Pathophysiology and Epidemiology
Incidence of GDM is 5-10%. It is characterized by hyperglycemia due to insufficient insulin to meet the demands of pregnancy. This results from approximately 10% of women demonstrating an autoimmune β-cell defects; Genetic abnormalities; and/or β-cell deterioration and dysfunction related to chronic insulin resistance. Data was presented supporting all three of these causes. The majority of women that are diagnosed with GDM will eventually develop DM. In the first 10 years there is a linear increase in the incidence of DM, regardless of ethnicity. Two forms of insulin resistance exist in women with GDM, They are chronic insulin resistance and β-cell dysfunction leads predominantly to DM. As we already know lifestyle intervention and Metformin can preserve β-cell dysfunction and improve insulin sensitivity.

Women with the autoimmune β-cell defect, and includes abnormal insulin signaling) and the acquired insulin resistance. All of these are exacerbated by pregnancy. The abnormal insulin signaling continues for up to a year after delivery in women that have normal glucose tolerance post delivery. Women with GDM have lower insulin secretion in comparison to the normal glucose tolerance (NNGT) population. This chronic insulin resistance and β-cell dysfunction leads predominantly to DM.

Perinatal Programming of Obesity – Does it Start in the Brain
Sylvie Hauguel De Mouzon; Richard Simerly; Kevin Grove; Andreas Plegmann; Michael Ross
Abnormal glucose homeostasis and hormones such as leptin resets the hypothalamic feeding circuits of the offspring. Leptin that is affected during pregnancy, will affect food intake and weight. Alternating nutrition postnatally will also affect the leptin levels and its set points in the brain. Without leptin or with malprogramming of these circuits there is an increase in blood glucose and insulin resistance (IR).

Chronic high fat diets in primates demonstrated that there is a genetically protected (40%) the dietary resistant group. This was contrasted with a dietary sensitive group (60%). The dietary sensitive group had increased leptin levels, body fat, IR, insulin levels and pregnancy weight gain when fed high fat diets. Many of these had higher lipid levels and inflammatory markers. These markers shifted the blood brain barrier and increased receptors/transport within the brain. This resulted in abnormal development in these feedback systems. Perinatal hyperinsulinism and malprogramming of body weight regulation. Increased obesity and impaired glucose tolerance (IGT). This is associated with increased amniotic insulin levels. Infants with high amniotic fluid insulin gained the most weight in their first 4 months of life and had the highest obesity rates. So early feeding affected the incidence of obesity.

Continued on page 2
Kaiser has seen a 50% increase in the GDM rate. This is also seen in the offspring of GDM rats. This early neuroendocrine malprogramming leads to an abnormal response to hormones such as insulin and leptin. Early intervention and reprogramming with lower glucose and insulin levels prevent or decrease the abnormal neuroendocrine mal-programming. This malprogramming can also be decreased with attainment of a normal prepregnancy BMI, slower pregnancy weight gain, lower dietary fat intake. It is buffered with breastfeeding and early infant feeding practices.

Intra-hypothalmic administration of insulin in rats increased weight, hyperphagia, and decreased glucose tolerance. This is also seen in women that smoke, in multiple gestations, and it improves survival when food is scarce. Calorie restriction during pregnancy resulting in IUGR is associated with increased HTN, lipids, body fat, obesity, decreased glucose tolerance, and increased insulin levels. Appetite centers are reset so that, when presented with a free meal plan they eat in excess. They demonstrate a decreased response to food in the anorexogenic hypothalamic pathway. They don’t get full. They are more resistant to leptin, resulting in increased fat and greater lipogenisis.

Mutations vs. programming The thrifty phenotype is seen with intrauterine growth restriction. It is also seen in women who smoke, in multiple gestations, and it improves survival when food is scarce. Calorie restriction during pregnancy resulting in IUGR is associated with increased HTN, lipids, body fat, obesity, decreased glucose tolerance, and increased insulin levels. Appetite centers are reset so that, when presented with a free meal plan they eat in excess. They demonstrate a decreased response to food in the anorexogenic hypothalamic pathway. They don’t get full. They are more resistant to leptin, resulting in increased fat and greater lipogenisis.

Epidemiological Advances in Gestational Diabetes

Wanda Nicholson

In recent years we have seen an increase in surveillance, obesity, DM, hyperglycemia and changing diagnostic criteria. The NHANES study demonstrated an 8% increase in FBS in women 20-39 year olds. In the Kaiser system there has been an increase in weight in 2nd trimester, coupled with an increase in A1c. There are more women who are over 35 years old, from a high risk ethnic group, increasing pre-pregnancy BMI, increased usage of hormonal contraceptives, lifestyle, increased body fat (central obesity) in the pregnant population. When looking at the BMI at age 20, the average woman increases 2.3 Kg every 5 years. This doubles the rate of GDM in 5 years. Weight gain between pregnancies is also a risk factor (Henderson). Increased leptin and decreased adiponectin leads to increased rates of GDM. In the last 10 years Kaiser has seen a 50% increase in the GDM rate.

Contributing factors are obesity, retention of pregnancy weight, lifestyle, and medication usage.

Ravi Thandhani

Insulin resistance (IR) and inflammation are both contributory factors to GDM. During pregnancy there is a superimposed IR and insulin secretion defects are discovered. This is even greater in women with DM 2. Both IR and inflammation negatively affect insulin secretion. IR is associated with increased rates of preeclampsia. Postpartum screening at 4-5 years postpartum after GDM identified 50% of these women with DM. This is similar to the Pima Indian studies. In both studies there is an increase in white cell count (macrophage) during the 1st trimester. CRP is another inflammatory factor increased in the 1st trimester, in women with IR. CRP is closely related to obesity. Other factors are increased serum ferritin, sex hormone binding globulins, TNF-alpha, and cytokines. Both TNF-alpha, and cytokines, are made by the placenta and are increased with IR and obesity. IR negatively effects insulin secretion. In women that have IR this defect continues and will not return to normal at postpartum. In women with preeclampsia we see an increase in Veg-f and S-fit. These are both placental and inflammatory factors that are associated with vascular disease.

Darryl Carr

GDM women per Kim have an increased DM diagnosis rate by 5-10 years postpartum. Women with this history have decreased insulin secretion, increased IR, decreased HDL, increased cholesterol, TG and LDL, decreased adiponectin, increased Pai-1, increased CRP, increased systolic blood pressure (SBP), increased BMI and abdominal circumference. These women have demonstrated endothelial dysfunction. This is seen in both obese and non-obese women with a history of GDM. Women with a GDM history have a 40% incidence of metabolic syndrome (MS). This increases the incidence of cardiovascular disease at younger ages. There is an increased incidence of a first cardiovascular event by mid-forties and first stroke by early 50s, in comparison to women without a GDM history. A history of GDM should be a trigger to screen for cardiovascular disease.

Maternal low birth weight (<2499 grams) increased DM and GDM. Adiposity as teens doubled the GDM rate. From the age of 18 every 2.5 kg gained increased the risk of GDM.

Higher fat diets increased the reoccurrence of GDM (Moses). This association was stronger with saturated
fats. Diets with polyunsaturated and non-saturated fats decreased the GDM rate (Saldama). Prepregnancy dietary intake of more fruits, vegetables and fish was associated with a decreased incidence of GDM (Zhang). Diets with adequate vitamin C was protective in comparison to those with an inadequate vitamin C intake had a 3.7 fold increase in GDM. Dietary fiber of >22 Grams/day decreased the risk of GDM by 33%. Lower glycemic load foods had similar effects. So encourage diets with low saturated fats, increased fruit and vegetables, high fiber, low glycemic load foods, fish and adequate vitamin C.

Women that participated in any leisure time exercise had a 55% reduction in GDM. One and a half hours per week of exercise before and during pregnancy reduced the GDM rate by 48%. There was a 60% reduction if this was for 1 year before and during pregnancy, and continued through the next pregnancy.

**Weight Gain in Pregnancy with Obesity**

D Sacks

It is unclear how much is adequate and what is excessive. Present targets are based on low birth weight. The gain recommendations were to prevent SGA. Now, obesity is a major issue. So how do we prevent obesity? These older guidelines may not apply with our more obese and diverse ethnic population.

Weight loss of more than 10 lbs between pregnancies decreased the GDM risk. Minimal or excessive weight gain did increase fetal weight. Obese women have larger babies even with normal weight gain. In LGA babies, of women with GDM, the proportion of fat to muscle is larger when compared to LGA infants of non-GDM women. Maternal obesity alone increased the body fat of the infant. What can be done? Recommendations are to encourage prepregnancy weight loss, obesity prevention, lactation, exercise, modify environmental influences, and to alter the maternal diet. Influences on fetal growth also come from cultural beliefs and practices, maternal placental and fetal cytokines, and hormonal regulation. In the future some of these factors maybe modifiable.

S Kjos

**Weight gain restriction in pregnancy?**

In 1993 Institute of Medicine (IOM) recommended 35 Kcal/Kg/day. There has been no change since. We have seen an increase in preeclampsia, HTN of pregnancy, macrosomia, GDM and C/S rates since those guidelines came into effect. We have also seen and increase in MS, increasing prepregnancy BMI and postpartum obesity. Women that gain excessive weight during a pregnancy are more likely to retain it into their next pregnancy. Weight gain above 16 kg, increased the risk of obesity in the mother and LGA in the infant. This was also associated with increased weight in the child as they grew. Both low birth weight (<5lbs) and high birth weight (>10lbs), increased the risk of lifetime obesity. Normal weight did not increase this risk.

In a study that looked at what information was given to women, in relation to their weight gain and based on their prepregnancy BMI, found that the majority did not receive the correct weight gain recommendations. Women without GDM gained more weight in a comparison study. Prepregnant obesity is strongly associated with excess weight gain and more LGA infants, even without excessive weight gain during pregnancy.

A minimum of 1800 kcal to a maximum of 2300 kcal is recommended. Ketones are used to detect starvation ketosis. Ultrasound is recommended if starvation is suspected. Historically, ketones were negatively associated with IQ and development. Most low CHO meal plans do not result in that level of ketosis. It would have to be similar to an Atkins meal plan. With poor weight gain, if the baby appears normal on ultrasound that should be sufficient to demonstrate adequate nutrition.

The IOM is rewriting its guidelines and we expect a reduction in the weight gain recommendations.

G Hotamisligi

**Inflammatory Basis of Obesity and DM**

Obesity is related to IR, type 2 DM, CVD, dyslipidemia, fatty liver disease and HTN. Secondary conditions are airway disease, metabolic syndrome, neurodegenerative (such as Alzheimer’s), and cancer.

Obesity increases TNF alpha, which interferes with insulin receptors and increases inflammatory factors such as cytokines, JUNK and so on). This stress occurs on and in the cell and thereby increases obesity. With obesity there is macrophage infiltration of visceral adipose tissue leading to increasing adiposity, fatty liver disease and metabolic syndrome. Interestingly over nutrition increases this immune response and under nutrition decreases this immune response. So under nutrition does result in weight loss, by changing the immune response and changing both the make (less macrophages) and the amount of fat. The less of these macrophages there are, the less fat is stored.
defects demonstrated autoimmune defects similar to DM 1. The incidence rate is similar to the expected rate in the normal population. The autoimmune factors identified were cytoplasmic islet cell antibodies, antibodies directed against GAD65, membrane tyrosine phosphate and insulin antibodies.

The placental metabolism and transfer of glucose are normal in GDM pregnancies. Evidence demonstrated that fetal insulin modifies the placental gene expression, glycogen deposition and vascular expansion in the placenta. So fetal gene expression modified the impact of GDM on pregnancy outcomes, not just maternal hyperglycemia.

There has been a global increase in GDM, DM 2 and obesity. This increase is greater in non-white ethnic groups and there has been a disproportionate increase in younger women verse older. Other factors associated with GDM were obesity, low levels of physical activity, and birth weight of the woman. Discussion was given to identifying potentially alterable factors and implementing prevention strategies.

**Therapeutic Interventions**

GDM therapeutic interventions, and maternal and fetal surveillance very significantly and are inconsistent. Average blood glucoses of 87-110 mg/dl had the lowest Maternal and fetal complications. Yet, no clear recommendations were identified since treatment again varies significantly between research projects. Discussion was given to identifying potentially alterable factors and implementing prevention strategies.

Fetal growth remains a major concern. This is primarily due to hyperinsulinemia of the fetus. Many of the maternal and fetal outcomes again are not defined in a standard manor. LGA (large for gestational age) / Macorsomia are defined as > 4,000/4,250/4,500 grams. Consequences of GDM are also birth trauma, maternal morbidity from operative deliveries, and life-long increased risk of obesity, IGT, and DM in the offspring. Immediate fetal outcomes include hypoglycemia, hyperbilirubinemia, hypocalemia, polycythemia, and poor feeding. Also associated maternal/fetal outcomes were preterm delivery and hypertensive disorders of pregnancy such as preecampsia.

A recommendation for screening was deferred until after the HAPO study was completed. Goals for therapy are based on the 4th international meeting and are FBS < 95 mg/dl; 1 hour < 140 mg/dl and 2 hour < 120 mg/dl. The timing of these values is from the start of the meal. Average values less then 87 mg/dl resulted in SGA infants. In women with normal glucose tolerance the peak post meal values are 110 ± 16 mg/dl.

Memory meters were recommended and CGMS has been shown to provide some beneficial information. Alternate site testing is discussed and if considered the lag time for changes in post-prandial glucose concentrations need to be taken into consideration.

Evidence was presented to utilize ultrasound information to modify the metabolic management of women. For example, if growth is > 75%, lower glucose targets may be indicated to slow the fetal growth.

Urine ketones are recommended for significant elevations in glucose and to check for starvation ketosis. Psychosocial assessment is encouraged to identify issues such as depression, eating disorders and anxiety that may interfere with treatment.

Minimal recommendations were made per medical nutrition therapy. Primarily to utilize carbohydrate counting, food records, and BG testing with the meal plan. This summary reinforced the continued use of the IOM recommendations for weight gain during pregnancy. Emphasis to limit excess weight gain since it is associated with macrosomia and excess weight retention postpartum.

Exercise recommendations are 30 minutes per day, broken into 10 minutes after each meal.

Insulin analogs of lispro and aspart demonstrated in comparison to regular human insulin, no teratogenesis; less postprandial hypoglycemia; improved postprandial hyperglycemia and similar antibody titers. So the insulin analogs of lispro and aspart are recommended for use. The use of intermediate acting insulin NPH is still recommended. The long acting agents of glargine and detemir have not been studied so these drugs are not recommended at this time.

Only glyburide (glibenclamide) is recommended for use during pregnancy. It is less successful in obese women, and in women with significant hyperglycemia. Metformin crosses the placenta so at present it is only being utilized in clinical trials until offspring follow-up.
Breastfeeding benefits are well established and new mothers are offered much support to maximize their success. However, using certain medication while lactating complicates the decision to breastfeed for mothers and professionals who care for them. Given the prevalence of psychiatric illness during the perinatal period(1) a significant number of women may be using psychotropic medication while breastfeeding. Best practice is always an individualized risk-benefit analysis of the severity of the mother's depression and potential known risks to the infant.

Concern is raised regarding the safety of medication as none are FDA approved for breastfeeding and limited safety data is available(2). No professional medical association has issued formal guidelines regarding pregnant or lactating women and use of psychiatric medication treatment including SSRIs. Current research does indicate that, while all medications are secreted into the breast milk, the incidence of adverse effects on nursing infants appears to be relatively low (3,4). Data indicates that all psychotropic medications, including antidepressants, lithium, anti-psychotics, anticonvulsants, and benzodiazepines, are secreted into breast milk although concentrations vary significantly. Long-term neurodevelopmental effects for the infant may not be predictable but maternal-children relational difficulties in untreated depression are well documented (5).

Antidepressants
In recent years more information has been compiled on the use of antidepressants in nursing women. Data on tricyclic antidepressants and sertraline and fluoxetine has been encouraging, suggesting that the infant's exposure to amounts of the drug is low and that neonatal complications appear rare. (6,7) To this point, data is reassuring. Most often serum levels of the drug in the nursing infant is very low or undetectable. One report indicates that exposure to SSRIs during nursing does not result in significant blockage of serotonin reuptake in infants (8). SSRIs are the drug category of choice in pregnancy when treating depression but more safety data on breastfeeding is ultimately needed.(9)

- Fluoxetine (Prozac) has been the most studied SSRI in pregnancy but it has a long half-life and is not recommended in breastfeeding as it may accumulate in infant sera.(11)
- Citalopram (Celexa) and also escitalopram (Lexapro) unlike sertraline, have been studied more frequently but have a higher fetal-maternal serum level. These are viewed as the next choice after sertraline or fluoxetine (12)

Mood Stabilizers
Bipolar disorder poses more significant difficulties to breastfeeding women. On demand breastfeeding disrupts a mother’s sleep and can increase the possibility of relapse. Toxicity has been reported with mood stabilizers, including lithium, carbamazepine and valproic acid.(13, 14,15). AAP determined carbamazepine and valproic acid are appropriate for breastfeeding women and lithium was contraindicated.(16)

Anti-Anxiety
Data on benzodiazepines, diazepam (Valium), clozapine (Klonopin), lorazepam (Ativan) is limited (17) with some adverse effects noted. Data suggest that a nursing infant's exposure to the drug is small especially if drug dosages are kept low.

Antipsychotics
Information about use of antipsychotic drugs is limited, especially for newer atypical antipsychotics such as risperidone (Risperdal), quetiapine (Seroquel), ziprasidone (Geodon), and aripiprazole (Abilify) (18) Data on clozapine suggests it is concentrated in breast milk but there is no data on infant serum levels. Significant adverse effects of clozapine are evident including decreased white blood count. (19)

Treatment Guidelines
As studies and clinical experience with breastfeeding mothers and concomitant drug use increase, reassuring results for the mothers and professionals will help in the decision-making process. As with any informed critical decision, up to date information is needed by the health professional to assist the mother in making the best decision for herself and her family. Careful coordination with the prescribing psychiatrist and pediatrician is essential.
studies are available. It has also been used in women with PCOS to improve fertility and decrease spontaneous abortions rates. The efficacy of Acarbose for reducing post parandial glucose excursions has been demonstrated in several small studies. This medication has not been fully explored, but appears to have potential benefits.

Thiazolidinediones, glinides, and glycagon-like peptide 1 agonist during pregnancy is considered experimental and is not recommended at this time.

Fetal / Maternal Surveillance
GDM treatment and surveillance is extremely inconsistent. This is even more dramatic when treatment is compared between women with and without medication treatment are compared. In women that require medications the fetal and maternal surveillance are basically the same as Sweet Success recommendations. Women presenting with A1c > 7.0% or FBS >120 mg/dl demonstrate an increase in major birth defects. Ultrasound for major malformations and macrosomia are recommended. But for women without medication intervention there is variation in the use of ultrasound for growth and delivery planning. One study presented utilizing ultrasounds every 2-4 weeks and only intervening when the baby was > 75%.

Fetal movement monitoring should be utilized in the last 8-10 weeks of pregnancy in all women. In the summary article they state “type and frequency of surveillance for fetal well-being should be influenced by the severity of maternal hyperglycemia or the presence of other adverse clinical factors”. No hyperglycemia limits were given. Average BG of > 100 mg/dl was associated with increased mortality and morbidity. In women utilizing medications for metabolic control Non-Stress Test (NST) after 32 weeks is recommended if utilizing insulin and near term in diet controlled. Bio-Physical Profile (BPP) and Doppler velocimetry is recommended in cases of excessive or poor fetal growth or with co-morbid conditions. NST were recommended for women without insulin in near term of if other contributing factors exist. Amniocentisis is still recommended in poorly dated or planned deliveries before 38 weeks.

Another interesting point that is maternal lipid levels affect fetal growth. Limiting fat intake or monitoring maternal lipid levels will not be considered during treatment and care. Women, with GDM and overt DM. have higher triacylglycerol, VLDL and lower HDL levels then women with normal glucose tolerance. This combination is associated with macrosomia. Should we be monitoring and intervening in women with higher then normal levels? No normal levels for pregnancy are presented.

Offspring
Birth weight both large (>4,000 grams) and small (definitions vary 5 to 5 and ½ lbs) is a risk factor for obesity, future abnormal glucose tolerance (including type 2 DM and increased risk of GDM), HTN and CVD. Genetic factors and phenotypes also affected growth and were impacted by glucose control. Breastfeeding modified the risk of obesity and is encouraged. It decreased obesity and glucose intolerance in both mother and her infant.

Maternal Follow-up
Initial postpartum management is to encourage maternal-infant well-being, healthy nutrition, physical activity, weight reduction, smoking cessation, breastfeeding and appropriate contraception. Also screening with a 75 gram OGTT will unmask IGT and type 2 DM. A diagnosis of abnormal glucose tolerance postpartum can be utilized to prevent future complications for both future offspring and the long-term health of these women. Interventions for these women should be implemented postpartum. Abnormal lipid metabolism and risk of CVD was demonstrated in GDM women.

Lipid screening maybe included in postpartum recommendations in the future. Data demonstrated an increased incidence of metabolic syndrome in women with a GDM history. Screening and interventions may potentially be directed in this direction.

Most contraceptive methods are the same for GDM women. The only limitation is to avoid progestin only contraceptives in breastfeeding women.

Sweet Success has plans to change the data that we collect. If you have any question or suggestions contact Leona in region 4 at Leonad@stanford.edu
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Beyond the Number: Breastfeeding and Psychiatric Medication
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REFERENCES


Omega-3 Fatty Acids and Pregnancy
Geetha Desai, MS, RD, CDE, CLE

Research emphasizes the fact that increasing dietary omega-3 fatty acids may have a number of health benefits. Infants born to mothers with higher levels of omega-3 fatty acids (DHA) at delivery had advanced levels of attention spans well into their second year of life.

DHA is found naturally in breast milk and is now available in infant formulas and some baby foods. It is recommended that pregnant women get their DHA through algae-derived supplements available in health food stores. Omega-3 fortified eggs are another good source of DHA.

Studies suggest that women need about 250 mg of DHA daily during pregnancy although it is not very clear what the exact amount of omega-3 fatty acid is needed during pregnancy.
Conferences

Sweet Success Affiliate Training – Preceptorships. September 5; October 17, 18, November 14, 15, 2007. Each session can accommodate 3 people of different disciplines. For more information please contact Ramona at 916-208-2811.


September 15, 2007 Santa Clara. December 8, 2007 San Diego. Taking Control of Your Diabetes. client focused conference. For more information call 858-755-5683 or go to: www.tcoyd.org


October 9, 2007. Meeting the Contraceptive Needs of the Woman with Diabetes, and Asian Food Challenges & Solutions: Teaching the GDM Diet. For information call 310-222-3651.

Los Angeles, CA. Or email: SoBayPeriP@labiomed.org

October 12-14, 2007. Lactation Professionals Conference 2007: Nurture Mind, Body and Spirit: Breastfeed! Sacramento, CA. For more information please call 925.754.1284 or email LLLConference@yahoo.com

