care of 20%? A lot of work needs to be done, but at least the issue is being recognized.

Q: Can I just ask you a bit more about lean body mass? We have been looking at placental functioning in more detail, looking at some of the transport systems. We see that first, they relate back to maternal nutrition, but second, they relate specifically to neonatal and subsequent childhood lean body mass moreso than to fat mass. So my take on this would be definitely there are genetic influences operating across all of the compartments but that the environmental regulators of fat are different.

Dr Catalano: I agree that there is a genetic component to it. The data from India suggest that the issue may be that the lean body mass component is decreased.

Q: I think that may in part be environmental and nutritional in origin. When we use direct measures of mother's lean mass, we find that those predict offspring lean body mass. I think the fact that Indian women tend to be thin probably is due more to nutritional influences than genetic influences.

Dr Catalano: I want to bring up the issue that when we look at who is at risk, we find it is not so much how much fat a person has, it is how much fat that person has relative to how much lean mass. If a person has a tendency to put excess nutrients in the liver or in the muscle, the metabolic effect, enlargement, occurs because it happens to be in tissue that is more of a regulatory tissue than a storage tissue.