Medicine Grand Rounds
December 3, 2010

Medical Care after Gestational Diabetes

María A. Ramos-Román, MD
Division of Endocrinology
Department of Internal Medicine

This is to acknowledge that María A. Ramos-Román, MD has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Ramos-Román will not be discussing off-label uses in her presentation.

Research Interest:

Dr. Ramos-Román is interested in the hormonal mechanisms by which lactation protects women with a history of gestational diabetes from type 2 diabetes in the postpartum period. A synopsis of her project *Contribution of the hormone prolactin to intramuscular fat in women 4 to 12 weeks after delivery* can be found at the UT Southwestern's website under Find a Clinical Trial (FaCT).

Gestational diabetes mellitus (GDM) is glucose intolerance that is first recognized during pregnancy (1). GDM is a composite of two groups of diabetic women (2). One group is unaware of its diabetic status before conception (unrecognized pre-GDM). The other group has onset of diabetes during the third trimester of pregnancy. Both the time of onset and the duration of uncontrolled diabetes have important implications for pregnancy outcomes (3).

Uncontrolled pre-GDM threatens fetal-maternal health because of an increased risk of miscarriages and birth defects compared with non-diabetic pregnant women, as well as a risk for deterioration of preexistent maternal microvascular complications (4). Diabetes with onset during late gestation bypasses the temporal risk for early complications seen in uncontrolled pre-GDM. However, any uncontrolled diabetes during late pregnancy contributes to perinatal morbidity and mortality (fetal overgrowth, traumatic deliveries, stillbirths, neonatal hypoglycemia); and increases the lifetime risk for metabolic syndrome, impaired glucose tolerance (IGT) and type 2 diabetes in both the mother and her offspring (5, 6).

This presentation has 3 objectives. The first objective is an introduction to hormonal control of carbohydrate metabolism during a normal pregnancy and a pregnancy complicated by GDM. The second objective is the justification of medical care after GDM. The third objective is a discussion on interventions for prevention of diabetes and vascular complications after GDM.

Epidemiology of GDM and postpartum diabetes

The annual number of pregnancies in the United States approximates 6 million (7). GDM is diagnosed in 2 to 5% of all pregnancies, which translates into 120,000 to 300,000 mother-newborn pairs affected by GDM each year (8). The prevalence of GDM varies among racial/ethnic groups being higher among Native-American, Asian, African-American, and Hispanic women compared with non-Hispanic white women (6, 9).

Many clinical and obstetric characteristics have been associated with the development of GDM (4). These characteristics include ethnicity, advanced maternal age, family history of diabetes, overweight status before pregnancy, amount of weight gain during pregnancy, physical inactivity, polycystic ovarian syndrome, parity, >1 fetus per pregnancy, fetal overgrowth, and stillbirth on a previous pregnancy. In addition, a history of GDM is a strong risk factor for recurrent GDM, particularly if associated with weight gain between pregnancies or with an early diagnosis of GDM that required insulin therapy (10).

Ninety percent of women with GDM experience a return to normal glucose concentrations shortly after delivery because the decrease in insulin sensitivity characteristic of pregnancy improves to pre-pregnancy levels once the placenta is out (11, 12). Reports on the risk for subsequent type 2 diabetes have spanned 6 weeks to 28 years postpartum, and indicated a prevalence of type 2 diabetes ranging from 2.6 to 70% depending on the criteria used to diagnose GDM, length of postpartum follow-up and retention rates (Figure 1) (13). Fifty percent of women with a history of GDM will develop type 2 diabetes by 5 years postpartum and 10 to 31% of parous women with diabetes would have a history of GDM (14).

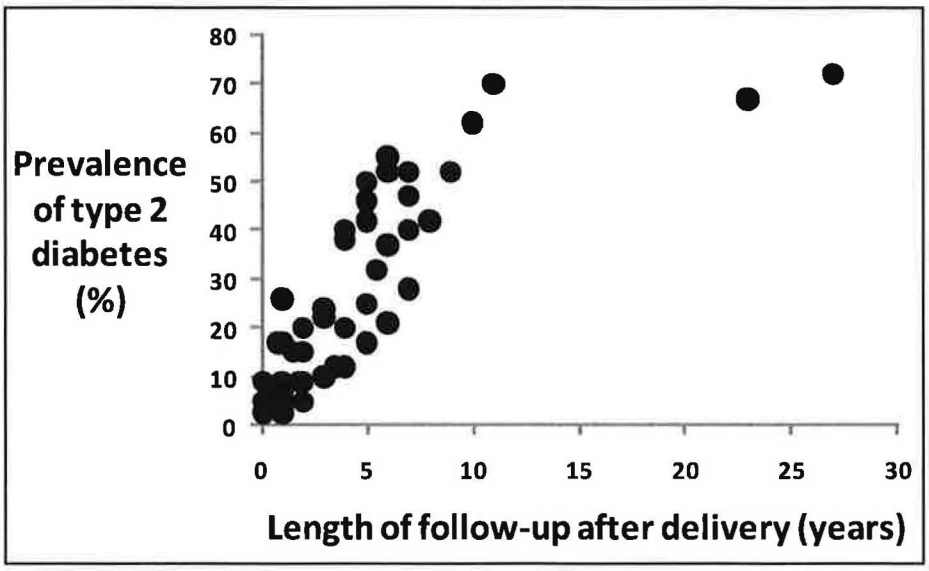


Figure 1. Prevalence of type 2 diabetes after GDM. Adapted from Reference 13.

The predictors of type 2 diabetes after GDM are as many as the predictors of GDM (15-17). Large observational studies in Hispanic women during pregnancy and postpartum have shown that the strongest predictor for type 2 diabetes after GDM was the glucose tolerance assessed 4 to 16 weeks postpartum with a 2- hour 75-gram oral glucose tolerance test (OGTT). This predictor was assessed as glucose area under the curve. Next in the hierarchy of risk factors was the severity of fasting hyperglycemia during pregnancy, a diagnosis of GDM early in pregnancy, and the glucose area under the pregnancy 3-hour 100-gram OGTT curve. Although weight gain and parity have also been associated with deterioration to type 2 diabetes, these associations disappeared with inclusion of multiple predictors in multivariate analysis (18).

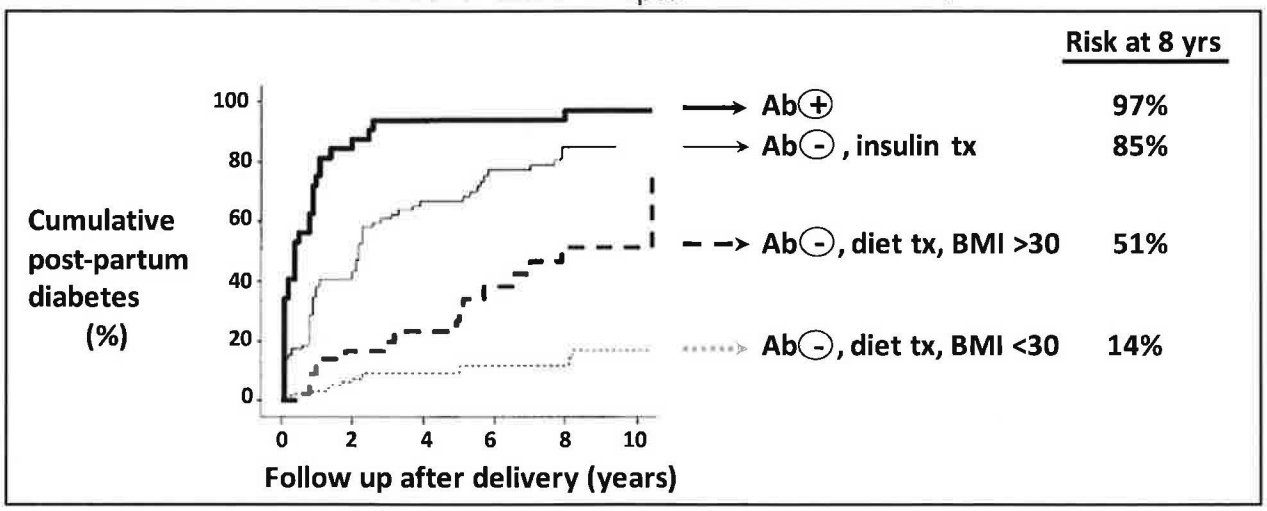
Up to 10% of women with GDM have autoantibodies to pancreatic islets or to β-cell antigens at delivery (19, 20). These women are often white, lean, from European descent, and likely to require insulin therapy during pregnancy. Thirty four percent of autoantibody positive GDM women remained hyperglycemic after delivery and 81% of them progressed to diabetes within one year postpartum (Figure 2). These women seemed to have type 1 diabetes in evolution and most deteriorated rapidly to uncontrolled diabetes in the postpartum period. Postpartum progression to diabetes in women with GDM without autoantibodies was affected by the requirement of insulin during pregnancy, BMI and the number of previous pregnancies (19). Concentration of C-reactive protein was not a significant predictor of diabetes in women with GDM without autoantibodies after adjusting for BMI. Mutations responsible for maturity onset diabetes of the young (MODY) have been found in women with GDM and are favored to represent preexistent diabetes detected during pregnancy (1).

Diagnosis of diabetes in pregnancy

Large medical centers serving groups traditionally classified as ethnic minorities in the United States have a universal screening policy for GDM. A fasting plasma glucose (FPG) ≥126 mg/dL or a random plasma glucose ≥200 mg/dL, confirmed on a subsequent day, is diagnostic of

diabetes at any time during pregnancy (4). Most obstetric care in the United States follows a 2-step process to diagnose diabetes between 24 and 28 weeks of gestation (Figure 3) (21).

Figure 2. Predictors of diabetes after GDM. No stratification by number of pregnancies was done because of a limited number of cases. Adapted from reference 19.



The first step is a screening test with a 50-gram oral glucose challenge done at any time of the day regardless of the time of the last meal (22). A plasma glucose concentration ≥140 mg/dL at 1 hour after the glucose challenge is an abnormal screening result that needs confirmation with the diagnostic 3-hour oral glucose tolerance test (OGTT). The glucose load during the 3-hour test is 100 grams. Two abnormal plasma glucose concentrations are needed to diagnose GDM during the 3-hour test.

These diagnostic criteria date back to the work started by Wilkerson, O'Sullivan and Mahan in the late 1950s in Boston (23-25). These criteria were developed to identify women at risk for type 2 diabetes after pregnancy. Their cutoff values for abnormal glycemia in whole blood were modified by Carpenter and Coustan to the 14% higher plasma equivalents used today by many international organizations including the American Diabetes Association (4).

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study was designed to address the lack of uniform international standards for the diagnosis of GDM (26). HAPO analyzed data from 23,316 pregnant women in 15 centers from 9 countries. The purpose of the study was to examine the risk of perinatal morbidity and birth trauma associated with maternal glucose intolerance less severe than the glucose concentrations in diabetes. All participants had a 2-hour OGTT with 75 grams of glucose at a mean gestational age of 28 weeks. The results on perinatal morbidity were reported in 2008 and it is anticipated that further data analysis will provide new guidelines for uniform diagnosis of GDM worldwide.

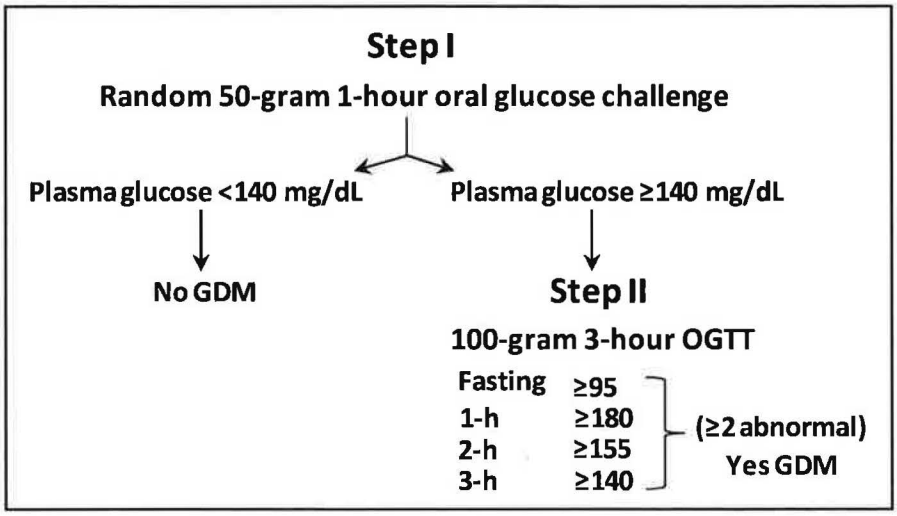


Figure 3. Two-step process to diagnose GDM (4, 21).

Carbohydrate metabolism during pregnancy

Maternal fasting glucose concentrations decrease and postprandial glucose concentrations increase during a normal pregnancy (4). Physiologic insulin resistance manifests around mid pregnancy to secure the availability of glucose for the fetus at a time of accelerated growth (3, 27, 28). Concurrently, maternal energy requirements rely more on fat metabolism. A normal pregnancy balances physiologic insulin resistance with a doubling of insulin secretion by pancreatic β-cells (4).

Lean and obese women in the planning stages of a pregnancy have been studied longitudinally 2 to 3 months before pregnancy, at 12 to 14 weeks of gestation and at 34 to 36 weeks of gestation (Figure 4) (29-31). Some lean and some obese women developed GDM. When matched by percent body fat, the magnitude of the decrease in insulin sensitivity between the baseline non-pregnant state and late gestation was 50 to 56% in all women regardless of percent body fat and GDM status.

Although the magnitude of the change in insulin sensitivity during pregnancy was similar in the 4 groups of women studied, the baseline non-pregnant insulin sensitivity was not. Healthy lean women were the most insulin sensitive before conception as determined by the glucose infusion rates at the end of euglycemic hyperinsulinemic clamps. Next were the healthy obese, GDM lean, and GDM obese women. Therefore, women destined for GDM had worse baseline insulin sensitivity than women destined for normal glucose tolerance during pregnancy.

Studies done 2 to 36 months after delivery have shown a persistent difference in carbohydrate metabolism between women with and without a history of GDM (Figure 5) (32, 33). When normoglycemic women with and without GDM were matched for age and percentage of ideal body weight, the GDM group had lower insulin secretion and lower insulin sensitivity as measured by intravenous glucose tolerance tests (IVGTTs) (34). Women with GDM had 40 to 70% lower insulin secretion for any degree of insulin resistance throughout pregnancy and the postpartum period (1, 35).

Figure 4. Insulin sensitivity before and during pregnancy stratified by percent body fat and GDM status. Adapted from references 29-31.

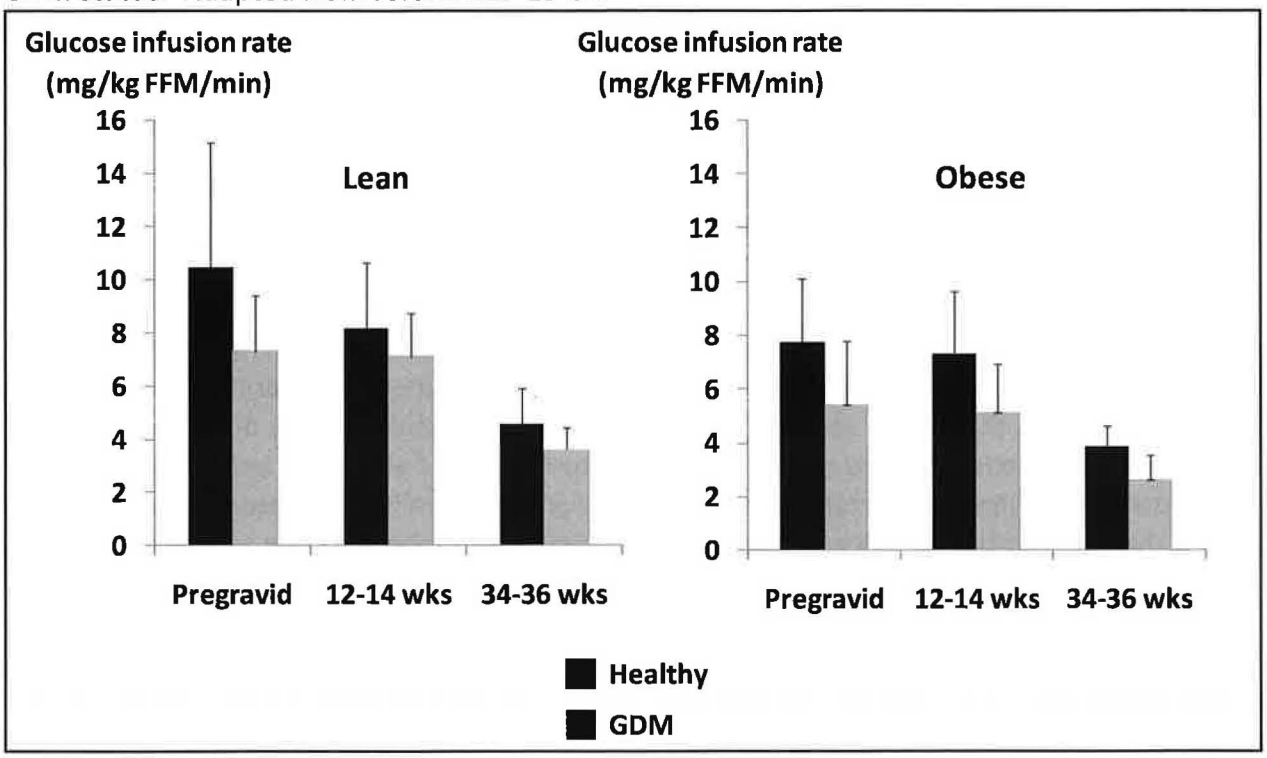
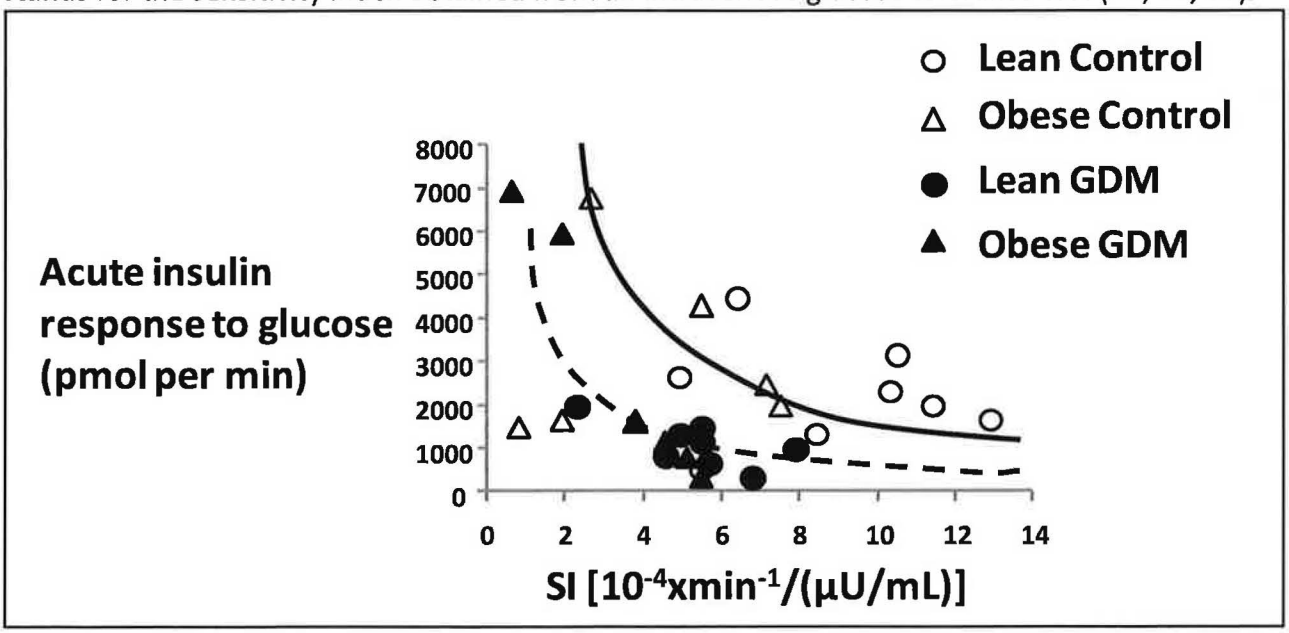


Figure 5. Insulin secretion and insulin sensitivity examined after pregnancies with and without GDM. Acute insulin response to glucose is a measurement of insulin secretion. SI stands for the sensitivity index obtained from an intravenous glucose tolerance test (32, 33, 36).



Maternal cardiovascular risk after GDM

Women with a history of GDM have a higher risk for the metabolic syndrome, markers of subclinical cardiovascular disease, and clinical cardiovascular disease compared with women without such history (37-42). Specifically, women with previous GDM have higher BMI, higher blood pressure, increased LDL-C, increased triglycerides, decreased HDL-C, impaired endothelial function, higher prevalence of microalbuminuria, higher prevalence of abnormal electrocardiograms, and higher prevalence of cardiovascular events. Women with a history of GDM and pre-pregnancy obesity have the highest risk for metabolic syndrome years after delivery (43).

Women with a history of GDM, normal blood pressure and normal glucose tolerance postpartum have endothelial dysfunction independent of obesity (44). Endothelial dysfunction was measured in this study as the percent increase in brachial artery diameter following deflation of the blood pressure cuff. Endothelial function was abnormal before development of glucose intolerance postpartum. Women with prior GDM also have increased carotid intima-media thickness in the absence of metabolic syndrome or diabetes when compared to lean, control women (45).

A subanalysis of the Genetics of Non-Insulin Dependent Diabetes (GENNID) study on parous, obese women with first-degree relatives with type 2 diabetes showed a 3-fold higher risk for metabolic syndrome in women with prior GDM compared with women with no GDM 30 years after the index pregnancy (46). Women with prior GDM also had a higher frequency of self-reported cardiovascular events, which occurred at a younger age (average age of 46 vs. 53 years, P=0.02). These results agree with a higher prevalence of cardiovascular events in women with family history of type 2 diabetes and history of GDM.

Effect of the intrauterine environment on the health of the offspring

Exposure to maternal diabetes in late gestation is associated with increased risk of obesity and carbohydrate intolerance in the offspring (47). Serial amniocenteses done for assessment of lung maturation showed increased insulin concentrations in amniotic fluid near term and higher cord C-peptide to glucose ratio in diabetic pregnancies compared with non-diabetic pregnancies (48). A strong correlation between amniotic fluid insulin levels and increased BMI in adolescents has been interpreted as evidence of an association between fetal hyperinsulinemia and childhood obesity (49).

This section discusses 3 studies that control for a genetic contribution to diabetes risk in type 1 diabetes, type 2 diabetes and a rodent model of drug-induced diabetes (50-52). It is worth mentioning a study of mother-daughter pairs showing that shared lifestyle habits after birth also contribute to early onset of obesity and metabolic abnormalities in the offspring (53).

Contribution of maternal type 1 diabetes to diabetes risk in the offspring

Adult non-diabetic offspring of only one parent with type 1 diabetes were selected if born after the parental diagnosis of diabetes, if autoantibodies associated with type 1 diabetes were not

detected, and in the absence of a family history of type 2 diabetes in a first-degree relative (50). In order to control for the genetic contribution of type 1 and type 2 diabetes, offspring of type 1 diabetic fathers were the control group and offspring of type 1 diabetic mothers were the group with intrauterine exposure to diabetes.

The adult offspring was evaluated with a 2-hour OGTT, a continuous glucose infusion with increases in glucose delivery rates at pre-specified times, and a euglycemic hyperinsulinemic clamp. All offspring from type 1 fathers had normal glucose tolerance (NGT). The offspring from type 1 mothers either had NGT or impaired glucose tolerance (IGT). No significant differences in insulin sensitivity or adiposity were identified between the control and the exposed offspring. However, insulin secretion was compromised in the exposed group, more so in the IGT exposed offspring than the NGT exposed offspring compared with the NGT control offspring. These results suggest that exposure to a diabetic environment during a pregnancy complicated by type 1 diabetes increases the risk of IGT and type 2 diabetes in the offspring.

Contribution of maternal GDM or type 2 diabetes to diabetes risk in the offspring

The Pima Indians of Arizona have participated in a longitudinal study of diabetes since 1965 (54). The protocol includes 2-hour 75-gram OGTTs every other year after age 5. Discordant uterine exposure to maternal diabetes was examined in siblings born before and after a maternal diagnosis of diabetes (55). The results revealed that 73% of the Pima Indian siblings exposed to maternal diabetes during pregnancy became diabetic during childhood or youth compared to 33% of the Pima Indian siblings not exposed to maternal diabetes during pregnancy (OR=3.7, P=0.02). Likewise siblings exposed to diabetes in the womb were more prone to obesity than siblings not exposed to diabetes before birth (P for mean difference=0.003) (56).

Studies in rodents - Contribution of drug-induced diabetes to diabetes risk in the offspring

Adult female Wistar rats received one dose of IV streptozotocin on the day of mating to cause drug-induced diabetes (52). The morphology of the pancreas was studied in this group of rats as well as in the next 2 generations. Generation 1 (exposed to STZ) and generation 2 (exposed to the diabetic intrauterine environment) failed to respond to the physiologic insulin resistance of pregnancy with an increase in the percent of β-cells in late gestation. A study of the fetuses in generation 2 and generation 3 showed lower percent of β-cells compared with control fetuses.

Interventions to prevent type 2 diabetes after GDM

Three interventions are associated with decreased risk of type 2 diabetes after a pregnancy with GDM. These interventions are lifestyle modification, pharmacologic treatment and lactation. The three interventions seem to work by fighting the deleterious effect of a second metabolic insult like obesity and/or insulin resistance (57).

Lifestyle changes

A subanalysis from the Diabetes Prevention Program (DPP) focused on the incidence of diabetes in parous women (58-60). The main inclusion criterion in this multiethnic cohort was

the combination of impaired fasting glucose and IGT. Sixteen percent of the DPP women reported a history of GDM and had their baseline evaluations an average of 12 years after their GDM pregnancy. Specifically, this subanalysis compared the responses to intervention with intensive lifestyle modification, metformin or placebo in parous women with (n=350) and without (n=1,416) history of GDM (Table 1). The number needed to treat over 3 years with intensive lifestyle or metformin to prevent one case of diabetes was estimated to be 5 to 6.

Table 1. Incidence of diabetes after GDM in subanalysis from the DPP (58).

	Placebo		Metformin		Intensive lifestyle	
	GDM (n=122)	No GDM (n=487)	GDM (n=111)	No GDM (n=464)	GDM (n=117)	No GDM (n=465)
Incidence of diabetes (per 100 person-years)	15.2 *	8.9	7.8	7.8	7.4	4.7
Reduction in incidence (compared with placebo)		*	50.4	14.4	53.4	49.2
			*			
NNT (to prevent one case in 3 yr compared with placebo)			6.1	24.0	5.3	9.0

*P=0.05

Pharmacologic treatment of insulin resistance

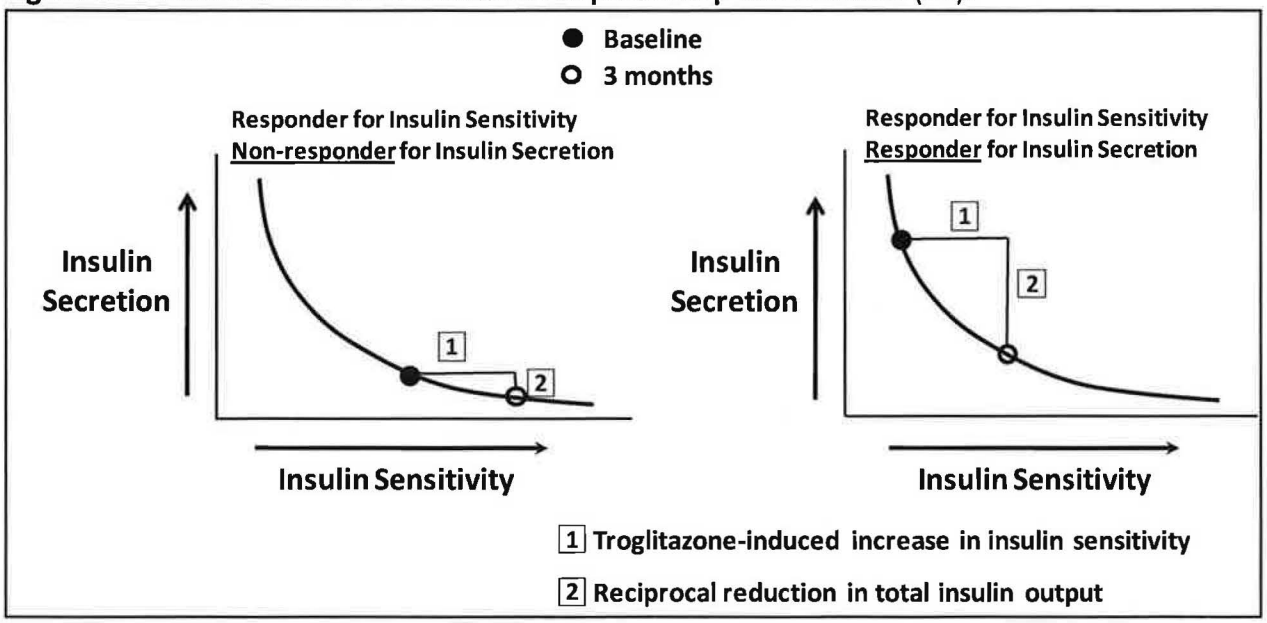
The Troglitazone in Prevention of Diabetes (TRIPOD) study randomized 236 Hispanic women with GDM in the previous 4 years to the thiazolidinedione drug troglitazone or placebo (61). All participants had a predicted risk of diabetes in the next 5 years of 70%. Experimental assessments included a frequently sampled-IVGTT at screening and 3 months after randomization. The primary outcome was development of diabetes. The average annual incidence rates of diabetes were 12.1% in the placebo group and 6.0% in the troglitazone group. Troglitazone reduced the incidence of diabetes by 50%.

Diabetes prevention required an early increase in insulin sensitivity and a large reduction in insulin secretion (Figure 6). Protection from diabetes was restricted to the 2/3 of women with the greatest increase in insulin sensitivity and the 1/3 with the greatest reduction in insulin secretion during the first 3 months of treatment with troglitazone. This means that women with worse insulin sensitivity and highest insulin secretion at baseline got the most benefit from the intervention. Protection from diabetes persisted 8 months after discontinuation of troglitazone. The findings in this study suggest that treatment of insulin resistance preserves β-cell function.

The TRIPOD study was stopped because troglitazone was withdrawn from the market. The Pioglitazone in Prevention of Diabetes (PIPOD) study followed as an open-label observational study with the thiazolidinedione drug pioglitazone (62). PIPOD enrolled 95 Hispanic women who did not have diabetes at the end of TRIPOD. Frequently sampled-IVGTTs were done at

study entry and after one year of treatment. The results from PIPOD echoed the results from TRIPOD in that a reduction in insulin secretion was instrumental for diabetes prevention.

Figure 6. Treatment of insulin resistance to preserve β-cell function (61).



Lactation

Lactation is associated with health benefits for both the mother and her offspring (63). Lactating women maintain increased concentrations of the hormone prolactin and decreased concentrations of estradiol and progesterone compared with non-lactating women (64, 65). Lactation facilitates a return to pre-pregnancy weight because maternal fat stores are used to support milk production (66). Five hundred calories are required daily to feed an infant when the only source of food is breast milk. However, lactation does not make a major impact on weight loss and body composition when those 500 calories per day are balanced by extra intake of calories (67).

Lactation improves glucose tolerance in the postpartum period in both women with normal pregnancies and women with a history of GDM (Figure 7) (68, 69). Women with longer duration of lactation categorized with the use of a lacation index scoring system tend to be more insulin sensitive. Lactation promotes a less atherogenic lipid profile and affects body fat distribution (66). Lactating women mobilize more fat from their thighs than their trunks with no effect on visceral fat mass at 3 months postpartum (67, 70). Lactating women with a history of GDM have 50% lower prevalence of type 2 diabetes at 6 to 16 weeks postpartum (Table 2) (65).

Analysis of the full health benefits of lactation needs to account for exclusivity, frequency and duration. A subanalysis of the Coronary Artery Risk Development in Young Adults (CARDIA) study examined the incidence of the metabolic syndrome in women of reproductive age according to GDM status and duration of lactation (66). This study showed that longer duration

of lactation was associated with lower incidence of the metabolic syndrome during a 20-year follow-up period after GDM. The findings in CARDIA support the recommendation issued by the American Academy of Pediatrics about 6 months of exclusive breastfeeding and continuation of breastfeeding for at least 12 months (71).

The findings of the two Nurse's Health Studies agree with the statement that increasing duration of lactation reduces the incidence of type 2 diabetes (72). However, stratification by history of GDM in the Nurse's Health Study II showed that lactation provided no additional protection in women with a history of GDM compared with those without a history of GDM.

In terms of lactation and the offspring, the composition of breast milk changes so that hind milk with higher fat content is available in short supply at the end of each feeding episode. Higher fat content at the end may prompt satiety (63). In contrast, infant formulas have a uniform composition and the amount of milk consumed is determined instead by the volume fed. This difference between breast and bottle feeding may result in overfeeding of infants on formula.

In closing on the subject of lactation it is important to comment on hormonal contraception during lactation. Progestin-only oral contraceptives (PO-OCs) are prescribed to lactating women who prefer hormonal contraception. In this situation PO-OCs are chosen because of less interference with milk production. However, lactating women with a history of GDM who are on PO-OCs had a 2.5-fold increase in the rate of conversion to type 2 diabetes compared with non-lactating women on combination oral contraceptives 6 months after postpartum introduction of oral contraception (73, 74). The risk was increased with duration of exposure to PO-OC.

An attractive explanation for these findings is an unopposed effect of progestin in lactating women on PO-OCs because of a physiologic low concentration of estradiol during lactation. In contrast, non-lactating women on a combination of low-dose progestin and estradiol have predominance of the estrogenic effect. Although speculative, this explanation makes sense if we consider that progestins decrease glucose tolerance and insulin sensitivity, and that estrogens are neutral on insulin sensitivity and beneficial for insulin secretion (75). Non-hormonal methods for contraception are preferred for lactating women with a history of GDM.

Recommendations from the Fifth International Workshop-Conference on GDM and the latest reports from the American Diabetes Association (2, 76)

The testing frequency for diabetes and cardiovascular risk factors is based on recommendations from the panel of experts at the Fifth International Workkshop-Conference on GDM due to lack of large population studies (Table 3). Postpartum testing should be done at 6-12 weeks postpartum and 1 year postpartum. Women with IGT should be retested every year and women with NGT should be retested at least every 3 years. The panel of experts also recommended the use of standard screening guidelines for assessment of cardiovascular risk factors when glucose metabolism is tested, encouragement of exclusive breastfeeding, and

caution with the use of PO-OCs and long-acting injectable depomedroxyprogesterone acetate during lactation. Education on lifestyle modification is the main intervention.

Figure 7. Effect of lactation on carbohydrate metabolism. Adapted from reference 69.

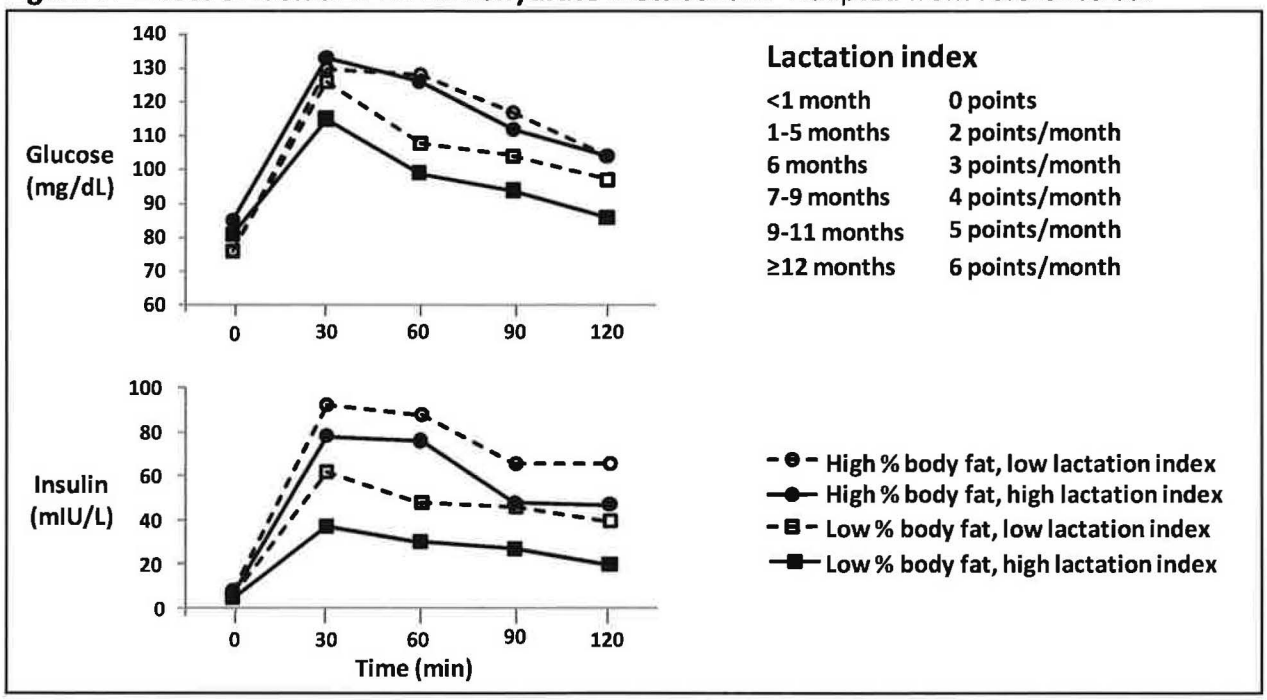


Table 2. Effect of lactation 6 weeks after delivery (65).

	Lactation n=404	No lactation n=405	*P*
Fasting glucose (mg/dL)	93 ± 13	98 ± 17	0.0001
2-h glucose (mg/dL)	124 ± 41	134 ± 49	<0.01
Diabetes (%)	4.2	9.4	0.01
BMI (kg/m^2)	28.8 ± 5.1	28.8 ± 4.5	NS
HDL-C (mg/dL)	48 ± 11	44 ± 10	<0.01

Table 3. Evaluations recommended after GDM (2, 76).

Time	Test	Other*
1-3 days postpartum	FPG or random	Encourage exclusive BF Discuss contraception
6-12 wks postpartum	2-h OGTT	Encourage exclusive BF Start contraception CVD risk factor evaluation
1 year postpartum	2-h OGTT	CVD risk factor evaluation
Every year	FPG	CVD risk factor evaluation
Every 3 years	2-h OGTT	
Pregnancy planning	2-h OGTT	CVD risk factor evaluation

*Education on lifestyle modification at every opportunity

Comment

Most parous women will spend 2 to 10% of their reproductive years in the pregnant state under the care of obstetricians. Primary physicians will provide medical care for the remaining 90% of this reproductive time, menopause and beyond. Medical surveillance after GDM is critical for prevention and early detection of diabetes and cardiovascular risk factors in these women, and for preparation of an intrauterine environment as close to normal as possible (if not normal) in anticipation of a planned or unplanned pregnancy. Periodic monitoring of glycemic status and cardiovascular risk factors, education on weight loss or weight maintenance, physical activity, awareness of hyperglycemic symptoms, and family planning can aid in the prevention of diabetes and its complications. Most of these strategies are important at any age, but more so during the reproductive years because unrecognized metabolic complications can cause unintended harm on the offspring.

References

1- Buchanan TA, Xiang A, Kjos SL, Watanabe R. What is gestational diabetes? Diabetes Care 30:S105-S111, 2007

2- Metzger BE, Buchanan TA, Coustan DR, De Leiva A, Dunger DB, Hadden DR, Hod M, Kitzmiller JL, Kjos SL, Oats JN, Pettitt DJ, Sacks DA, Zoupas C. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diabetes Care 30:S251-S260, 2007

3- Catalano PM, Kirwan JP, Haugel-de Mouzon S, King J. Gestational diabetes and insulin resistance: Role in short- and long-term implications for mother and fetus. J Nutr 133:1674S-1683S, 2003

4- McCance DR, Maresh M, Sacks DA. A practical manual of diabetes in pregnancy. 1st ed. West Sussex, UK: Wiley-Blackwell Publishing, 2010

5- Metzger BE. Long-term outcomes in mothers diagnosed with gestational diabetes mellitus and their offspring. Clin Obstet Gynecol 50:972-979, 2007

6- Ferrara A. Increasing prevalence of gestational diabetes mellitus – a public health perspective. Diabetes Care 30:S141-S146, 2007

7- Ventura SJ, Abma JC, Mosher WD. Estimated pregnancy rates for the United States, 1990-2005: An update. Natl Vital Stat Rep 58:1-16, 2009

8- Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with type 2 diabetes. Diabet Med 21:103-113, 2004

9- Dabelea D, Snell-Bergeon JK, Hartsfield CL, Bischoff KJ, Hamman RF, McDuffie RS. Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort – Kaiser Permanente of Colorado GDM Screening Program. Diabetes Care 28:579-584, 2005

10- Kjos SL, Buchanan TA, Greenspoon JS, Montoro M, Bernstein GS, Mestman JH. Gestational diabetes mellitus: the prevalence of glucose intolerance and diabetes mellitus in the first 2 months post partum. Am J Obstet Gynecol 163:93-98, 1990

11- Kim C, Berger DK, Chamany S. Recurrence of gestational diabetes mellitus – a systematic review. Diabetes Care 30:1314-1319, 2007

12- Carpenter MW. Gestational diabetes, pregnancy hypertension, and late vascular disease. Diabetes Care 30:S246-S250, 2007

13- Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes – a systematic review. Diabetes Care 25:1862-1868, 2002

14- Cheung NW, Byth K. Population health significance of gestational diabetes. Diabetes Care 26:2005-2009, 2003

15- O'Sullivan JB. Body weight and subsequent diabetes mellitus. JAMA 248:949-952, 1982

16- Kjos SL, Peters RK, Xiang A, Henry OA, Montoro M, Buchanan TA. Predicting future diabetes in Latino women with gestational diabetes – utility of early postpartum glucose tolerance testing. Diabetes 44:586-591, 1995

17- Gunderson EP, Lewis CE, Tsai AL, Chiang V, Carnethon M, Quesenberry Jr CP, Sidney S. A 20-year prospective study of childbearing and incidence of diabetes in young women, controlling for glycemia before conception – The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Diabetes 56:2990-2996, 2007

18- Nicholson WK, Asao K, Brancati F, Coresh J, Pankow JS, Powe NR. Parity and risk of type 2 diabetes – the Atherosclerosis Risk in Communities study. Diabetes Care 29:2349-2354, 2006
19- Löbner K, Knopff A, Baumgarten A, Mollenhauer U, Marienfeld S, Garrido-Franco M, Bonifacio E, Ziegler AG. Predictors of postpartum diabetes in women with gestational diabetes mellitus. Diabetes 55:792-797, 2006
20- De Leiva A, Mauricio D, Corcov R. Diabetes-related autoantibodies and gestational diabetes. Diabetes Care 30:S127-S133, 2007
21- American Diabetes Association. Gestational diabetes mellitus. Diabetes Care 27:S88-S90, 2004
22- Carr DB, Newton KM, Utzschneider KM, Tong J, Gerchman F, Kahn SE, Heckbert SR. Modestly elevated glucose levels during pregnancy are associated with a higher risk of future diabetes among women without gestational diabetes mellitus. Diabetes Care, 31:1037-1039, 2008
23- Wilkerson HL, Remein QR. Studies of abnormal carbohydrate metabolism in pregnancy – the significance of impaired glucose tolerance. Diabetes 6:324-329, 1957
24- O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. Diabetes 13:278-285, 1964
25- Mestman JH. Historical notes on diabetes and pregnancy. Endocrinologist 12:224-242, 2002
26- The HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcomes. N Engl J Med 358:1991-2002, 2008
27- Porterfield SP. Endocrine physiology. 2nd ed. Mosby Inc, 2001
28- Buchanan TA, Metzger BE, Freinkel N, Bergman RN. Insulin sensitivity and β-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. Am J Obstet Gynecol 162:1008-1014, 1990
29- Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EA. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. Am J Obstet Gynecol 165:1667-1672, 1991
30- Catalano PM, Tyzbir ED, Wolfe RR, Calles J, Roman NM, Amini SB, Sims EA. Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. Am J Physiol 256:E60-E67, 1993
31- Catalano PM, Huston L, Amini SB, Kalhan SC. Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. Am J Obstet Gynecol 180:903-916, 1999
32- Ward WK, Johnston CL, Beard JC, Benedetti TJ, Halter JB, Porte Jr D. Insulin resistance and impaired insulin secretion in subjects with histories of gestational diabetes mellitus. Diabetes 34:861-869,1985
33- Ward WK, Johnston CL, Beard JC, Benedetti TJ, Porte Jr D. Abnormalities of islet β-cell function, insulin action, and fat distribution in women with histories of gestational diabetes: Relationship to obesity. J Clin Endocrinol Metab 61:1039-1045, 1985
34- Xiang AH, Kawakubo M, Trigo E, Kjos SL, Buchanan TA. Declining β-cell compensation for insulin resistance in Hispanic women with recent gestational diabetes mellitus –

association with changes in weight, adiponectin, and C-reactive protein. Diabetes Care 33:396-401, 2010
35- Homko C, Sivan E, Chen X, Reece EA, Boden G. Insulin secretion during and after pregnancy in patients with gestational diabetes mellitus. J Clin Endocrinol Metab 86:568-573, 2001
36- Kahn SE. The importance of β-cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab 86:4047-4058, 2001
37- Verma A, Boney CM, Tucker R, Vohr BR. Insulin resistance syndrome in women with prior history of gestational diabetes mellitus. J Clin Endocrinol Metab 87:3227-3235, 2002
38- Pallardo LF, Herranz L, Martin-Vaquero P, Garcia-Ingelmo T, Grande C, Jañez M. Impaired fasting glucose and impaired glucose tolerance in women with prior gestational diabetes are associated with a different cardiovascular profile. Diabetes Care 26:2318-2322, 2003
39- Shah BR, Retnakaran R, Booth GL, Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. Diabetes Care 31:1668-1669, 2008
40- Rivero K, Portal VL, Vieira M, Behle I. Prevalence of the impaired glucose metabolism and its association with risk factors for coronary artery disease in women with gestational diabetes. Diabetes Res Clin Pract 79:433-437, 2008
41- Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 325:157-160, 2002
42- Kim C, Cheng YJ, Beckles GL. Cardiovascular disease risk profiles in women with histories of gestational diabetes but without current diabetes. Obstet Gynecol 112:875-883, 2008
43- Heitritter SM, Solomon CG, Mitchell GF, Skali-Ounis N, Seely EW. Subclinical inflammation and vascular dysfunction in women with previous gestational diabetes mellitus. J Clin Endocrinol Metab 90:3983-3988, 2005
44- Anastasiou E, Lekakis JP, Alevizaki M, Papamichael CM, Megas J, Souvatzoglou A, Stamatelopoulos SF. Impaired endothelium-dependent vasodilatation in women with previous gestational diabetes. Diabetes Care 21:2111-2115, 1998
45- Bo S, Valpreda S, Menato G, Bardelli C, Botto C, Gambino R, Rabbia C, Durazzo M, Cassader M, Massobrio M, Pagano G. Should we consider gestational diabetes a vascular risk factor? Atherosclerosis 194:e72-e79, 2007
46- Carr DB, Utzschneider KM, Hull RL, Tong J, Wallace TM, Kodama K, Shofer JB, Heckbert SR, Boyko EJ, Fujimoto WY, Kahn SE, The American Diabetes Association GENNID Study Group. Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. Diabetes Care 29:2078-2083, 2006
47- Martin AO, Simpson JL, Ober C, Freinkel N. Frequency of diabetes mellitus in mothers of probands with gestational diabetes: Possible maternal influence on the predisposition to gestational diabetes. Am J Obstet Gynecol 151:471-475, 1985
48- Silverman BL, Rizzo T, Green OC, Cho NH, Winter RJ, Ogata ES, Richards GE, Metzger BE. Long-term prospective evaluation of offspring of diabetic mothers. Diabetes 40:S121-S125, 1991

49- Silverman BL, Metzger BE, Cho NH, Loeb CA. Impaired glucose tolerance in adolescent offspring of diabetic mothers – Relationship to fetal hyperinsulinism. Diabetes Care 18:611-617, 1995
50- Sobngwi E, Boudou P, Mauvais-Jarvis F, Leblanc H, Velho G, Vexiau P, Porcher R, Hadjadj S, Pratley R, Tataranni PA, Calvo F, Gautier JF. Effect of a diabetic environment in utero on predisposition to type 2 diabetes. Lancet 361:1861-1865, 2003
51- Knowler WC, Pettitt DJ, Saad MF, Bennett PH. Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. Diabetes Metab Rev 6:1-27, 1990
52- Aerts L, Van Assche FA. Is gestational diabetes an acquired condition? J Dev Physiol 1:219-225, 1979
53- Egeland GM, Meltzer SJ. Following in mother's footsteps? Mother-daughter risks for insulin resistance and cardiovascular disease 15 years after gestational diabetes. Diabet Med 27:257-265, 2010
54- Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC. Congenital susceptibility to NIDDM – role of intrauterine environment. Diabetes 37:622-628, 1988
55- Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, Roumain J, Bennett PH, Knowler WC. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity – A study of discordant sibships. Diabetes 49:2208-2211, 2000
56- Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC. Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. N Engl J Med 308:242-245, 1983
57- Ryan EA, Imes S, Liu D, McManus R, Finegood DT, Polonsky KS, Sturis J. Defects in insulin secretion and action in women with a history of gestational diabetes. Diabetes 44:506-512, 1995
58- Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, Fowler S, Kahn SE, The Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 93:4774-4779, 2008
59- Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393-403, 2002
60- Perreault L, Ma Y, Dagogo-Jack S, Horton E, Marrero D, Crandall J, Barrett-Connor E. Sex differences in diabetes risk and the effect of intensive lifestyle modification in the Diabetes Prevention Program. Diabetes Care 31:1416-1421, 2008
61- Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP. Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. Diabetes 51:2796-2803, 2002
62- Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Kawakubp M, Buchanan TA. Effect of pioglitazone on pancreatic β-cell function and diabetes risk in Hispanic women with prior gestational diabetes. Diabetes 55:517-522, 2006
63- Pettitt DJ, Forman MR, Hanson RL, Knowler WC, Bennett PH. Breastfeeding and incidence of non-insulin-dependent diabetes mellitus in Pima Indians. Lancet 350:166-168, 1997
64- Tolis G, Guyda H, Pillorger R, Friesen HG. Breast-feeding: effects on the hypothalamic pituitary gonadal axis. Endocr Res Commun 1:293-303, 1974

65- Kjos SL, Henry O, Lee RM, Buchanan TA, Mishell Jr DR. The effect of lactation on glucose and lipid metabolism in women with recent gestational diabetes. Obstet Gynecol 82:451-455, 1993
66- Gunderson EP, Jacobs Jr DR, Chiang V, Lewis CE, Feng J, Quesenberry Jr CP, Sidney S. Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: a 20-year prospective study in CARDIA (Coronary Artery Risk Development in Young Adults). Diabetes 59:495-504, 2010
67- McManus RM, Cunningham I, Watson A, Harker L, Finegood DT. Beta-cell function and visceral fat in lactating women with a history of gestational diabetes. Metabolism 50:715-719, 2001
68- Taylor JS, Kacmar JE, Nothnagle M, Lawrence RA. A systematic review of the literature associating breastfeeding with type 2 diabetes and gestational diabetes. J Am Coll Nutr 24:320-326, 2005
69- Diniz JM, Da Costa TH. Independent of body adiposity, breast-feeding has a protective effect on glucose metabolism in young adult women. Br J Nutr 92:905-912, 2004
70- Rebuffé-Scrive M, Enk L, Crona N, Lönnroth P, Abrahamsson L, Smith U, Björntorp P. Fat cell metabolism in different regions in women – effect of menstrual cycle, pregnancy, and lactation. J Clin Invest 75:1973-1976, 1985
71- American Academy of Pediatrics Work group on breastfeeding. Breastfeeding and the use of human milk. Pediatrics 100:1035-1039, 1997
72- Stuebe AM, Rich-Edwards JW, Willet WC, Manson JE, Michels KB. Duration of lactation and incidence of type 2 diabetes. JAMA 294:2601-2610, 2005
73- Kjos SL, Peters RK, Xiang A, Thomas D, Schaefer U, Buchanan TA. Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes mellitus. JAMA 280:533-538, 1998
74- Damm P, Mathiesen ER, Petersen KR, Kjos S. Contraception after gestational diabetes. Diabetes Care 30:S236-S241, 2007
75- Ryan EA, Enns L. Role of gestational hormones in the induction of insulin resistance. J Clin Endocrinol Metab 67:341-347, 1988
76- Kitzmiller JL, Dang-Kilduff L, Taslimi MM. Gestational diabetes after delivery – short-term management and long-term risks. Diabetes Care 30:S225-S235, 2007