

# Notes from the GDM Pasadena II: An International Conference on Gestational Diabetes

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**DAY 3 - 4/10/10**

## Management of GDM

**Caroline Crowther, FRANZCOG, MD, FRCOG, CMFM;** Professor of Obstetrics,  
University of Adelaide, Australia

Consideration of cost-consequence analysis of treating women with mild GDM by advice, blood glucose monitoring and insulin therapy vs. routine pregnancy care.

For every 100 women singleton pregnancy and positive oral glucose tolerance test:

\$53,985 additional direct costs at hospital

\$6,521 charges to women and their families

9.7 additional women had induction of labor

8.6 more babies admitted to neonatal nursery

*2.2 fewer babies experienced serious perinatal complication*

*1.0 fewer babies experienced perinatal death.*

*Findings indicate treatment of GDM is cost effective*

## **Implications of the MFMU Network: NICHD RCT of the Treatment of Mild GDM**

**Mark B. Landon, MD:** Ohio State University College of Medicine, Columbus, Ohio

Treatment of mild GDM reduced the risk for fetal overgrowth, neonatal fat mass, shoulder dystocia, cesarean delivery and hypertensive disorders of pregnancy.

One abnormal OGTT value confers significant perinatal risks

## **Macronutrient Intake and GDM: The effect of low GI diet**

**R G Moses, MD:** Senior Medical Officer: New South Wales, Australia

Study: Did a low Glycemic Index (GI) diet reduce the need for insulin in women with GDM?

- 9 of 31 (29%) women on low GI diet required insulin
- 19 of 32 (59%) assigned a higher GI diet required insulin and these women were changed to a low GI diet and 9/19 were able to avoid insulin use.

2<sup>nd</sup> Study effect of diets on normal women during normal pregnancy

70 women, 2 arms: Low GI diet with total fiber intake increased

Normal GI diet with increased fiber

Outcome: higher GI diet women had infants who were heavier, and a higher prevalence of LGA infants

## **Micronutrient Intake as part of Medical Nutrition Therapy for GDM**

**Aidan McElduff, MB,BS; PhD FRACP;** Associate Professor of Medicine, University of Sydney, Australia

Minerals trace elements and vitamins

NIH's position: there is not enough scientific evidence to prove that dietary supplements have substantial benefits for type 2 diabetes

GDM associated with high homocystine levels which might be indicative of low folic acid or B12 intake, low Vit D, low Vit C, low selenium and others, but little data on cause and effect relationship with any of these

Vit D a highly regulated steroid hormone can potentially regulate up to 3% of the human genome and associated with a large variety of metabolic/cardiovascular effects.

A number of studies suggest the V D deficiency contributes to increased risk for type 2 DM and GDM. Pancreatic B-cells have both Vit D receptors and activating enzyme 1- $\alpha$  hydroxylase and muscle cells have Vit D receptors

B-12 deficiency could impair protein synthesis and muscle development = insulin resistance.

Variations of nutrients found in foods e.g. wild salmon contain 75% more Vit D than farm raised.

Best to buy fresh (not in a box),do less to it, walk

## **Assessment of Glycemia and GDM**

**Yariv Yogev, MD**; Associate Professor of Obstetrics, Tel Aviv University, Israel

Two studies of continuous blood glucose (CGM) monitoring:

- First study with non-diabetic women. In this study obese women were characterized by a significantly higher postprandial glucose peak, increased 2 hr postprandial glucose, increased time interval for glucose peak and significantly lower mean blood glucose during the night.
- Second study in women with GDM Conclusion CGM helpful for accurately detecting high postprandial blood glucose levels and nocturnal hypoglycemic events that may go unrecognized by intermittent blood glucose monitoring

## Physical Activity (Walking) and GDM Treatment

**Raul Artal, MD**; Professor and Chair of Obstetrics, St Louis University, Missouri

GDM precedes Type 2 DM and has similar pathophysiology of insulin resistance, pancreatic beta-cell dysfunction and for most, genetic predisposition and lifestyle factors. 10-31% of Type 2 DM had GDM. First.

### **Lifestyle interventions – diet and exercise prevent GDM or prevent progression of GDM to type 2 DM**

Physical activity during preconception and pregnancy reduce GDM and normalize glucose levels in pregnancy **One study risk of GDM reduced by 17% with pre-pregnancy light exercise (30 minutes a day - especially after meals) and 30% with more vigorous exercise.** Make sure the exercise involves large muscles.

One study showed that GDM pts showed benefit within 10 days of exercising. **Due to the danger of hypoglycemia do not exercise continuously for > 45 minutes.**

#### **SUMMARY:**

1. Physical activity prior and during pregnancy can prevent GDM
2. Physical activity is safe therapeutic adjunct in pts with GDM
3. Exercise programs should expend approximately 1400 kcal/week to attain euglycemia
4. Weight gain restriction /loss is a safe intervention in obese GDM pts resulting in less LGA newborns
5. Need additional large studies to confirm these trends

## **Oral Hypoglycemic Agents in Pregnancy**

**Oded Langer, MD;** Professor and Chair of Obstetrics, Roosevelt Hospital, Columbia University, New York City, New York

Looked at safety and efficacy for the mom and baby

Glyburide 9 Randomized studies

Absorbed within 1 hr short elimination 6-8 hrs High protein binding The timing of administration affects the drug's concentration Seems to be as effective as insulin including in obese pts. glycemic control and more cost effective than insulin.

Metformin 3 Randomized studies

Had more failure rates than glyburide

## **Glyburide – Placental Interactions**

**Jason G. Umans, MD, PhD, FACP;** Associate Professor of Medicine & OB/GYN, Georgetown Univ., MedStar Research Institute, Washington, D.C.

The human placenta has the capacity both to oxidatively biotransform glyburide to its metabolites (Biochem Pharmacol 2009;78:1483-90) and to transport glyburide from the fetal to maternal side, in *ex vivo* perfusion studies, by various transporters including breast cancer resistance protein (BCRP). In their landmark study (NEJM 2000;343:1134-8), Langer and colleagues failed to detect glyburide in cord plasma at delivery (detection limit = 10ng/ml) when maternal concentrations were still 50-150ng/ml at ~8h following the last dose prior to delivery. By contrast, in our study, which used a more sensitive assay (detection limit = 0.13ng/ml), we unexpectedly observed much lower maternal glyburide concentrations (0-32.7ng/ml) and cord venous plasma values of 0-12.5ng/ml, which averaged  $0.7 \pm 0.4$  of simultaneous maternal values, with no apparent ill effect.

There remains much uncertainty regarding the concentration-effect relationship for the hypoglycemic effect of glyburide as well as the hypoglycemic potencies of its metabolites. It is possible that changes in dose or dose interval may lead to improved glycemic control in glyburide-treated women with GDM who have suboptimal responses to usual doses extrapolated from nonpregnant populations, though fetal exposure to glyburide and its metabolites would likely increase.

## Metformin Treatment of GDM

**Janet Rowan, MD, FRACP;** Professor of Medicine, Auckland, New Zealand

MiG Trial compared metformin with insulin

Metformin is a logical treatment for women with GDM. The MiG Trial, a prospective randomized trial comparing metformin (with supplemental insulin if required) with insulin treatment showed that metformin was not associated with increased perinatal complications. There were no differences in caesarean section rates, maternal hypertensive complications or neonatal anthropometric measurements. Women gained significantly less weight in the metformin arm and preferred metformin treatment. Subsequently, some centres have started using metformin for treatment of GDM and others are waiting for two year old follow up data. Still others are trying to address whether glyburide is a better first line oral agent than metformin. At present, data suggest glyburide alone may be more effective than metformin alone at achieving glucose targets, but further data are required regarding other pregnancy and long term outcomes. Since June 2007 at NWH women with GDM requiring medication have been given the option of metformin or insulin treatment. In women who choose metformin and have fasting glucose levels above 6.0mmol/l (108mg/dl) we typically start supplemental bedtime isophane insulin at the same time. Supplemental meal time insulin analogue is given as required after titrating up the daily metformin dose to 2500mg (occasionally 3000mg). Of note, in this multiethnic clinic, of the 75% of women with GDM who do a follow up OGTT at 6-8 weeks postpartum, 30% have glucose intolerance or type 2 diabetes.

From the hospital database during 2007 and 2008 there were 763 women with GDM who delivered at NWH; 250 women were treated with diet, 298 with insulin and 215 with metformin. In the metformin group, 91 were treated with metformin alone and 126 had insulin treatment as well. In the insulin and metformin treatment groups respectively, rates of preeclampsia were 5.0% vs 2.8% ( $p=0.73$ ), caesarean deliveries were 45.6% vs 33.5% ( $p=0.03$ ), mean gestation at delivery was 38 weeks and median (25-75th IQ range) birth weight was 3268g (2850-3630g) vs 3220g (2900-3545g) ( $p=0.95$ ). Customised birth weight <10th percentile was 11.3% vs 9.2% ( $p=0.73$ ) and >90th percentile was 18.5% vs 12.9% ( $p=0.16$ ). Rates of preterm birth were 17.9% vs 12.9% ( $p=0.03$ ). Neonatal unit admission was 19.5% vs 13.4% ( $p=0.04$ ) and iv dextrose was given in 9.9% vs 4.6% ( $p=0.05$ ).

From the initial MiG trial, follow up of 2 year olds has been completed in Auckland and Adelaide. Data have been analysed on 144 children whose mothers were randomized to metformin and 154 children whose mothers were randomized to insulin. In the metformin group the upper arm circumference was significantly bigger (17.3cm vs 16.7 cm,  $p=0.003$ ) and subscapular skinfold was also bigger (6.38 vs 6.10 cm  $p=0.03$ ) than in the insulin group. There were no differences in other measurements or the subscapular:triceps or waist:hip ratios. After adjusting for maternal glucose control and

ethnicity, (baseline differences) there was no difference in subscapular skinfolds, but the difference in upper arm circumference remained. With DEXA measurements, total fat, abdominal fat, thigh fat and the abdominal:thigh fat ratio were no different. These data support the safety and efficacy of metformin treatment for GDM in routine clinical practice.

Initial analyses of two year old data do not show any adverse effects of metformin on growth and adiposity.

## **Advances of Insulin Therapy for GDM**

**David Sacks, MD;** Adjunct Investigator, Department of Research, So. California Permanente Medical Group, Pasadena, California

The in-vitro affinity of glargine for IGF-1 receptors and its mitogenicity in culture with osteosarcoma cells have raised concerns regarding its potential for promotion of teratogenicity, tumor growth, and fetal macrosomia. Further investigation is needed to determine the risks and benefits of the use of insulin and its analogues in gestational diabetes.

Insulin analogs cost 2x the price of regular insulin.

## **Fetal Assessment and Gestational Diabetes**

**Barak Rosenn, MD**; Professor of Obstetrics, Roosevelt Hospital and Columbia University, New York City, New York

Maternal diabetes has long been recognized as a risk factor for fetal loss and stillbirth. The cause of stillbirth in pregnancies complicated by maternal diabetes is uncertain, but studies in humans and in animals have demonstrated that maternal hyperglycemia and fetal hyperinsulinemia are associated with increased oxygen consumption, lactic acidemia, hypoxia, and oxidative stress. Even mild fetal hypoxia in combination with minimal hyperglycemia may result in severe acidosis and fetal death. Other possible mechanisms leading to stillbirth include placental vascular dysfunction, maternal ketoacidosis, and fetal myocardial dysfunction.

Although it is clear that pregnancies in women with pre-gestational diabetes are at increased risk for adverse outcome, particularly in the presence of systemic complications, the risk associated with gestational diabetes is less well defined. To the extent that maternal hyperglycemia, per se, imposes on the fetus the potential for adverse outcome, it should not matter whether maternal hyperglycemia (and consequently, fetal hyperglycemia) is the result of gestational or pre-gestational diabetes. Indeed, recently published studies have demonstrated that even minor degrees of maternal hyperglycemia may adversely affect the fetus without any identifiable threshold effect. However, these studies did not demonstrate an association between minor maternal hyperglycemia and an increased risk of fetal loss. The data regarding the association between gestational diabetes and stillbirth are inconsistent and many published studies suffer from methodological deficiencies. Nevertheless, both factually and logically, it appears that the risk of stillbirth in gestational diabetes depends on the level of maternal hyperglycemia and fetal hyperinsulinemia.

Thus, in considering antenatal testing for these pregnancies, the scarcity of evidence needs to be tempered by clinical judgment in formulating a logical approach. For the woman who is well controlled with diet and whose fetus shows no evidence of diabetic fetopathy, antenatal testing is unlikely to yield any benefit. In these women, the risk of stillbirth is minimal, possibly even lower than in the general population, due to the focused care and attention they receive during pregnancy. Conversely, in women who have difficulty maintaining good glycemic control, or in the presence of diabetic fetopathy, as determined by ultrasound, antenatal testing appears prudent.

As for the woman who has achieved good glycemic control with medical therapy, the preferred strategy is less clear. Certainly, the need for medications reflects a more severe state of underlying hyperglycemia that may have adversely affected the fetus before being identified and successfully treated. This usually means several weeks of maternal (and fetal) hyperglycemia that may have led to irreversible fetal pancreatic beta cell hyperplasia and hyperinsulinism, placing this fetus at risk. Similarly, in a woman with poorly controlled gestational diabetes whose fetus does not show any

evidence of diabetic fetopathy on ultrasound, hyperglycemia has most likely generated fetal hyperinsulinism that simply failed to be detected. Indeed, the sensitivity of ultrasound in detecting abnormal fetal growth is no more than 70-80%, such that the absence of sonographically evident fetopathy should not instill a false sense of security. But can antenatal fetal testing achieve the desired goal of improving perinatal outcome and decreasing the risk of stillbirth in these pregnancies? In the absence of prospective randomized trials, this question cannot be answered and is unlikely to be answered in the foreseeable future. Thus, gestational diabetes is no different from other "high risk" pregnancies in which antenatal testing is commonly practiced, based more on empirical and anecdotal experience than on any solid evidence of its benefit. Surely, periodic sonographic evaluation may detect the fetus who is demonstrating the effects of hyperinsulinism, prompting a more cautious approach in surveillance and timing of delivery.

The benefit of antenatal fetal monitoring with the non-stress test, or with a biophysical profile, is less clear. Although fetuses of diabetic mothers may demonstrate evidence of chronic hypoxia, stillbirth in these pregnancies is often an acute, unpredictable event resulting from the detrimental combination of transient hyperglycemia and hypoxia. Indeed, stillbirth has been reported in women with well controlled gestational diabetes soon after reassuring fetal testing.

Thus, most obstetricians are destined to continue subjecting women with gestational diabetes to some form of antenatal testing protocol, driven by the fear (founded or not) of an avoidable stillbirth but without being convinced of any clear associated benefit. It remains to be seen whether the newly adopted bill on health care reform will generate government mandated evidence based practices in this, as well as in numerous other medical conditions.regnancies at increased risk for adverse outcome, although no prospective randomized trials have ever demonstrated any improved outcome based on this strategy.

## **Planning and Management of Delivery**

**Deborah Conway, MD:** Associate Professor of Obstetrics, University of Texas Health Sciences at San Antonio, Texas

Decisions regarding the timing and route of delivery for women with GDM must strike an appropriate balance between maternal and fetal safety. Severe/permanent injury from a shoulder dystocia event is rare, as is significant maternal morbidity from a planned cesarean delivery.

## **Women with Diabetes: Management during Lactation**

**Denice Feig, MD:** Associate Professor of Medicine, University of Toronto, Canada  
**Use of Oral Hypoglycemic Agents**

Some women with gestational diabetes continue to have elevated glucose levels postpartum (they are actually missed type 2's) and the question of whether they can safely use oral agents during breastfeeding may arise. As well, women with established type 2 diabetes who have been on oral agents pre-pregnancy may wish to return to oral agents postpartum. The main issue is whether these drugs will be secreted into breast milk, posing a risk to infants. In three studies which have looked at the transfer of metformin into breast milk, all three have found that metformin crosses into breast milk, albeit in very small quantities (Hale, Briggs *Obstet Gynecol*, Gardiner). The mean estimated infant dose as a percentage of the mother's weight-adjusted dose was 0.65%, far below the arbitrary cutoff level of 10%. As well, blood glucose levels taken from 3 infants of nursing mothers were normal (Briggs). At 6 months of age, the weight, height and motor-social development of infants of mothers taking metformin while breastfeeding did not differ from formula-fed infants (Glueck *J Pediatr* 2006).

The first generation sulphonylureas, tolbutamide and chlorpropamide, have been shown to cross into breast milk. To date only one study has looked at the transfer of glyburide and glipizide into breast milk (Feig). In this study eight women received a single oral dose of 5 mg or 10 mg of glyburide, while five women were given 5 mg of glyburide or glipizide daily from the first day postpartum. Neither glyburide nor glipizide was detected in the breast milk of any of the women.

There is no data on thiazolidinediones, GLP-1 agonists, DPP IV inhibitors or alpha-glucosidase inhibitors and breastfeeding.

In summary, glyburide, glipizide and metformin appear compatible with breastfeeding. Caution is advised using metformin while nursing premature infants and those with renal impairment. While taking glyburide and glipizide, because of the paucity of data, it is prudent to watch for hypoglycemia and/or monitor glucose levels in the infant.

## **PANEL DISCUSSION**

### **Use of Antihypertensive Agents While Breastfeeding**

Often women with gestational diabetes or overt diabetes have chronic hypertension or preeclampsia with hypertension that persists into the first few months postpartum. The three drugs most preferred in pregnancy, methyldopa, labetalol and nifedipine, are all compatible with breastfeeding. Beta-blockers are variable in their transfer into breastmilk and their effects on the baby. Acebutolol and atenolol have been associated with adverse effects such as bradycardia, and are not recommended while breastfeeding. Metoprolol, oxyprenolol and propranolol are not transferred in significant amounts and are compatible with breastfeeding. Use of angiotensin converting enzyme inhibitors may be important in women with diabetic nephropathy. Enalapril, captopril and quinapril are compatible with breastfeeding. There is no data, however, on angiotensin receptor blockers and breastfeeding.

### **Contraception and Breastfeeding**

2 excellent reviews:

Damm P, Mathiesen ER, Petersen KR, Kjos S. Contraception after gestational diabetes. *Diabetes Care* 2007;30:S236-241.

Kjos SL. After pregnancy complicated by diabetes: Postpartum care and education. *Obstet*

*Gynecol Clin N Am* 2007;34:335-349.

**POST CONFERENCE SESSION:  
Personal Reflections on Diagnosis of DM2 During and After Pregnancy**

**Oded Langer, MD;** Professor and Chair of Obstetrics, Roosevelt Hospital, Columbia University, New York City, New York

It's Time to Redefine the Diagnostic Criteria of Type 2 Diabetes in Pregnancy:  
*Wh en it smells like a rose, it is a rose...*

**David McIntyre, MB,BS; FRACP;** Professor of Medicine, Brisbane, Australia

The recent IADPSG recommendations on the diagnosis and classification of hyperglycemia in pregnancy recommend that women with marked elevation of glycemia in pregnancy be classified as having “overt diabetes”, even if this abnormality is first detected during pregnancy. This represents a departure from previous definitions of gestational diabetes.

In reaching this recommendation, the IADPSG consensus panel favored pragmatism and clinical relevance over strict scientific rigor. It was recognized that in many cases, it would be impossible to determine whether hyperglycemia definitely antedated pregnancy and that even reclassification with oral glucose tolerance testing following pregnancy would not provide diagnostic precision in all cases. (Although Dr McIntyre does re check postpartum with an OGTT)

Further, the panel elected not to propose any new, pregnancy specific, glycemic thresholds to be used to define “overt diabetes”, opting instead to adopt those commonly used outside pregnancy: Measure Consensus threshold of FPG  $\geq 7.0$  mmol/L (126 mg/dL); HbA1c  $\geq 6.5\%$  (DCCT / UKPDS standardized) or Random PG  $\geq 11.1$  mmol/L (200 mg/dL) + confirmation.

This pragmatic approach, implemented at the first antenatal visit, should identify a group of women with marked hyperglycemia and allow them to receive rapid treatment and close follow up during pregnancy. The panel did not make a firm recommendation regarding universal vs. selective testing for overt diabetes in early, leaving this decision to local / regional bodies.

Acknowledged weaknesses of this approach include the arbitrary, non pregnancy specific thresholds, the lack of firm recommendations regarding lesser degrees of hyperglycemia and the fact that screening at the booking obstetric visit is too late to influence the risk of major congenital anomalies in the index pregnancy.

These contentious issues provide important topics for future research.

Further, a major challenge for all those attending the Pasadena meeting is to develop and implement programs for effective, well implemented pre pregnancy detection and care for women with Type 2 diabetes, especially in the context of the increasing prevalence of obesity and other risk factors in younger women.