The management of gestational diabetes

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Abstract: The incidence of gestational diabetes is increasing. As gestational diabetes is associated with adverse pregnancy outcomes, and has long-term implications for both mother and child, it is important that it is recognized and appropriately managed. This review will examine the pharmacological options for the management of gestational diabetes, as well as the evidence for blood glucose monitoring, dietary and exercise therapy. The medical management of gestational diabetes is still evolving, and recent randomized controlled trials have added considerably to our knowledge in this area. As insulin therapy is effective and safe, it is considered the gold standard of pharmacotherapy for gestational diabetes, against which other treatments have been compared. The current experience is that the short acting insulin analogs lispro and aspart are safe, but there are only limited data to support the use of long acting insulin analogs. There are randomized controlled trials which have demonstrated efficacy of the oral agents glyburide and metformin. Whilst short-term data have not demonstrated adverse effects of glyburide and metformin on the fetus, and they are increasingly being used in pregnancy, there remain long-term concerns regarding their potential for harm.

Keywords: gestational diabetes, insulin, oral antidiabetic agents, pregnancy, type 2 diabetes

Background

Gestational diabetes (GDM) is defined as "carbohydrate intolerance with onset or first recognition during pregnancy".[1] Large studies have found that GDM occurs in 2.2%–8.8% of pregnancies, depending on the ethnic mix of the population and the criteria used for diagnosis.[2] In some specific populations however, the incidence can be considerably higher. The incidence of GDM is increasing, in parallel to the increase in type 2 diabetes. Essentially, women at risk of type 2 diabetes are at risk of GDM.

During pregnancy, an increase in insulin resistance occurs. Euglycemia is maintained through a compensatory increase in insulin secretion. The key factor which results in the development of gestational diabetes appears to be a failure to compensate with increased insulin secretion.[3] As the increase in insulin resistance is greatest in the third trimester, GDM usually develops going into this period. Therefore, screening for GDM usually occurs around 24–28 weeks into the pregnancy. The diagnosis is made with an oral glucose tolerance test, though the criteria vary around the world (Table 1). Risk factors for the development of GDM include obesity, older age, family history, previous history of GDM or poor obstetric outcomes, ethnicity, polycystic ovary syndrome and as more recently noted, hypertension.[4,5]

The major significance of GDM is that it is associated with adverse pregnancy outcomes. Macrosomia, shoulder dystocia with its attendant risks of brachial plexus injury and clavicle fracture, and neonatal hypoglycemia are the serious complications which most commonly occur.[6–11] Jaundice, polycythemia, respiratory distress, and hypocalcemia have also been reported. Additionally, there are some data that suggest an increase in fetal malformation and perinatal mortality.[7,12–15] The above risks can be minimized with good glycemic control and judicious obstetric care. Cesarean sections are also more common, and GDM is associated with a higher risk of pre-eclampsia.[9–11]

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Table 1 Diagnostic criteria for GDM

	Glucose load	Glucose tolerance test (mmol/L)				Abnormal values for diagnosis
		Fasting	1 hour	2 hours	3 hours	
ADA	75 g	5.3	10	8.6		Two or more
	100 g	5.3	10	8.6	7.8	Two or more
ADIPS	75 g	5.5		8.0		One
CDA	75 g	5.3	10.6	8.9		Two or more = GDM
						One value = IGT of pregnancy
WHO	75 g	7.0		11.1		One

Abbreviations: ADA, American Diabetes Association; ADIPS, Australasian Diabetes in Pregnancy Society; CDA, Canadian Diabetes Association; GDM, gestational diabetes mellitus; WHO, World Health Organisation.

Exposure of the fetus to hyperglycemia may also predispose the child to a diabetes phenotype in later life. This has been elegantly demonstrated by the long-term follow-up of the offspring of Pima Indian mothers.[16,17] Offspring who were born to mothers who were already diabetic when pregnant had a 45% likelihood of type 2 diabetes by the age of 20–24, whereas it was 8.6% amongst those with mothers who only developed diabetes after pregnancy (ie, were prediabetic). Amongst sibships discordant for exposure to hyperglycemia, the sibling exposed to hyperglycemia had a considerably higher risk of subsequent diabetes, suggesting that genetic factors were not predominantly responsible for the difference in diabetes incidence. Since then, numerous other observational studies have shown that the offspring of diabetic pregnancies have a higher risk of developing a diabetes phenotype.[18,19] There is also concern that this leads to an intergenerational effect, with GDM promoting diabetes in the offspring, with perpetuation of the vicious cycle when the offspring herself develops GDM, thereby predisposing the grandchild to the development of diabetes as well.[20] It is unknown however, what degree of hyperglycemia, or indeed if it is related metabolic disturbances, which increases the risk of diabetes to the offspring.

Additionally, the diagnosis of GDM indicates that the mother has a predisposition to diabetes. In most cases, this is type 2 diabetes. In the longest follow-up of women who have had GDM 36% of women had developed diabetes within 22–28 years (by WHO criteria).[21] This was in a predominantly white population in Boston from the 1960s. Evidence from more contemporary populations is that the likelihood of subsequent diabetes may be substantially higher.[22] Women who have had GDM account for a significant burden of the population prevalence of diabetes. It has been estimated that up to one third of women with diabetes, had a GDM pregnancy earlier in their life,[2] though this was not evident in a recent survey of women with type 2 diabetes.[23]

This review will focus on the medical management of GDM, in particular self monitoring of blood glucose and diabetes education, dietary therapy and physical activity, pharmacotherapy, and post-partum management. For an excellent discussion of the obstetric management of GDM, I will refer the reader to the review by Conway.[24]

Diabetes education, self-monitoring of blood glucose, dietary therapy, and exercise

Self-care is an important component of the management of GDM. Therefore it is commonplace for the diabetes care team to provide the women with information and education to facilitate self-care. This includes information regarding GDM, self-monitoring of blood glucose, dietary counseling, and advice regarding healthy lifestyle measures post-partum. The involvement of a dietician and diabetes educator experienced in the care of women with GDM will facilitate these areas of management.

Blood glucose monitoring

Women with GDM should perform home blood glucose monitoring. Blood glucose levels are usually monitored in the fasting state and 1–2 hours after meals. Treatment to post-prandial targets results in superior pregnancy outcomes compared to pre-prandial targets.[25] The recommended treatment targets vary from country to country (Table 2). These are largely consensus-based as the risk of complications is continuous and there are no obvious thresholds above which the risk markedly increases.

The initial intervention usually entails dietary advice, individualized if possible, and given by a dietitian. Lifestyle measures can provide adequate control in the majority of cases. If glucose targets are not adequately met by lifestyle measures, and perhaps a review of dietary intake, then

pharmacotherapy should be introduced. This usually means the commencement of insulin.

Rather than basing the need for insulin on glycemic parameters alone, some have advocated the combined use of ultrasound assessment of fetal abdominal circumference in combination with blood glucose levels. When the fetal abdominal circumference was <70th percentile, a higher glucose threshold for initiating insulin therapy did not result in an increase in fetal morbidity or macrosomia.[26] This protocol allowed more women to avoid insulin therapy.

Dietary therapy

It is generally accepted that dietary therapy is the cornerstone of treatment of GDM. Therefore all women with GDM should receive counseling from a specialist dietitian. Recommendations are individualized after a dietary assessment of each patient. The aim is to achieve normoglycemia whilst providing the required nutrients for normal fetal growth and maternal health. A secondary aim is to prevent excessive maternal weight gain, particularly in women who are overweight or have gained excess weight in pregnancy.

There are few trials examining the efficacy of dietary therapy for GDM, However, a cluster randomized controlled study has provided support for Medical Nutrition Therapy (MNT) for GDM, as recommended by the American Diabetes Association (ADA) (2004). In this study, 215 women with GDM were seen at sites randomized to deliver either MNT or standard care.[27] Fewer subjects in the MNT group required insulin (24.6% vs 31.7%, p = 0.05) and there was a trend to fewer women having a glycated hemoglobin (Hb_{A1c}) >6% (8.1% vs 13.6%, p = 0.25). The ADA states that all women should receive individualized counseling to provide adequate calories and nutrients to meet the needs of pregnancy and consistent with the blood glucose goals (fasting ≤105 mg/dl [5.8 mmol/L], 1 hr ≤155 mg/dl [8.6 mmol/L], and 2 hrs ≤130 mg/dl [7.2 mmol/L]). For obese women, a 30%–33% calorie restriction to approximately 25 kcal/kg actual weight per day is recommended. Carbohydrate should be restricted to 35%–40% of calories.

There are also data to support low carbohydrate diets in pregnancy, and for the carbohydrate to be of low glycemic index. In a nonrandomized study, women with GDM on a diet comprising less than 42% carbohydrate, had lower post-prandial glucose levels, were less likely to require insulin, and had a lower incidence of large for gestational age.[28] A small study which randomized pregnant women to low glycemic index (GI) or high GI diets found that the former resulted in lower glucose levels, a blunting of the pregnancy

associated rise in insulin resistance, and lower birthweight.[29] In another study of GI, women assigned to a low GI diet during pregnancy gave birth to infants who were lighter (3408 ± 78 g vs 3644 ± 90 g) and had a lower incidence of large for gestational age, compared to women given a high GI diet.[30] Both diets comprised 55% carbohydrate. Whilst the latter studies were not specifically performed in women with GDM, they suggest that the concept of GI is valid in pregnancy, and it would be appropriate to recommend low GI carbohydrate to women with GDM.

Additional dietary measures are usually based upon the general recommendations for diabetes mellitus. A reduction in simple carbohydrates and fat intake is advisable. Emphasis is given to spreading the dietary intake over six meals daily, with three main meals and three snacks, in order to avoid large carbohydrate loads at any time. Except for saccharin, which can cross the placenta and is therefore not recommended, other noncaloric sweeteners may be used in moderation.

Physical activity

In people with type 2 diabetes, there is ample evidence that regular physical activity enhances insulin sensitivity, facilitates weight loss, and thereby improves glucose control. Several small studies have examined whether regular exercise is also beneficial in the management of GDM Jovanavic-Petersen randomized 19 women with GDM to a regime of diet alone, or diet with 20 minutes of supervised aerobic training three days per week for six weeks.[31] This modest amount of physical activity resulted in lower fasting glucose levels, lower glucose responses to a glucose challenge, and a lower Hb_{A1c}. Another study randomized 29 women with GDM to 30 minutes of exercise at 70% estimated maximal heart rate, 3–4 times per week, or control.[32] There was a trend to improved glucose levels in those who exercised, which did not reach significance. There were no differences in neonatal outcomes. Measures of cardiorespiratory fitness however, improved. A study of 32 women randomized to circuit type exercise three times a week or control, found that resistance training resulted in lower postprandial glucose levels, and a delay in the requirement of insulin.[33] Amongst women with a prepregnancy BMI > 25, those who were in the exercise arm were less likely to require insulin.

Therefore, it seems reasonable to recommend that when there is no medical or obstetric contraindication, women with GDM should maintain a sensible level of light and moderate intensity physical activity until the latter stages of the pregnancy. The above studies provide reassurance

that moderate intensity activities such as walking for 20–30 minutes each day, and attendance at antenatal exercise classes can be safely encouraged, and that modest improvements in glycemic control might be achieved.

Insulin therapy for gestational diabetes

When treatment targets are not achieved by dietary means, then insulin is required. A basal-bolus regimen of insulin gives the most effective glucose control, and produces better fetal outcomes than a twice daily regime.[34] Prandial fast-acting insulin is administered to control post-prandial hyperglycemia, and bedtime basal insulin is given if there is fasting hyperglycemia. In some cases, an additional morning injection of basal insulin may further improve glycemic control. As the level of insulin resistance varies from person to person, it is common practice to commence the woman on small doses of insulin, and then to increase the doses at frequent intervals until target glucose levels are attained.

The required dosage of insulin usually increases gradually over the third trimester of pregnancy. Towards the end of the pregnancy, insulin requirements can drop. This may be an early indicator of placental insufficiency. Frequent review and titration of the insulin dosage is recommended. Unlike the situation for women with pre-existing type 1 diabetes however, significant hypoglycemia is uncommon in women with insulin-treated GDM. Nonetheless the woman should be advised regarding appropriate hypoglycemia prevention and management measures.

For many years, fast-acting (regular) insulin, and intermediate-acting (isophane) insulin have been the preferred insulins for the treatment of GDM. Human insulin does not normally cross the placenta, though antibody bound animal insulin has been reported to do so.[35] However, it has been shown by[36] Jovanovic that it is maternal glucose control, rather than maternal anti-insulin antibody levels which influence birthweight.[36] Human insulin is considered safe in pregnancy as years of experience has not suggested an increase in fetal complications as a consequence of its use.

There is now increasing evidence that the newer rapid acting insulin analogs lispro and aspart are also safe in pregnancy, and indeed, they are commonly used. Although there was an initial small uncontrolled report which suggested that Lispro may have teratogenic effects when used in type 1 diabetic pregnancy,[37] this has not been borne out in subsequent studies. No increase in pregnancy complications have been found in observational studies where lispro was used, in either women with GDM[38,43] or pre-existing diabetes.[38–43] There are few reports regarding the use of aspart

in pregnancy. However, a large randomized controlled trial comparing aspart with regular human insulin in 322 pregnant women with type 1 diabetes has been performed.[44] Comparable birth outcomes were found between the two arms, suggesting that aspart is as safe and effective as human insulin.

With respect to GDM, there have been several small randomized studies comparing the use of rapid acting insulin analogues with regular insulin. They have all demonstrated that the rapid acting analogues are as effective as regular insulin in the treatment of GDM, with comparable, if not favorable, outcomes (Table 3). In one study, aspart was detected in the cord blood for one subject.[45] However, as it was not detected in other subjects, the authors postulated that this was due to the disruption of the uterine-placental barrier during delivery, when the mother had been receiving an aspart infusion. As yet there have been no reports of the use of glulisine in pregnancy.

Data regarding the long-acting insulin analogs are less clear than for rapid-acting analogs. There are a number of case reports and small case series of glargine being utilized without the development of pregnancy complications. The majority of these have been in patients with type 1 diabetes. There are also data from a total of 48 women with GDM.[46,47] To date no randomized controlled studies have been published. Concerns have been expressed about the use of glargine in pregnancy, because of its potential effect on mitogenesis, mediated by its high affinity to the IGF-1 receptor, which is six times that of natural insulin[48,49] Whilst insulin detemir has a lower binding affinity to the IGF-1 receptor than natural insulin, there is even less information regarding its use in pregnancy.

Long-acting insulin analogs, particularly glargine, are increasingly being used in women with type 1 diabetes, and they are often continued through the pregnancy. Although their safety has not been proven, it is often rationalized that a change in the basal insulin will result in deterioration in glycemic control, and therefore the risk of continuing glargine is less than the risk from changing insulins. However, until their safety in pregnancy can be clearly established, the initiation of long-acting insulin analog therapy in women with GDM cannot be recommended.

Table 2 Recommended glucose targets

	Fasting	**I hr postprandial**	**2 hr postprandial**
ADA	5.8	8.6	7.2
ADIPS	5.5	8.0	7.0
CDA	5.3	7.8	6.7

Abbreviations: ADA, American Diabetes Association; ADIPS, Australasian Diabetes in Pregnancy Society; CDA, Canadian Diabetes Association.

Table 3 Randomized trials comparing treatment of GDM with rapid acting insulin analogs and regular human insulin

Author, year	Subjects			Effect on Hb$_{Alc}$	Effect on hypos	Other comments
	Lispro	Aspart	Regular			
Jovanovic et al 1999[50]	19	–	23	Lower 3rd trimester Hb$_{Alc}$ with Lispro	Fewer hypos with lispro	Less 1 hr postprandial hyperglycemia with lispro
Mecacci et al 2003[51]	25	–	24	Not reported	Not reported	1 hr postprandial glucose higher with regular insulin
Pettitt et al 2007[45]	–	14	13	No difference	More minor, but not major hypos with aspart	Post-prandial glucose profile and maternal c-peptide lower with aspart
Di Cianni et al 2007[52]	33	31	32	No difference	No subjects had hypos	1 hr postprandial glucose and birthweight higher in regular insulin subjects

Abbreviation: Hb$_{Alc}$, glycated hemoglobin.

Oral antidiabetic agents in gestational diabetes

There is controversy regarding the use of oral hypoglycemic agents during pregnancy. Most government drug agencies have not approved their use in pregnancy, and major specialty diabetes organizations recommend that oral agents be ceased if the woman had been taking them pre-pregnancy[53–55] There have now however, been randomized trials conducted with both glyburide and metformin which have not demonstrated short term harm to the pregnancy.

Glyburide (Glibenclamide)

American authors have stated that glyburide has replaced insulin as first line pharmacological treatment of GDM in many practices.[56] This has largely occurred on the basis of a randomized controlled trial where 404 women with GDM were treated with glyburide (up to 20 mg/day) or insulin[57] In this study, the level of glycemic control achieved was the same in both groups (mean glucose concentration during treatment with glyburide 5.9 ± 0.9 mmol/L compared to 5.9 ± 1.0 mmol/L in insulin group). Only 4% of women treated with glyburide achieved inadequate control and required a switch to insulin. No differences in large for gestational age, macrosomia, neonatal hypoglycemia, admission to neonatal intensive care, or fetal anomalies were observed. The incidence of maternal hypoglycemia was lower in the glyburide group (2% vs 20%).

Additionally, a number of nonrandomized or retrospective studies examining the treatment of GDM with glyburide have been reported (Table 4). In general, these indicate that glyburide is effective in achieving glycemic control in the majority of patients. Most, but not all, suggest that glyburide is as safe as insulin for the fetus. A meta-analysis which included the above studies as well as others examining women with

pre-existing diabetes, with 745 glyburide exposed pregnancies and 637 treated with insulin, has been performed.[65] This study found that glyburide did not increase the risk of macrosomia, large for gestational age, or neonatal hypoglycemia, but did not examine more serious consequences such as perinatal mortality or congenital anomalies. Several studies have examined factors which predict failure of glyburide to achieve adequate glycemic control. Higher glucose levels, either in the glucose tolerance test upon which GDM was diagnosed, or on self-monitoring, and early dietary failure have been found to be associated with glyburide failure.[60,58] These findings lead to the logical conclusion that subjects with more severe GDM are more likely to require insulin.

Further evidence supporting the safety of glyburide for the fetus comes from a study using an in vitro perfusion, where it was not found to cross the placenta in significant amounts.[66] However, another in vitro study has found transplacental transfer of glyburide.[67] In the Langer randomized controlled trial, glyburide was not detected in the cord blood of the neonates and cord insulin levels were similar between the two groups.[57]

Metformin

A number of studies have provided conflicting information regarding the safety of metformin use in type 2 diabetic pregnancy.[68–70] There are studies which have used metformin during pregnancy in women with polycystic ovary syndrome, without any noticeable adverse effects on the fetus.[71] There are few publications of its use in GDM, and these are dominated by the Metformin in Gestational Diabetes (MiG) Study.

The MiG Study randomized 751 women with GDM to treatment with insulin or metformin.[72] The women in the metformin arm were treated with supplemental insulin if the maximal dose of metformin, 2500 mg daily, failed to meet

Table 4 Published studies of glyburide treatment for GDM

Author, year	Subjects on glyburide	Subjects on insulin	Nature of study	Effectiveness of glyburide compared to insulin	Safety of glyburide for neonate		Safety of glyburide for the mother	Failure of glyburide to achieve glycemic control
					Serious complications	Neonatal Hypoglycemia		
Langer et al 2000[57]	201	203	RCT	No difference in glycemic control, macrosomia, or neonatal complications	No difference in fetal anomalies (2% in each group) or perinatal mortality (1% in each group)	No difference between groups (9% vs 6%, p = 0.25)	Glyburide less likely to result in maternal hypoglycemia (2% vs 20%, p = 0.03)	4%
Conway et al 2004[58]	75	–	Retrospective cohort	N/A	Not reported	Not reported	Not reported	16%
Kremer and Duff 2004[59]	73	–	Prospective cohort	19% required cesarean section vs 14%–17% in general obstetric population	Nil	Not reported	12% noticed side effects	19%
Chmait et al 2004[60]	69	–	Prospective cohort	N/A	1 achondroplasia and 1 intrauterine death attributed to knot in umbilical cord	2%	Not reported	18.8%
Bertini et al 2005[a,61]	24	27	RCT	Glycemic control not reported. 25% large for gestational age in Glyburide group, vs 4% in insulin group (p = 0.07)	Nil	33% in glyburide group, 4% in insulin group.	No maternal hypoglycemia	21%
Jacobson et al 2005[62]	236	268	Retrospective cohort	More women on glyburide achieved glycemic goals (86% vs 63%, p < 0.001). No difference in birthweight, cesarean section, macrosomia	No difference in fetal anomalies (2% in each group). 3% in glyburide group had birth injuries (fractures and brachial plexus injury) compared to 1% in insulin group, p = 0.08)	No difference between groups (31% vs 27%, p = 0.42)	Glyburide higher incidence of pre-eclampsia (12% vs 6%, p = 0.02)	12%
Rochon et al 2006[63]	101	–	Retrospective cohort	N/A	9% shoulder dystocia	Not reported	Not reported	21%
Ramos et al 2007[b,64]	44	78	Retrospective cohort	No difference in birthweight, cesarean section, pre-eclampsia, prematurity, hyperbilirubinemia. Glyburide more macrosomia after adjustment for confounders (RR 3.5, (1.1–11.4)	Glyburide more congenital anomalies (9% vs 0%, p = 0.02)	Glyburide more neonatal hypoglycemia (34% vs 14%, p = 0.01)	No problems reported	16%

Notes: [a]This study included a 3rd arm of subjects randomized to receive Acarbose; [b]Subjects in the study of Ramos and colleagues were a subset of those in Jacobsen and colleagues, who had a 50 g glucose challenge test result ≥11.1 mmol/L and a fasting plasma glucose ≥5.8 mmol/L.
Abbreviation: GDM, gestational diabetes mellitus.

the glucose targets. The primary outcome variable was a composite of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, Apgar score less than 7, or prematurity. There was no difference in the primary outcome between the two groups (metformin 116 [32%] events, insulin 119 events [32.2%], RR 1.0 [0.9–1.1], p = 0.95). Interestingly fetal death and malformations were not a component of the primary outcome; however, 19 events in the metformin group were classified as serious fetal or neonatal adverse events (including 11 congenital anomalies) compared to 23 events in the insulin arm (including 18 congenital anomalies and one fetal death). None of these events were adjudged by the data and safety monitoring committee to be treatment related and there were no serious adverse events associated with the use of metformin. Additionally, more women using metformin indicated that their treatment was acceptable compared to those on insulin. From these results, the authors have suggested that metformin is a safe and effective treatment for GDM.

Several small studies comparing metformin to insulin for the treatment of GDM have also been performed (Table 5). Two have concluded that metformin is as effective as insulin for glycemic control in GDM, and that it is safe. However, one study, a randomised controlled trial, was underpowered to realistically address the effectiveness and safety of metformin in GDM.[73] In another study, a retrospective case control study, subjects treated with insulin had a greater degree of initial glucose intolerance, so the comparison was of limited validity.[74] A third study comprised a retrospective cohort which included a mixture of both GDM and women with Type 2 diabetes seen from 1966–1991. It found an increase in stillbirth and perinatal mortality, as well as pre-eclampsia amongst those treated with metformin, compared to women treated with insulin or sulphonylureas. However, as there was no evaluation of glycemic control early in pregnancy, and more women on metformin had pre-existing type 2 diabetes, the groups do not appear to be well matched. It is quite possible that the adverse findings in this study are due to more women in the metformin group having a greater severity of hyperglycemia early in the pregnancy.

Long-term concerns regarding glyburide and metformin therapy for GDM

Although the above randomized trials have demonstrated non-inferiority of glyburide and metformin in achieving glycemic control, and satisfactory birth outcomes compared to insulin therapy, concerns must remain as long-term issues have not yet been addressed. Repeated episodes of GDM are associated with the earlier development of diabetes, and this has been postulated to be due to the increased stress that the β-cells are exposed to with each pregnancy.[75] By treating the mother with glyburide, it is possible that this accentuates β-cell stress and accelerates their decline, whereas insulin therapy would conversely provide a degree of relief to the β-cells. Therefore glyburide has the potential to result in earlier development of maternal diabetes, and long-term follow-up of the mothers are needed to alleviate this concern.

In contradistinction, metformin reduces insulin resistance and hepatic gluconeogenesis, which theoretically would be beneficial for the preservation of β-cell function. In subjects with type 2 diabetes, the ADOPT Study has demonstrated that metformin is superior to glyburide in this regard.[76] As there is transplacental passage of metformin,[77,78] its effect on fetal insulin resistance might even provide further benefit in light of data of insulin resistance and insulin secretory defects in offspring of diabetic pregnancies.[19] However, any pharmacological agent which crosses the placenta must be viewed with caution as there always remains the possibility of unexpected long-term effects. Metformin alters gene expression in mice livers and has been demonstrated to have an antiproliferative effect through reductions in cyclin D1 and activation of AMP kinase.[79] The programming and developmental effects of these on a fetus are unknown. Furthermore, metformin can promote the development of lactic acidosis, which surely must be a concern in situations of fetal distress. Whilst 18-month follow-up data on 126 offspring of women with polycystic ovary syndrome treated with metformin during pregnancy have not revealed any deficiencies in growth or motor-social development, this may be too short a time frame for potential programming effects of metformin to become evident.[80]

In view of the above concerns regarding the potential of glyburide and metformin to have long-term effects on the mother and child, I would recommend caution with their use in the treatment of GDM. A subgroup of infants from the MIG Study are currently being followed up.[72] It may be circumspect to await the findings from this follow-up study before metformin can be considered safe for the routine treatment of GDM.

Other oral antidiabetic agents for gestational diabetes

There is one study which randomized women with GDM to treatment with insulin, glyburide, or acarbose.[61] Forty two percent of the acarbose subjects failed to achieve adequate

Table 5 Published studies of metformin therapy for gestational diabetes

Author, year	Subjects on metformin	Subjects on insulin	Nature of study	Effectiveness of metformin compared to insulin	Safety of metformin to the neonate		Safety of metformin for the mother	Inadequate glycemic control with metformin alone
					Major complications	Neonatal hypoglycemia		
Hellmuth et al 2000[a,68]	50	42	Retrospective cohort	No comparison of glycemic control. Birthweight similar Increased pre-eclampsia	8% stillbirth compared to 2.3% with insulin (p = 0.042). 11.6% perinatal mortality compared to 1.3% with insulin or sulphonylurea (p < 0.02)	26% in metformin group, 33% insulin group	–	–
Moore et al 2007[73]	32	31	RCT	No difference in glycemic control, cesarean section, birthweight	1 shoulder dystocia and 1 stillbirth in metformin group attributed to other causes	No difference compared to insulin	–	0%
Rowan et al 2008[72]	363	378	RCT	No difference in primary composite outcome of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, Apgar score less than 7, or prematurity	One fetal death in insulin group. 11 congenital anomalies in metformin group compared to 18 in insulin group.	3.3% in metformin group had BGL < 1.6 mmol/L compared to 8.1% in insulin group (p = 0.008)	10.7% significant GI side-effects	46.3%
Tertti et al 2008[74]	45	45	Retrospective case control	No difference in birthweight or neonatal outcomes apart from hypoglycemia	1 Trisomy 13 with Metformin, 1 clavicle fracture in each group. 1 Erb's palsy in insulin group	Higher in insulin group (p = 0.03)	–	18%

Notes: [a]GDM subjects in Metformin group included 19 with type 2 diabetes, and Insulin group had seven women with type 2 diabetes. There were an additional 68 women in a sulphonylurea group.
Abbreviations: GI, gastrointestinal; RCT, randomized, controlled trial.

glycemic control and ultimately required insulin therapy. The incidence of large for gestational age was 10.5%, compared to 3.7% for insulin and 25% for glyburide (p = 0.07). The rate of neonatal hypoglycemia (5.3%) was similar to insulin (3.7%), but lower than glyburide (33%) (p = 0.006). Whilst this study is inadequately powered to demonstrate safety of acarbose, it is not absorbed from the gut, and therefore would be unlikely to affect the fetus. However it is of low potency and insulin therapy will often need to be introduced. Furthermore, the high frequency of gastrointestinal side effects experienced by people with type 2 diabetes suggests that any future role of acarbose, even if subsequent studies confirm safety, will be limited.

There are no studies using glitazones in pregnancy. Transplacental transfer occurs,[67,81] and until studies demonstrating safety are performed, they should be avoided in pregnancy.

Evidence that treatment of gestational diabetes improves pregnancy outcomes

The strongest evidence that treatment of GDM is of benefit comes from the Australian Carbohydrate Intolerance Study (ACHOIS) in Pregnant Women.[82] In this randomized controlled trial, 1000 women fulfilling the 1985 WHO criteria for "gestational glucose intolerance" were recruited. These subjects had a fasting glucose up to 7.7 mmol/dl and a 2 hour level between 7.8 mmol/L and 11.1 mmol/dl. They were randomized to receive treatment for GDM, including dietary advice, blood glucose monitoring, and insulin as required, or standard pregnancy care. Those receiving standard care were unaware that they had GDM. In the treatment group, the aim was to maintain a fasting glucose level of <5.5 mmol/L, and 2 hour post-prandial reading <7.0 mmol/L. With this, there was a 1% incidence of serious perinatal outcomes (death, shoulder dystocia, fracture, and nerve palsy) compared to 4% amongst women provided with standard pregnancy care only (adjusted risk reduction 0.33, p = 0.01). Fewer neonates in the treatment group were large for gestational age, and there was no difference in the incidence of small for gestational age infants. There was no difference in the rate of cesarean section. Preeclampsia occurred less frequently in the intervention group (12% vs 18%, adjusted risk reduction 0.7, p = 0.02). One other important finding of this study was that intensively treated women had better quality of life and lower rates of depression.

Prior to ACHOIS, a large number of other studies had been performed to ascertain if treatment of GDM is of benefit.

These studies were largely retrospective, unrandomized, or lacked power to detect differences in serious adverse perinatal outcomes and will not be listed here. However, one large retrospective cohort study of 116,303 pregnancies, merits discussion. Because of changes in the diagnostic criteria for GDM over the years, Beischer (1996) was able to examine perinatal mortality amongst women who would have been diagnosed as having GDM by contemporary criteria, but were not considered to have GDM at the time, and were therefore untreated. The perinatal mortality rate was 2.6% in these women with 'mild GDM' in the 1970s, compared to 0.7%, in the 1980s after routine treatment had been introduced for this group. Their perinatal mortality rate was 2.3 times that of women with normal glucose tolerance. In the 1980s, with routine treatment for women with mild GDM, their outcomes were not different to women with normal glucose tolerance. It therefore seems likely that the decreased mortality rate was at least in part a consequence of treatment of GDM, rather than only to other improvements in obstetric outcome.

Post-partum management of gestational diabetes

The medical management of gestational diabetes should not conclude with the delivery of the fetus. Although hyperglycemia usually resolves with the conclusion of the pregnancy, women who have had GDM are at high risk of developing diabetes later in life. Apart from the development of diabetes, women who have had GDM have an adverse cardiac risk profile, including the metabolic syndrome.[83,84] A higher prevalence of cardiovascular disease that occurs at a younger age, independent of the metabolic syndrome and type 2 diabetes has also been demonstrated.[83]

In view of the above, it is important that the woman who has had GDM receive counseling and support to reduce her long-term risk of diabetes. Screening for diabetes, at regular intervals, is recommended by a number of diabetes societies.[4,85] This is important for the early diagnosis of diabetes, to facilitate the prevention of complications. Furthermore, if the woman is of reproductive age, the pre-pregnancy recognition of diabetes is vital so that early pregnancy conditions can be optimized to prevent diabetes fetopathy. Issues specific to pre-existing diabetes in pregnancy include tight glycemic control and adequate folate supplementation.[53,54] Additionally, post partum evaluation and management of reversible cardiovascular risk factors such as smoking, obesity, hypertension, and hyperlipidemia should be undertaken.

There is evidence that lifestyle modification, aiming for a 5%–7% reduction in body weight, is effective in preventing

or delaying the development of diabetes in people with impaired glucose tolerance. Both the Diabetes Prevention Program[86] and the Finnish Diabetes Prevention Study[87] demonstrated this, with an intensive intervention including lifestyle coaches, strict supervised exercise regimes and caloric restriction. As 15% of the women in the Diabetes Prevention Program and Diabetes Prevention Study had GDM, similar measures should be recommended to women after they have had GDM. However, it is unclear if less intensive interventions can be effective in this population. To date, small short-term studies focusing on dietary counseling alone, or a combination of behavioral strategies with weekly exercise classes, have not demonstrated an improvement in glucose tolerance.[88,89] In part, this is probably due to the real life challenges of maintaining motivation for healthy lifestyle change amongst young women at a time that they are having to deal with young children, return to work, and further education. Nonetheless, there are undisputed benefits to healthy eating and regular physical activity so these activities should be encouraged.

Summary and conclusions

Gestational diabetes is a common disorder which in the majority of cases, should initially be managed by dietary measures. These include a restriction in fat and simple carbohydrate intake, regular distribution of meals, carbohydrate foods favoring those with low glycemic index, and caloric restriction for those who are obese. Moderate physical activity should be encouraged. Fasting and post-prandial glucose testing is necessary for monitoring and guidance of therapy.

Where dietary measures are inadequate to achieve glycemic targets, insulin should be introduced. Insulin is still the mainstay of pharmacological treatment of GDM, and this is ideally administered in a basal bolus regimen. The rapid acting analogs lispro and aspart are considered safe, but the safety of the long-acting analogs are yet to be determined. Whilst there are studies demonstrating short-term safety of glyburide and metformin during pregnancy, I suggest that they be reserved for situations where implementation of insulin therapy is impractical or not possible. After all, we know that insulin therapy is safe and usually effective. ACHOIS has shown that it is acceptable to the majority of women. By eschewing insulin, doctors may actually be treating their own perceived fear of injections, rather than providing the best therapy to the patient. Based on our current information, insulin is still the best option, with the least potential for long-term risk to the mother and child.

With good medical and obstetric care, the risks to the pregnancy should be minimal. However, a woman with GDM is a woman at high risk of future diabetes. Therefore after the pregnancy, healthy lifestyle measures should be encouraged to minimize the likelihood of developing diabetes, and regular screening for diabetes should be undertaken.

Disclosure

The author reports no conflicts of interest in this work.

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