Introduction

The rising prevalence of gestational diabetes mellitus (GDM), along with perinatal complications secondary to GDM, and a growing understanding of the significant long-term impacts on offspring of women with GDM, is of increasing importance to obstetric and neonatal clinicians at both an individual and population health level. This resonant or this study aims to corpse The GDM effects on baby health both the perinatal.

GDM: definition, prevalence, and diagnostic criteria

GDM has been defined as “any degree of glucose intolerance with onset or first recognition during pregnancy”. Consequently, the diagnosis of GDM includes both previously undiagnosed abnormality of glucose tolerance, and glucose intolerance related to the pregnancy alone which disappears postpartum. However, a definitive diagnosis can only be made in the postpartum period. The prevalence of GDM is rising worldwide and has been reported in the range of 3%–14% globally, and in the range of 3%–5% in North America, Europe, and Australia. In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended a standardized international approach to screening and diagnosis of GDM based on risk of adverse pregnancy outcome. The adoption of diagnostic criteria has been predicted to result in a per-pregnancy incidence of GDM of almost 20%, and a two- to threefold increase in prevalence. (Table 1). In the UK, the

NICE guidelines continue to recommend screening only of high-risk women (raised body mass index, previous macrosomic infant, previous GDM, first degree relative with diabetes, family origin with high prevalence of diabetes). In the United States, the “two-step” National Institutes of Health (NIH) nonfasting one-hour 50 g glucose load test (GLT) at 24–28 weeks, followed by a fasting 100 g OGTT for those who test positive, remains an alternative option to the IADPSG “one-step” OGTT. The Australasian Diabetes in Pregnancy Society (ADIPS) has adopted the World Health Organization (WHO) recommendations for the diagnostic classification of hyperglycemia first detected at any time during pregnancy; this is currently under consideration by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

	IADPSG	NIH	NICE	ADIPS/WHO 2006
Target population	Universal: all pregnant women	Universal: all pregnant women	Women with risk factors for GDM: • BMI >30 kg/m² • Previous baby ≥4.5 kg • Previous GDM • First-degree relative with DM • Family origin with high prevalence of diabetes: South Asian, Black Caribbean, Middle Eastern	Universal: all pregnant women
Type and timing of screening	2-hour 75 g OGTT at 24–28 weeks	1-hour 50 g nonfasting GLT at 24–28 weeks If plasma venous glucose at 1 hour is ≥10 mmol/L, proceed to fasting 3-hour 100 g OGTT	2-hour 75 g OGTT • At 16–18 weeks if previous GDM • At 24–28 weeks if other risk factors	2-hour 75 g OGTT at 24–28 weeks
Criteria for diagnosis of GDM	Any one or more of: Fasting, ≥5.1 mmol/L 1-hour, ≥10 mmol/L 2-hour, ≥8.5 mmol/L	3-hour ≥7.8 mmol/L	Any one or more of: Fasting, ≥7.0 mmol/L 2-hour, ≥7.8 mmol/L	Any one or more of: Fasting, 5.1–6.9 mmol/L 1-hour, >10 mmol/L 2-hour, 8.5–11 mmol/L

Table 1 Comparison of IADPSG, NIH, NICE, and ADIPS guidelines for GDM screening

Note: All values given are for plasma venous glucose.

Abbreviations: IADPSG, International Association of Diabetes and Pregnancy Study Groups; NIH, National Institutes of Health; NICE, National Institute for Health Clinical Excellence; ADIPS, Australasian Diabetes in Pregnancy Society; WHO, World Health Organization; BMI, body mass index; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; GLT, glucose loading test.

Perinatal complications of GDM

In order to meet the metabolic demands of the developing fetus, normal pregnancy is a state of insulin-resistance which in turn results in an increase in insulin production by pancreatic β-cells. In a pregnancy affected by GDM, pancreatic β-cell dysfunction means that increased insulin secretion cannot be mounted in response to insulin resistance, leading to maternal hyperglycemia. The effect of this on the fetus is described by the Pedersen hypothesis. Maternal hyperglycemia results in increased transplacental transfer of glucose to the fetus. Fetal hyperglycemia in turn stimulates fetal pancreatic β-cells to release insulin, and as insulin is an important growth factor, the outcome is fetal macrosomia. Macrosomia is variably defined as a birth weight greater than 4,000, 4,500, or 5,000 g, and is characterized by increased subcutaneous fat, increased muscle mass, and a head circumference which plots on a lower centile than weight.

The Pedersen hypothesis is supported by the strong correlation between fetal size and umbilical, free insulin, In addition to the effects of maternal hyperglycemia, maternal insulin resistance also gives rise to excessive fetal growth through increased placental transfer of other growth substrates, such as amino acids and lipids.

The risks to the fetus and newborn arising from maternal GDM are related to both macrosomia and to other proposed pathophysiological effects of fetal hyperglycemia and hyperinsulinism.

Intrauterine fetal death and perinatal asphyxia

Increased fetal substrate uptake arising from chronic fetal hyperinsulinism increases tissue oxygen consumption. This gives rise to relative fetal hypoxia, which increases the risk of intrauterine fetal death, although the risk of this is less compared to that in maternal type 1 and 2 diabetes mellitus (DM), and it has been argued that the reported increased risk may be in fact be attributable to undiagnosed type 2 DM. Perinatal asphyxia is also purported to be a potential outcome of relative fetal hypoxia, although macrosomia in itself increases the risk of asphyxia.

Premature birth

It has been found the continuous linear relationship between the results of glucose tolerance tests and preeclampsia, which is a risk factor for preterm birth. It has also been shown that, independent of other predisposing factors (including pre-eclampsia, polyhydramnios, and pregnancy induced hypertension), GDM carries an increased risk of spontaneous preterm birth. Preterm birth is the leading cause of perinatal morbidity and mortality in developed countries.

Polycythemia, hyperviscosity, and hyperbilirubinemia

Fetal hypoxia drives erythropoiesis, leading to polycythemia, which is defined as a venous hematocrit greater than 65%. The clinical manifestations of polycythemia and resulting blood hyperviscosity may include plethora, cyanosis, lethargy, jitteriness, hypotonia, feeding difficulties, respiratory distress, hypoglycemia, and hyperbilirubinemia. Less commonly, necrotising enterocolitis, thrombocytopenia, and venous thrombosis (for example, renal vein thrombosis) may result, is low.

Neonatal respiratory distress

There is evidence from animal models that fetal hyperinsulinism inhibits lung surfactant synthesis. Surfactant deficiency can result in respiratory distress syndrome (also known as hyaline membrane disease), requiring neonatal intensive care (NICU) admission for respiratory support. Other potential causes of respiratory distress in infants born to mothers with GDM include increased risk of premature birth (also a risk factor for surfactant deficiency) and elective cesarean section delivery due to macrosomia. Elective cesarean section increases the risk of respiratory distress through the mechanism of retained fetal lung fluid. In a literature review in 2010, Mitanchez found there was limited data from which to report on the prevalence of respiratory distress in infants born to mothers with GDM, but that as for many other short-term neonatal complications of GDM, there appeared to be an increased risk in macrosomic infants.

Birth injuries

Shoulder dystocia, and resulting birth injury, is a risk of macrosomia, even in the absence of maternal GDM. Potential birth injuries include brachial plexus injuries (including Erb's palsy) and fractures of the clavicle and humerus. In a large cohort study in the United States, Zhang et al[37]confirmed that the risk of birth injury increases with birth weight: odds ratio (OR) =2.4 (95% confidence interval [CI] =2.2–2.5) with a birth weight between 4,500 and 4,999 g, and OR =3.5 (95% CI =3.0–4.2) with a birth weight >5,000 g. In a study of perinatal outcomes in women with and without GDM, Esakoff et al found that GDM increases the odds of shoulder dystocia (adjusted odds ratios [aORs], 16.4 [GDM] vs 9.6 [non-GDM]) and Erb's palsy (aORs, 41.9 [GDM] vs 6.7 [non-GDM]) associated with a birth weight ≥4,000 g.

Hypoglycemia

The mechanism for hypoglycemia in infants born to mothers with GDM is transient hyperinsulinism, which both inactivates the usual counter-regulatory responses (glycogenolysis, gluconeogenesis, lipolysis, and β-oxidation of fatty acids) to loss of glucose supply from the placenta, and increases peripheral glucose utilization. The mainstay of prevention and management of hypoglycemia is prefeed blood glucose monitoring and early and frequent enteral feeding (preferably breast-feeding). Approximately 5% of infants will have hypoglycemia that cannot be managed with enteral feeding alone and will require intravenous glucose therapy. Esakoff et al found that macrosomia increases the risk of hypoglycemia in infants born to mothers with GDM: neonates with a birth weight of ≥4,000 g, compared with those with a birth weight <4,000 g, had higher frequencies of hypoglycemia (5.3% vs 2.6%; $P<0.04$). Hyperglycemia in labor also increases the risk.

Congenital malformations

The prevalence of major congenital anomalies in the general population has been reported at 23.9 per 1,000 births. Diabetic embryopathy is well recognized; the risk of major congenital anomalies in infants born to mothers with type 1 or 2 DM is at least twofold higher compared to the general population, predominantly driven by congenital cardiac disease and nervous system anomalies. In a recent systematic review, Balsells et al found that infants born to women with GDM were at higher risk of congenital malformation compared to the reference population (relative risk [RR] and 95% CI =1.16 [1.07–1.25] in cohort studies and OR =1.4 [1.22–1.62] in case control studies). However, the risk was much lower than for infants born to mothers with preexisting diabetes, and the contribution of factors such as overt diabetes, age, and maternal BMI, could not be ascertained.

The role of maternal obesity

The association of obesity with GDM and impact on perinatal outcomes is an important consideration, given that the prevalence of obesity is increasing worldwide, including in women of childbearing age. For example, in the United States, approximately 60% of women of childbearing are overweight or obese. Applying the IADPSG diagnostic criteria to make a post hoc diagnosis of GDM, and basing definitions of obesity and overweight at 28 weeks gestation on WHO BMI categories, the HAPO study group showed that both GDM and obesity are independently associated with adverse perinatal outcomes (birth weight, newborn adiposity, and cord C-peptide >90th percentile, primary cesarean section delivery, and pre-eclampsia), and that the combination of obesity and GDM substantially increased the ORs of these outcomes compared to either GDM or obesity alone.

Prevention of GDM

Prevention of GDM would certainly negate both the maternal and offspring complications of GDM, as well as the debate around optimal diagnostic criteria for and treatment of GDM. Preventative measures include weight management and physical activity. Prepregnancy obesity, as measured by prepregnancy BMI, is a risk factor for the development of GDM, as is excessive gestational weight gain. In a review of published literature between 1975 and 2009, Morisset et al[72] concluded that while nutritional strategies could be beneficial in reducing the risk of GDM, specific nutritional interventions (such as diet composition) could not be recommended based on available evidence. Higher levels of physical activity both prepregnancy and during early pregnancy appear to protect against development of GDM.

Treatment of GDM

In terms of perinatal complications, the two largest studies to date of effect of treatment of GDM have been the ACHOIS trial[75] and that of Landon et al. In the ACHOIS trial, the composite primary outcome (one or more of death, shoulder dystocia, hyperinsulinemia, and birth trauma), but there were significant reductions in the rates of pre-eclampsia and gestational hypertension, in mean birth weight, neonatal fat mass, frequency of LGA infants, birth weight greater than 4,000 g, shoulder dystocia, and cesarean section delivery.

A number of systematic reviews have summarized the effectiveness of GDM treatment with regards to perinatal outcomes, two of which included the ACHOIS and Landon et al studies. Based on studies which employed a two-step screening approach (glucose challenge test [GCT] and/or screening for risk factors, followed by an OGTT), Horvath et al found evidence of a significant reduction in shoulder dystocia and macrosomia with

treatment. Falavigna et al could not distinguish between the benefits of lifestyle interventions vs pharmacological treatments.

additionally reduces preeclampsia. Horvath et al reported that the strongest evidence for benefit from treatment came from studies in which the only pharmacological agent used to manage hyperglycemia was insulin. Falavigna et al could not distinguish between the benefits of lifestyle interventions vs pharmacological treatments.

There is a paucity of evidence regarding the long-term impacts of treatment of GDM. Neither of the systematic reviews performed by Horvath et al and Falavigna et al could report on long-term benefits of treatment for either women or their offspring.

In a study of the children of women who participated in the ACHOIS trial, Gillman et al found that even though the prevalence of macrosomia at birth was lower in the intervention group, this did not translate to any significant difference in BMI *z* score between the intervention and control groups at 4–5 years of age. The authors postulated that the long-term effects of treatment of GDM may not be seen until later in childhood, but did not have access to growth data beyond 5 years of age in the study population. Similarly, Malcolm et al followed-up offspring of women who had participated in a randomized controlled trial of minimal intervention (control) vs tight glycemic control (intervention) for GDM. Seventy-one children underwent an OGTT between 7 and 11 years of age. There was no significant difference in impaired glucose tolerance between the offspring of the two groups. BMI <85th percentile was found in 75.8% of offspring of the treatment group and 84.6% of the offspring of the control group (difference in percentage =−8.9, 95% CI =−27.2 to

7.8). The study was limited by small sample size and potential bias.

Postnatal interventions in offspring

Feeding mode presents one opportunity for modifying risk in the offspring of women with GDM. In the general population, breast-feeding in comparison to breast milk substitutes is protective against hypertension, insulin resistance and type 2 diabetes, dyslipidemia, and obesity. In particular, Harder et al have reported a “dose–response” effect of breast-feeding with respect to obesity, where each additional month of breast-feeding is associated with a 4% reduction in childhood obesity risk (95% CI =−0.06 to −0.02). The beneficial effects of breast milk feeding appear to be mediated through bioactive nutrients found only in breast milk, a higher protein content, and a slower postnatal growth pattern compared to formula fed infants. In a retrospective study, Crume et al examined the impact of breast-feeding on

childhood adiposity following in utero exposure to diabetes (prepregnancy diabetes or GDM). They reported that breast-feeding for 6 months or longer (compared to less than 6 months) was associated with significantly lower BMI, waist circumference, and visceral and subcutaneous adipose tissue at 6–13 years of age.