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MATERNAL AND FETAL COMPLICATIONS OF GESTATIONAL DIABETES- REVIEW

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ABSTRACT
GESTATIONAL DIABETES MELLITUS (GDM) IS A COMMON MEDICAL COMPLICATIONS OF PREGNANCY, WITH IMPORTANT CONSEQUENCES FOR MOTHER AND CHILD. IN RECENT YEARS, STUDIES HAVE BEEN FOCUSED ON COMPLICATIONS OF GDM DUE TO THE TRANSGENERATIONAL VICIOUS CIRCLE OF CARDIOMETABOLIC DISEASES THAT THIS DIAGNOSE GENERATES. NUMEROUS STUDIES ANALIZED THE ROLE OF MATERNAL HYPERGLYCEMIA IN THE OCCURRENCE OF THESE COMPLICATIONS AIMING TO NORMALIZING MATERNAL BLOOD GLUCOSE VALUES AND REDUCE THE ASSOCIATED COMPLICATIONS. DESPITE TREATMENT OF GDM, INCREASED RATES OF ADVERSE NEONATAL OUTCOMES PERSIST. THE AIM OF THIS REVIEW IS TO DISCUSS CURRENT EVIDENCE ABOUT THE IMPORTANCE OF GDM, MATERNAL AND FETAL SHORT TERM RESPECTIVELY LONG TERM COMPLICATIONS.

KEYWORDS: GESTATIONAL DIABETES, COMPLICATIONS, CLINICAL CARE, OUTCOMES, RECOMMENDATIONS

1. INTRODUCTION
GDM is defined as glucose intolerance with onset or first recognition during pregnancy. The prevalence of GDM is estimated to be around 7% of all pregnancies worldwide and is rising fueled by advancing maternal age, obesity. During the first prenatal

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visit it is important to determine risk of developing GDM\textsuperscript{7}. The risk can be classified as low, average, or high. Low risk does not require a routine screening but women at average risk should be screened between the 24th and 28th weeks of gestation for GDM. The risk factors include: <25 years of age and obese, family history of diabetes in first degree relatives, member of an ethnic/racial group (Hispanic American, Native American, Asian American, African American, Pacific Islander). High risk implies the following characteristics and the presence of any of them recommend a screening for GDM as soon as possible: obesity, family history of diabetes, GDM in previous pregnancy and history of adverse outcomes\textsuperscript{8}.

The screening test for diagnosis of GDM is the 75g 2-hour OGTT (recommendations of National Institute for Health and Care Excellence(NICE), American Diabetes Association (ADA)). Gestational diabetes is diagnosed if one or more values is equal or exceeds the cut off values: FPG (5.1mmol/l [92 mg/dl]), 1-h plasma glucose (10 mmol/l [180 mg/dl]) and 2-h plasma glucose (8.5 mmol/l [153 mg/dl]).

The first strategy of prevention and management of GDM is lifestyle change and includes nutrition therapy and physical activity. The best moment to implement lifestyle change is before pregnancy. Management during pregnancy consists of monitoring of blood glucose, medical nutrition therapy and pharmacotherapy if glucose goals are not met. It is also necessary an weight management due to the association between overweight, obesity and GDM. Up to 39\% of women with GDM cannot obtain an optim glucose control through diet alone. Physical activity is an adjuvante to dietary therapy and may improve glucose tolerance by improving insulin sensitivity. General guidelines encourage at least 30 minutes of physical activity on several days a week. If women cannot achieve glycemic goals with these strategies pharmacotherapy with insulin is recommended.

Therapy for pregnant women with GDM should be targeted to treat 1-2h postprandial glucose. ACOG and ADA recommend the following glycemic targets: fasting glucose<95 mg/dl, 1-hour postprandial glucose< 140 mg/dl, 2 h-postprandial glucose < 120 mg/dl. Women with GDM are predisposed to develop short term complications as pre-eclampsia and experience perineal trauma or caesarean delivery. Despite the fact that in majority of cases glucose homeostasis return to normal postpartum, GDM is a strong risk factor for type 2 diabetes in later life. Offspring of women with GDM are predisposed to have a higher birth weight, neonatal hypoglycaemia, jaundice, birth trauma and even stillbirth. Long term complications can be metabolic syndrome, obesity and diabetes\textsuperscript{9}.

2. SHORT TERM COMPLICATIONS OF GDM

2.1 Short term complications of mother

2.1.1. Hypertensive disorders

Studies have showed that women with GDM have an increased incidence of hypertensive disorders during pregnancy. These disorders include gestational hypertension, chronic hypertension, pre-eclampsia and eclampsia and are associated with factors such as insulin resistance, inflammation, and maternal fat deposition patterns.


\textsuperscript{9} Thomas A, Buchanan, Anny H. Xiang, and Kathleen A. Page Gestational Diabetes Mellitus: Risks and Management during and after Pregnancy, Nat Rev Endocrinol. Author manuscript; available in PMC 2015 Apr 21
In Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, 25,505 pregnant women were enrolled and tested by a 75g 2-hour OGTT within 24 to 32 weeks. In this study approximately 2.5% of women had chronic hypertension (582 of 23,316 women), 5.9% had gestational hypertension and 4.8% had pre-eclampsia. Increased glucose levels on the OGTT were associated with a greater risk of pre-eclampsia 10.

In MiG trial (Metformin versus Insulin for the Treatment of Gestational Diabetes) about 5.0% of women had gestational hypertension and 6.3% had pre-eclampsia 11.

Another trial, ACHOIS (Australian Carbohydrate Intolerance Study in Pregnant Women) reported that 15% of its GDM population had pre-eclampsia, higher than other prospective studies.

2.1.2 Preterm delivery
Preterm delivery is usually defined as delivery <37 weeks’ gestation. The coexistence of pre-eclampsia and hypertensive-associated conditions, such as intrauterine growth restriction and placental abruption are considered to determine preterm delivery among the women diagnosed with GDM.

2.1.3 Shoulder dystocia
Shoulder dystocia is usually defined as the need for additional maneuvers to deliver the shoulders of the baby. In HAPO study shoulder dystocia was one of the least common outcomes, with only 1.3% of the women affected. The risk of shoulder dystocia increases with obesity and GDM. Despite the management of maternal weight, glucose intolerance during pregnancy increased the prevalence of dystocia.

2.1.4 Risk of stillbirth
Before the introduction of pharmacotherapy in the treatment of GDM, untreated GDM was associated with an increase risk of stillbirth by approximately four-fold. Insulin therapy combined with closer monitoring reduced stillbirth rates. In a study population consisting primarily of women with GDM, the stillbirth rate was approximately 1.4 per 1000 births. In HAPO study only 130 women (0.56%) of the 23,316 deliveries experienced a perinatal death, 89 of which were fetal and 41 of which were neonatal.

2.1.5 Cesarean delivery
Cesarean deliveries are common among women with GDM. In HAPO study, 16% of women underwent primary cesarean sections and 7.7% underwent repeat cesarean sections.

In the Toronto Tri-Hospital Study, women with treated GDM had a two-fold increased risk of cesarean delivery. These findings suggest that the GDM diagnosis itself is a risk factor for surgery. Cesarean delivery reduce complications associated with GDM, such as shoulder dystocia but because is a major surgery it is associated with risks for both the fetus and the mother. The operation itself can lead to maternal morbidities, such as wound infection and dehiscence, postpartum infection and bleeding, deep venous thrombosis, as well as the need for future cesarean section with subsequent pregnancies. The presence of obesity

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exacerbate these complications. Thus, the elevated rate of cesareans among GDM women can be interpreted as a side effect of diagnosis, as well as recommended treatment to the other morbid conditions associated with GDM, such as shoulder dystocia and elevated fetal weight.

2.2 Short term complications of offspring
2.2.1 Hypoglycemia in the newborn
Clinical hypoglycemia in the newborn is a complication of GDM. In HAPO study clinical hypoglycemia was diagnosed on the basis of treatment with intravenous glucose infusion or low levels of glucose, defined as <30.6 mg/dL in the first 24 hours after delivery or 45 mg/dL glucose after the first 24 hours. Considered this, only 480 of the 23,316 women (2.1%) had infants with clinical hypoglycemia. The cause for neonatal hypoglycemia include physiologic fluctuations of maternal glycemia in GDM women, despite the treatment. Maternal hyperglycemia is thought to lead to excess fetal glucose exposure and fetal hyperinsulinemia which lead to hyperplasia of fat tissue, skeletal muscle, and neonatal hypoglycemia.

In ACHOIS trial, the prevalence of clinical hypoglycemia was 7% in treated GDM and 5% in GDM not receiving intervention, which was a nonsignificant difference. Similarly, in a multicenter randomized trial in the US the prevalence of clinical neonatal hypoglycemia was similar in the intervention and control arms (5.3% and 6.8%, respectively).

2.2.2. Hyperbilirubinemia
Hyperbilirubinemia is more common among women with GDM than in women without GDM. Maternal hyperglycemia and the subsequent induction of fetal hyperinsulinemia and reduced oxygenation are hypothesized to lead to increased fetal oxygen uptake, fetal erythropoiesis which lead to hyperbilirubinemia. In HAPO study hyperbilirubinemia was defined as necessity of treatment with phototherapy after birth or at least one laboratory report of a bilirubin level ≥20 mg/dL, or readmission to the hospital for hyperbilirubinemia. Approximately 8.3% of women were affected.

2.2.3 Macrosomia
Maternal diabetes is characterized by an increased placental transport of glucose and other nutrients from the mother to the fetus, resulting in macrosomia. Macrosomia is defined as a birth weight ≥ 4,000 g and affect 12% of newborns of normal women and 15–45% of newborns of women with gestational diabetes mellitus (GDM). The increased insulin resistance of the mother with GDM lead to an increased risk of macrosomia. In GDM, a higher amount of blood glucose passes through the placenta into the fetal circulation and extra glucose goes to the fetus and is stored as body fat causing macrosomia or „large for gestational age“. Macrosomia increases the risk of shoulder dystocia, clavicle fractures and brachial plexus injury and increases the rate of admissions to the neonatal intensive care unit. HAPO study examine the incidence of LGA infants, anthropometric measures and their association with index glucose levels. Approximately 9.6% of babies had a birthweight above

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the 90th percentile. In the Toronto Tri-Hospital Study, women with treated GDM had a lower rate of macrosomia than women without glucose control.\(^{14}\)

### 3. LONG TERM COMPLICATIONS OF GDM

#### 3.1. Long term complications of mother

#### 3.1.1 Type 2 diabetes mellitus

Studies demonstrated the association between GDM and postpartum diabetes in the mother. Due to the high prevalence of diabetes in the population, approximately 5%–10% of cases of GDM are considered to be previously undetected cases of diabetes. The remaining and vast majority of GDM cases are related to the metabolic stresses of pregnancy combined with impaired insulin secretory response. The reduced beta-cell reserve in GDM women can manifest in the decade after delivery. Even though women have a normal postpartum glucose tolerance test, the risk of future diabetes may be up to seven-fold higher than in women without histories of GDM. Up to 10% of patients with prior GDM are diagnosed with T2D (type 2 diabetes) soon after delivery and in a ten-year follow-up, the risk of developing T2D is approximately 40%. The incidence of T2D is highest in the first 5 years after pregnancy and then it decreases, reaching a plateau at ten years postpartum. The risk of diabetes mellitus in the mother after GDM is much higher than the risk of perinatal complications associated with GDM, so GDM can be considered to be a form of prediabetes similar to impaired glucose tolerance in nonpregnant individuals. Longitudinal studies of glucose regulation after GDM reveal falling β-cell compensation for chronic insulin resistance that may also worsen over time. Risk factors for an early onset of diabetes mellitus after pregnancy include: high glucose levels, marked insulin resistance and poor β-cell function. Risk factors for relatively high rates of the deterioration in β-cell function that causes diabetes mellitus include weight gain, insulin resistance, rising levels of C-reactive protein and falling levels of adiponectin. These findings suggest that metabolic effects of obesity are important determinants of the β-cell deterioration that leads to diabetes mellitus.

Damn P. et al. studied the development of diabetes after GDM in pregnancy in Denmark over the years. Their results showed that at 6 years after pregnancy, in 241 women with previous diet-treated GDM between 1978 and 1985, almost 18% had developed diabetes (4% type 1 diabetes and 14% type 2 diabetes) and 17% had prediabetes (defined as impaired glucose tolerance and/or impaired fasting glucose). After a median of 19 years, 37% of the 151 participants had diabetes (5% type 1 diabetes, 32% type 2 diabetes), while 29% had prediabetes, meaning only a third had normal glucose tolerance. They found that increasing pre-pregnancy BMI, higher fasting glucose at GDM diagnosis, early gestational age at GDM diagnosis and post-partum impaired glucose tolerance were risk factors for the subsequent development of overt diabetes.

A review by Bellamy et al. reported that in women with previous GDM the risk of developing diabetes is more than seven times that in women who had a normoglycaemic pregnancy, underlining the importance of prevention or postponement of development of diabetes and cardiovascular disease in these women. It has been estimated that GDM is the best known predictor of type 2 diabetes, and that approximately one-third of women with

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type 2 diabetes may have had previous GDM. Considered these, there is a large potential for preventing or delaying the onset of type 2 diabetes in these women.

Epidemiological studies indicate that women with previous GDM who are physically active or do not gain weight after pregnancy have a reduced risk of progressing to overt diabetes. Randomised controlled trials showed that lifestyle intervention and medical treatment decrease the number of diabetes cases by approximately 50% in women with previous GDM. Most guidelines recommend breastfeeding, a lifelong healthy lifestyle including weight loss if necessary, as well as an OGTT 2–6 months post-delivery. After delivery, glucose tolerance should be assessed every 1–3 years using either fasting glucose, OGTT or HbA1c.

3.1.2 Metabolic syndrome

Women with GDM often have an increased risk for metabolic syndrome, and shortly after delivery these women express markers of vascular diseases (disturbed endothelial function and increased intima-media thickness of carotid arteries). The metabolic syndrome is defined by several risk factors: central obesity, hypertension, insulin resistance and dyslipidemia and these risk factors are also associated with the development of CVD and T2DM. The metabolic syndrome has been demonstrated to increase the risk of both outcomes. Damn P. et al found that the risk of the metabolic syndrome in women with previous GDM was over three times that in the general group, even when adjusted for age and BMI.

3.1.3 Cardiovascular diseases (CVD)

The risk of CVD is found to be approximately 70% higher in women with previous GDM compared with women having normoglycaemic pregnancies when followed for 11.5 years after pregnancy. The greater risk of cardiovascular disease seems to occur primarily in women who develop diabetes, rather in women who remain glucose-tolerant.

Studies have demonstrated an association between GDM and risk of subsequent maternal cardiovascular morbidity. Women with previous GDM have an increased risk of cardiovascular risk factors such as hypertension, dyslipidemia, obesity and metabolic syndrome and GDM is an independent risk factor for long-term maternal risk of noninvasive diagnostic procedures, simple cardiovascular events, and cardiovascular hospitalizations. Goueslard et al. compared incidence of long-term maternal cardiovascular morbidity in women with GDM history to those without and showed that after 7 years of follow-up women with GDM history had significantly higher incidence of cardiovascular morbidity (e.g., angina pectoris, myocardial infarction (MI), and ischemic stroke including TIA) compared to controls. Bo et al. followed women with GDM 6.5 years postpartum, and found they had significantly higher levels of vascular endothelial dysfunction markers than women with normal pregnancies. The authors concluded that GDM mothers experience a higher risk of future cardiovascular diseases than do normoglycemic mothers.16

3.1.4 Recurrence of GDM in subsequent pregnancies

One of the major risk factors for GDM is having had a previous GDM pregnancy. GDM has a recurrence rate ranging from 30% to 84% in subsequent pregnancies. Kim et al. found that GDM's recurrence rate during subsequent pregnancies varied markedly across

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studies. The most consistent predictor of future recurrence appeared to be ethnicity. Minority populations had a markedly higher recurrence of GDM than did non-Hispanic white, even after preexisting diabetes before the subsequent pregnancy was considered. A study of predominantly Japanese women showed that 65.6% experienced GDM recurrence in subsequent pregnancies. In a study of primarily Hispanic (85%) patients, who were older and more parous, the GDM recurrence rate was 69%. Kwak et al. showed that among Korean women, 45.0% experienced GDM recurrence in subsequent pregnancies.\(^\text{17}\)

### 3.1.5 Malignancies

Women with a history GDM might have a higher future long-term risk for the development of malignancies. A study by Fuchs et al. demonstrated that hospitalizations due to malignancies years after postpartum were increased in women with GDM. They followed GDM women up to 26 years and found a significant association (but definitely not causation) between GDM and risk of developing ovarian, endometrial, and/or breast cancer. A scottish study with a cohort of 753 pregnant women examined the association between maternal gestational glucose intolerance and the long-term risk of malignant neoplasms. The results showed a positive association between higher glucose levels during pregnancy and increased risk of breast cancer.\(^\text{18}\)

Perrin et al., with a follow-up of 28–40 years, documented five cases of pancreatic cancer in women with GDM history, and an adjusted relative risk of 7.1 was documented. It also found a 4.5-fold risk of hematologic neoplasms, specifically non-Hodgkin’s lymphoma, in GDM women with more than five years of follow-up.\(^\text{19}\)

### 3.1.6 Renal Disease

Studies suggest that GDM is a significant risk factor for long-term renal morbidity. The most common future renal diagnoses were hypertensive renal disease without renal failure, hypertensive renal disease with renal failure, chronic renal failure, and end-stage renal disease. Studies monitored microalbuminuria, a marker of impaired glomerular filtration rate, years postpartum. Friedman et al., followed for 5-8 years postpartum, 72 women with GDM, and they conclude that a higher risk for microalbuminuria was in women with GDM history than in the control group.\(^\text{20}\)

Bomback et al., found that GDM without subsequent T2DM is a risk factor for future development of microalbuminuria. In addition to microalbuminuria, patients with GDM history had increased risk for developing future chronic kidney disease.

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3.2 Long term complications of offspring
3.2.1 Type 2 diabetes mellitus
Maternal diabetic intrauterine environment is strongly associated with T2DM development in offspring. In a multiethnic population (African-American, Hispanic, and non-Hispanic) aged 10-22 years, it was found that 30.4% of youth with T2DM had been exposed to maternal diabetes, compared to 6.3% of nondiabetic youth controls. Holder et al. showed that 31.1% of obese children with normal glucose tolerance with mother diagnosed with GDM developed impaired glucose tolerance/diabetes over a relatively short follow-up period (avg. < 3 years). The results indicate that offspring of mothers with GDM history have at least 5 times greater risk of developing impaired glucose tolerance than those not exposed to gestational diabetes.

3.2.2 Overweight and obesity
In the HAPO study, higher levels of maternal glucose tolerance were found to be positively associated with high birth weight, fetal hyperinsulinemia, and neonatal adiposity. Deierlain et al. measured blood glucose concentration at around 27 weeks of gestation, and found an association between maternal glucose concentration ≥130 mg/dl and a significantly increased risk of children being overweight or obese at 3 years, independent of maternal pre-pregnancy BMI.
A Danish study found a significant association between offspring birth size and obesity risk at 7 years of age and fasting plasma glucose concentrations during pregnancy in women with GDM, even after adjusting for maternal pre-pregnancy BMI. Zhao et al. found an association between maternal GDM and childhood obesity.

3.2.3 Neurodevelopmental outcome and neuropsychiatric morbidity
Studies analysed whether exposure to intrauterine hyperglycaemia can induce impaired cognitive function in the offspring. A systematic review and meta-analysis compared cognitive function in children of diabetic mothers and of nondiabetic mothers, and indicated that infants of diabetic mothers have lower mental and psychomotor development than their counterparts in the first few years of life. Deboer et al. investigated the impact of abnormal fetal environment on explicit memory performance. After controlling for differences in gestational age and global cognitive functioning, they found that, at one year of age, children of diabetic mothers perform worse on delayed recall tasks than do controls. In the first few years of life, offspring of diabetic mothers are at risk of impaired linguistic, mental, psychomotor development, impairment of neural development of facial expression, memory performance. They develop an increased risk of neuropsychiatric diseases such as autistic spectrum disorder, eating disorders, cerebral palsy, obstructive sleep apnea, epilepsy, and infantile spasms.

4. CONCLUSIONS
GDM have important consequences on the future health of both mother and offspring. The prevalence of GDM is increasing in most populations, and GDM plays a significant role in the global diabetes epidemic. Despite the fact that in majority of cases glucose homeostasis return to normal postpartum, GDM is a strong risk factor for type 2 diabetes in later life.

Offspring of women with GDM are predisposed to have a higher birth weight, neonatal hypoglycaemia, jaundice, birth trauma and even stillbirth. Long term complications can be metabolic syndrome, obesity and diabetes.

There is an acute necessity of effective intervention strategies for preventing or reducing metabolic derangement in the mother after delivery.
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