

Research Article

IMPLICATIONS OF GESTATIONAL DIABETES MELLITUS: MATERNAL AND FOETAL OUTCOMES

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ABSTRACT

Background: Gestational diabetes mellitus was established for the first-time during pregnancy. It should be noted that GDM does not include obvious diabetes in pregnancy. The hyperglycaemia was diagnosed as fasting plasma glucose was at least 105 mg/dL or plasma glucose at two hours after meal was at least 200 mg/dL. The current study aimed to conduct a literature review of the implications of gestational diabetes mellitus: Maternal and foetal outcomes reported for pregnant women with gestational diabetes mellitus. **Methodology:** The current articles were searched using a variety of key words such as "Diabetes mellitus and/or pregnancy," "Gestational diabetes mellitus and/or maternal and foetal outcomes", without limit of language to document assembling of as various cases as possible. Those articles were derivative from the World Health Organization (WHO) agendas and rules. Other data related to gestational diabetes mellitus and reported cases were conducted utilizing seven electronic databases (CINAHL, MEDLINE, ProQuest, PubMed, Scopus, Science Direct, and Cochrane) for studies published in various languages from October 2020 to February 2021. **Results:** The current study concluded that women with GDM is powerfully accompanying to adverse pregnancy outcome, with vibrant evidence that exposure to maternal diabetes in utero has short- and long-term adverse effects on the offspring. GDM has both maternal and foetal risks: for the mother the risk is mostly long term; the development to type 2 DM and metabolic syndrome. For the foetus there are both short- and long-term complications; IUGR, abnormal foetal growth primarily macrosomia with its effect on delivery and risk of shoulder dystocia and metabolic hematologic changes such as hypoglycaemia, hypokalaemia, hyperbilirubinemia, hypocalcaemia, polycythaemia and respiratory distress syndrome. The long-term complications for the foetus are adverse neurological and cognitive consequences and mostly early onset metabolic syndrome.

Keywords: Gestational diabetes mellitus, Maternal and foetal outcomes, Pregnancy, Implications.

INTRODUCTION

Background

The International Diabetes Federation (IDF) evaluates that no less than 425 million persons in the world have diabetes [1]. From 1980 to 2014 the diabetes prevalence was more than doubled in men and improved nearly 60% in women. If these trends continue, the World Health Organization (WHO) goal line of uncertain the rise of diabetes by 2025 will not be achieved [2]. The increasing burden of diabetes challenges individuals, families and health systems worldwide [3]. Gestational diabetes mellitus (GDM) is defined by new-onset glucose intolerance during pregnancy. About 2.5% of all pregnant women develop GDM during their pregnancies and the prevalence has increased significantly during the last period. This metabolic condition is established when pancreatic cells lose their capability to recompense for increased insulin resistance during pregnancy, however, the pathogenesis of the disease remains mainly indefinite. GDM is powerfully accompanying with adverse pregnancy outcome as well as with long-term adverse effects on the offspring which likely occurs due to epigenetic modifications of the foetal genome [4]. GDM diagnosed in the second or third trimester of gestation that was not obviously noticeable diabetes preceding to pregnancy, aims to provide greater clarity [5]. The prevalence of GDM varies widely depending on population characteristics and the diagnostic criteria used. Cohort studies accomplished in the UK and Ireland preceding to 2010 established 1–3% of pregnancies were complicated by GDM [6]. In divergence, the prevalence of GDM varied between 9% and 26% (mean 18%) at the 15 centres' complicated in the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) Study

when more strict diagnostic criteria were practiced [7]. In 2017, it was assessed that one in every seven live births globally were exaggerated by GDM. This characterized 85% of the total 21.3 million live births affected by diabetes during pregnancy globally [8]. The causes for the upsurge in GDM prevalence comprise the obesity, physical inactivity, and increasing maternal age [9]. However, GDM is now one of the most common pregnancy complications, significant arguments endure concerning timing of screening, diagnostic thresholds, ideal management, and postpartum follow-up [10]. The Hyperglycaemia Adverse Pregnancy Outcome (HAPO) Prime outcomes included birth weight of not less than the 90 percentile, percentage of caesarean section (CS), neonatal hypoglycaemia, and cord serum C-peptide of not less than the 90 percentiles; lesser outcomes comprised premature labour, shoulder dystocia, hyperbilirubinemia, neonatal intensive care unit management, and pregnancy-induced hypertension syndrome. Newly, it has become vibrant that slight abnormal glucose tolerance upsurgers the incidence of perinatal maternal-infant problems [11, 12]. GDM is a communal illness during gestation that affects accumulative number of pregnant women in the worldwide population. GDM increases the risk of short-term and long-term problems in pregnant women, including pre-eclampsia, the rate of CS, miscarriage and diabetes later in life. Furthermore, offspring of mothers with GDM is further probable to have respiratory distress syndrome and hypoglycaemia during the neonatal period, and develop diabetes, obesity and metabolic disorders later in life [13, 14, 15, 16, 17]

Statement of the problem

The diagnosis and management of GDM has abundant argument, so, it is significant to discuss GDM as the risk of foetal and maternal complications are increased in GDM. A 2-hours 75 g OGTT at 24-28 weeks of gestation is being recommended nowadays both by the European Association for the Study of Diabetes, International

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Association of Diabetes and Pregnancy Study Group (IADPSG), ADA and World Health Organization (WHO)[18, 19, 20]. The prevalence of GDM is around 5% of pregnancies but numbers vary substantially depending on the criteria used and demographic characteristics of the population. Increasing of the prevalence is anticipated to as the epidemic of over weightiness remains. Pregnancies affected by GDM impose a risk for both mother and foetus as the risk of CS and operative vaginal delivery, macrosomia, shoulder dystocia, neonatal hypoglycaemia and hyperbilirubinemia is increased. Women with a history of GDM are also at an increased risk of developing type 2 diabetes mellitus (T2DM) in the years following their pregnancy and their children have a higher risk of developing obesity and T2DM early in life [19]. So, it is significant to compensate laborious care to implications of GDM and the aim of this review is to discuss the implications of GDM and the short- and long-term outcomes of GDM for both mother and foetus.

Research Question

- What are the short- and long-term implications of gestational diabetes mellitus?
- What are the maternal and foetal outcomes of gestational diabetes mellitus?

Study Objective

The main aim of this study was to investigate the implications of gestational diabetes mellitus. Afterward, the maternal and foetal outcomes of gestational diabetes mellitus; short- and long-term implications.

METHODOLOGY

Research Design

The current study was designed as integrated literature review to stand on the implications of gestational diabetes mellitus. Afterward, the maternal and foetal outcomes of gestational diabetes mellitus; short- and long-term implications.

Data collection

The current articles were searched using a variety of key words such as "Diabetes mellitus and/or pregnancy," "Gestational diabetes mellitus and/or maternal and foetal outcomes", without limit of language to document assembling of as various cases as possible. Those articles were derivative from the World Health Organization (WHO) agendas and rules. Other data related to gestational diabetes mellitus and reported cases were conducted utilizing seven electronic databases (CINAHL, MEDLINE, ProQuest, PubMed, Scopus, Science Direct, and Cochrane) for studies published in various languages from October 2020 to February 2021.

Study inclusion criteria

All studies about the implications of gestational diabetes mellitus. Correspondingly, the studies that discovered the several maternal and foetal outcomes of gestational diabetes mellitus; short- and long-term implications were included.

DISCUSSIONS

Gestational diabetes mellitus with primary start and evaluation in pregnancy, has been a scientific object tense with debate since its first explanation in 1964 [21]. While continuing debate in the

subsequent half-century has centred around the diagnostic criteria and the ideal procedure for its screening and discovery, there is world-wide evaluation that GDM recognizes upcoming risk of type 2 diabetes. Certainly, even though glucose tolerance naturally reverts to usual in the immediate postnatal period, women with GDM have a 20–70% risk of progressing to type 2 diabetes in the first decade after delivery. Therefore, GDM is recognized clinical predictor of future diabetes risk, with affected women displaying a bigger than seven-fold advanced overall incidence of type 2 diabetes, as equated with their peers [22]. Women with GDM experience an increased risk of developing other pregnancy complications, such as preeclampsia, and their offspring are at higher risk of developing short-term adverse outcomes such as macrosomia, neonatal hypoglycaemia and neonatal cardiac dysfunction, and long-term complications, such as obesity, impaired glucose tolerance (IGT), and diabetes in adolescence or early adulthood [4].

Maternal outcomes

Initially, the association between hyperglycaemia in pregnancy and subsequent type 2 diabetes has been known for more than 50 years. Women who have had GDM have a noticeably increased risk for advance of type 2 diabetes mellitus (T2DM), even though most women return to a normoglycaemic state shortly after delivery. The evidence of this association is enormous, but the extent of the risk differs among studies, primarily explained by differences in length of follow-up, number of women participating in follow-up, diagnostic criteria and in the selection of the population. In addition, studies provide mark that numerous of the known T2DM risk genes are more frequent in women with previous GDM, and various risk factors such as a raised body-mass index (BMI), old age, and family history of diabetes [23]. The metabolic syndrome is characterized by several risk factors, including central obesity, hypertension, insulin resistance and dyslipidaemia. These risk factors are also associated with the development of CVD and T2DM, and the metabolic syndrome has been demonstrated to increase the risk of both outcomes [24]. Nearly 60% of women with a past history of GDM develop T2DM later in life. Each additional pregnancy also confers a threefold increase in the risk of T2DM in women with a history of GDM. Extra, women with a previous case of GDM have a yearly risk of change to T2DM of near 2 to 3%. Developing evidence also suggests that the vasculature of women with a prior case of GDM is enduringly altered, predisposing them to CVD. One study stated a 63% increased jeopardy of CVD amongst women with a history of GDM, which was partially, but not completely, explained by BMI [25]. This is of main concern, as CVD is the number one cause of death in the world [26, 27]. One study has established that the 3 times postpartum prevalence of the metabolic syndrome increases progressively from 10% in women with normoglycaemic pregnancies to 17.6% in women with gestational impaired glucose tolerance and to 20% in women with previous GDM [28]. 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 the index pregnancy. The increased risk may also extend to women with only mild glucose intolerance during pregnancy [19]. Many studies have argued that an increased cardiovascular disease (CVD) risk can manifest even in the absence of diabetes [29, 30, 31, 32]. This conflicting evidence holds fundamental implications for clinical CVD risk assessment in women. Specifically, if an increased CVD risk only manifests upon progression to T2DM, then clinical monitoring of glucose tolerance should suffice for prompting vascular evaluation in women with a history of GDM. In deduction, the diagnosis of GDM recognizes young women who have a twofold elevated risk of rising CVD in the years afterward, as compared with their peers. Therefore, the diagnosis of GDM should be standard as providing a sole opening

into a woman's future risk of CVD, and hereafter chance for early risk adjustment and possibly prevention of the leading cause of mortality in women [22]. Moreover, maternal complications include pregnancy-induced hypertension syndrome (PIH), polyhydramnios, shoulder dystocia, and CS. Vigilant care should also be paid to diabetic ketoacidosis, deteriorating of diabetic retinopathy and diabetic nephropathy, and hypoglycaemia. For PIH, 2% to 8% of all pregnant women are complicated with preeclampsia, which deteriorates perinatal outcomes. It is important to mention that, 80% of all cases of PIH, is of maternal origin and is often associated with old age, obesity, diabetes mellitus, and chronic hypertension. Subsequent, it has been reported that 0.5% to 0.7% of normal pregnant women and 2.0% to 2.1% of patients with GDM are complicated with polyhydramnios. Polyhydramnios induces complications leading to perinatal death including premature labour, premature rupture of membranes, foetal malpresentation, weak labour, umbilical cord prolapse, premature separation of normally implanted placenta, and atonic haemorrhage after delivery. For pregnant women with GDM, it has been reported that glucose concentration in amniotic fluid is related to maternal plasma glucose level and that there is a positive correlation between amniotic fluid volume and glucose concentration in amniotic fluid [12]. Shoulder dystocia is a condition in which after the head of the infant is delivered in cephalic vaginal delivery, the shoulder of the infant is not delivered. It is a disease which may cause dystocia in both the mother and the infant. It is known that macrosomia is a risk factor for shoulder dystocia; on the other hand, it has been reported that pregnant women with abnormal glucose tolerance tend to experience shoulder dystocia regardless of the presence or absence of macrosomia. For these reasons and also because of complications of foetuses as mentioned later, the percentage of CS is clearly developed in pregnant women with abnormal glucose tolerance; the percentage is 10.7%-18.9% in normal pregnant women, compared with 19.3%-30.9% in pregnant women with GDM and 45.2% in pregnant women with GDM [12]. In addition, the most common maternal outcome of GDM is CS; one study revealed outcome of preeclampsia which associated with gestational hypertension (no less than 140/90 mmHg happening for the first time after mid-pregnancy) and proteinuria. GDM is accompanied with a 50% increased risk of severe preeclampsia and mild preeclampsia compared with gestation without metabolic abnormalities [33, 34, 35]. Women with GDM are at higher risk of hypertensive disorders including gestational hypertension, preeclampsia, and eclampsia. One study revealed that, 5.9% had gestational hypertension and 4.8% had preeclampsia. The study showed that the glucose level at the first glucose tolerance test was positively correlated with the risk of preeclampsia [36]. Similarly, another study [37] reported that 5% had gestational hypertension and 6.3% had preeclampsia. One study, confirmed a direct correlation between CS rate and maternal glycemia with an overall frequency of 23.7% [36]. On the same hand, another study [37] stated a non-elective CS rate for women with GDM of 19.5% compared to 13.5% for non-diabetic women [19]. Regrettably, GDM is a condition that expects all types of diabetes later in life particularly T2DM, the most prevalent form of diabetes. The development to T2DM in the years subsequently delivery is motivated by the deteriorating of insulin secretion defect [37, 38, 39, 40]. Both reduced insulin sensitivity and impaired pancreatic b-cell function may explain the increased risk of glucose intolerance among adult offspring [41, 42] suggesting that foetal exposure to maternal diabetes is associated with multi organ dysfunction at adult age. Another study [43] related increased maternal-induced methylation at guanine nucleotide binding protein alpha subunit of differentially methylated regions in foetuses of GDM compared to normal pregnancy with increased risk of metabolic diseases in later life of offspring [35]. Furthermore, the jeopardies of

various serious perinatal complications are increased in women with GDM, including gestational hypertension, pre-eclampsia, polyhydramnios, Caesarean section, and shoulder dystocia. The probability of repeated GDM in a following pregnancy was assessed as 48% in a meta-analysis of 18 studies [44]. It has generally been observed that increasing maternal BMI, early gestational age at GDM diagnosis, and postpartum impaired glucose tolerance are interpreters for future progress of T2DM [10, 45]. GDM upsurges the danger of a numeral of short-term and long-term maternal health issues. Additionally, to the stress of normal pregnancy, GDM is associated with antenatal depression [46]. There is also an increased risk of additional pregnancy complications, including preterm birth, preeclampsia, and surgical delivery of the baby is required [27]. Also, there are numerous studies also discuss morbidity and mortality adverse maternal outcome in short- and long-term outcomes [47- 53]. Subsequently, evidence has accumulated to support the findings of; GDM is accompanied with a variety of long-term adverse consequences for the mother and the offspring. Offspring born to mothers with GDM are at augmented danger of several immediate complications, including macrosomia, preterm birth, birth injury, shoulder dystocia, neonatal hypoglycaemia, neonatal unit admission, and respiratory distress [54]. It remains uncertain whether GDM is associated with an increased risk of perinatal death. A cohort study capturing all births in France during 2012, including 57 629 births with maternal GDM, showed the odds of perinatal mortality were increased by 30% in infants born at term (at or beyond 37 weeks) with maternal GDM, compared with the no diabetic population [55]. On the contrary, large population-based cohort studies, including over 1 million participants in Ontario, Canada (1996–2010) and Sweden (1991–2003), demonstrated perinatal mortality in offspring from GDM mothers (on treatment) was significantly lower than or similar to the non diabetic population, correspondingly [56]. Whereas many studies support an association between presentational diabetes and increased risk of congenital malformations, this is due to the impact of hyperglycaemia on embryogenesis during the first eight gestational weeks (i.e., before GDM is diagnosed). A study accomplished across five Irish centres reported there was no difference in rates of congenital anomaly observed in the offspring of 5500 women with GDM or normal glucose tolerance. However, GDM was connected with a raised danger of congenital anomaly in the Ontario cohort 37.5 per 1000 births in GDM, AR 29.04 per 1000 births in nondiabetic population, and of cardiac malformations in the French cohort compared with the nondiabetic population [55, 56]. The long-term impact of intrauterine exposure to GDM on offspring health remains uncertain. Studies in childhood have shown evidence of an adverse cardiovascular phenotype, including increases in adiposity, insulin resistance, systolic blood pressure, and risk of circulatory disease compared with offspring with no parental diabetes [57, 58]. Studies in adult offspring have established condensed insulin sensitivity and augmented danger of diabetes, metabolic syndrome, and higher BMI compared with the background population [59,60]. Unfortunately, there are many complications related to macrosomia as if the baby is unusually big, vaginal birth will be more complicated. There is a risk of prolonged labour in which the foetus might be fixed in the birth canal, instrumental delivery (with forceps or vacuum) may be needed, and even unplanned or emergency CS may be necessary. During birth, there is a greater risk of vaginal, perineal and anal laceration and tear. There is also a high chance of uterine atony. The uterus muscle may not properly contract, resulting in heavy bleeding and postpartum hemorrhage. The risk of postpartum bleeding and genital tract injury was about 3–5 times higher in macrosomic labour. Besides, if the mother has had a previous CS, there is a higher chance of uterus tear along the scar line of the previous surgery [61].

Foetal outcomes

GDM is associated with short- and long-term complications, both for the mother and for the foetus. Foetal and newborn short-term complications include respiratory distress syndrome, prematurity, breech presentation, hypoglycaemia, hyperbilirubinemia, macrosomia and death. Macrosomia (foetal weight over 4000 g) is the most important and common foetal complication, and is accompanying with several perinatal adverse outcomes, such as acute foetal distress, birth trauma and emergency CS. In addition to these immediate risks, there are substantial long-term risks of future life obesity, glucose intolerance, hypertension and CVD in children of GDM mothers [4]. About 15–45% of babies born to diabetic mothers can have macrosomia, which is a 3-fold higher rate when compared to normoglycemic controls. Macrosomia is typically defined as a birth weight above the 90th percentile for gestational age or >4,000 g. Disparate maternal hyperglycaemia, maternal obesity has a strong and independent effect on foetal macrosomia. Gestational age at delivery, maternal pre-pregnancy BMI, pregnancy weight gain, maternal height, hypertension and cigarette smoking also have a substantial influence. When obese women were compared to normal-weight women, the newborns of obese women had more than double the risk of macrosomia compared to those of women with normal weight [12]. Macrosomia in newborns of GDM mothers is characterized by improved body fat [62, 63]. The foetal insulin levels assessed by cord C-peptide level were powerfully positively correlated [64]. So, maternal glycaemia is directly related to neonatal adiposity. Consequently, shoulder dystocia is a serious complication of childbirth. A strong association between increased foetal size and the risk of shoulder dystocia has been shown once the birth weight exceeds 4 kg. The risk of stillbirth was increased fourfold. The risk is found to be lower; possibly due to the beginning of specialist care and treatment of GDM. In the HAPO study, there was no increased risk of prenatal death with increased maternal glucose levels. In contrast, another study observed five deaths in the control group (routine care) and none in the study (treatment) group [19]. In this setting, GDM also poses short- and long-term consequences for the infant. The increase in placental transport of glucose, amino acids, and fatty acids stimulate the foetus's endogenous production of insulin and insulin-like growth factor 1 (IGF-1). Together, these can cause foetal overgrowth, often resulting in macrosomia at birth. Excess foetal insulin production can strain the developing pancreatic β -cells, causal to β -cell dysfunction and insulin resistance, even prenatally. Macrosomia is also a risk factor for shoulder dystocia—a form of obstructed labour. Accordingly, babies of GDM mothers are usually delivered by CS [65,66]. Once delivered, these babies are at increased risk of hypoglycaemia, which is probable owing to formed dependence on maternal hyperglycaemia (foetal hyperinsulinemia), which can contribute to brain injury if not appropriately accomplished. There is also evidence that GDM increases the risk of stillbirth. In the long term, babies that are born of GDM mothers are at increased risk of obesity, T2DM, CVD, and associated metabolic diseases. Children born to mothers with GDM have almost double the risk of developing childhood obesity when compared with non diabetic mothers, even after adjusting for confounders such as maternal BMI [67], and impaired glucose tolerance can be detected as young as five years old [27]. Congenital anomaly is one of the complications of foetuses born from mothers with GDM. According to a report in Japan, the incidence of congenital anomaly does not increase obviously when hemoglobin A1c (HbA1c) during the early stage of pregnancy is below 7.4%; though, the incidence upsurges when HbA1c is 7.4% or more; the incidence is as high as 24.1% when HbA1c is 8.4% or more [68]. The hyperglycemia of mothers persuades hyperglycemia of fetuses, and hyperplasia of pancreatic β -cells of foetuses results in hyper secretion of insulin, leading to extreme growth of foetuses.

Such complications include hypoglycaemia, polycythaemia, hyperbilirubinemia, hypocalcaemia, neonatal respiratory distress syndrome, and myocardial hypertrophy [12]. In the same context, GDM may lead to foetal complications including foetal hypoglycaemia immediately after delivery when glucose input from the mother is disordered and the newborn is still hyperinsulinaemic, hypocalcaemia, respiratory distress, stillbirth and macrosomia associated sometimes with birth trauma [69]. Additionally, foetal malformation may occur when hyperglycaemia is present in first trimester particularly in unknown pre GDM [35]. Unfortunately, offspring of women with a history of GDM are also at augmented long-term risk of emerging metabolic diseases such as obesity, T2DM and the metabolic syndrome. This long-term risk depends on genetic susceptibility and is additional tempered by the postnatal environment. Maternal glucose easily crosses the placenta and as a result maternal hyperglycaemia leads to intrauterine hyperglycaemia, which induces foetal hyperinsulinemia and possible modification of growth and future metabolism of the foetus. Likewise, the relation between birth weight and risk of T2DM is observed as U-shaped and consequently both infants with reduced and those with enlarged birth weight are at augmented risk of emerging T2DM as compared to persons being born with a normal birth weight [70, 19, 20, 71]. Furthermore, the offspring that exposed to intrauterine hyperglycaemia due to GDM, mainly have decreased insulin sensitivity [72]. Long-term significances of GDM are the development of the metabolic syndrome and obesity in the offspring. Where the mean BMI was 2.6 kg/m² higher in offspring born to diabetic mothers compared to offspring born to non-diabetic mothers. This association is also seen in another study, where children of mothers with mainly GDM had a higher increase in BMI growth rapidity than unexposed controls, with the increase starting at the age of 10 to 13 [73]. Besides, according to a recent study, offspring of Caucasian women with GDM had a 2-fold increased risk of developing obesity and a 4-fold increased risk of the metabolic syndrome compared to the contextual population. Correspondingly, the genetics play an important role in the development of the metabolic syndrome and obesity together with an effect of intrauterine hyperglycaemia. The prevalence of obesity increases worldwide among all age groups and some of the predisposition to obesity in children may be due to epigenetic foetal programming [19]. Premature birth is considered immediate foetal complications. Owing to premature induction of labour before 39 weeks of pregnancy and/or premature rupture of membranes, there is a risk of preterm delivery. In addition to the risk of complications associated with new borns prematurity, including difficulties in respiration and feeding, infection, jaundice, neonatal intensive care unit admission and perinatal death. Shoulder dystocia and Erb's Palsy. Newborns with a birth weight of 4,500 g or more carry a 6 times higher risk of birth trauma and the risk of brachial plexus injury is around 20-folds higher when the birth weight is above 4,500 g. Hypoglycaemia at birth. Hypoglycaemia can lead to more grave complications similar severe central nervous system and cardiopulmonary disorders. Major long-term sequelae include neurologic damage resulting in mental retardation, recurrent seizure activity, growing delay and behaviour disorders. Neonatal Jaundice. Factors which may account for jaundice are prematurity, impaired hepatic conjugation of bilirubin and increased enter hepatic circulation of bilirubin resulting from poor feeding. In macrosomia, neonates have a high oxygen demand producing improved erythropoiesis and, eventually, polycythaemia. Consequently, when these cells failure, bilirubin increases resulting in neonatal jaundice [61]. The high blood sugar level of women with GDM can damage the developing organs of the foetus, leading to congenital anomalies such as heart defects and neural tube defects that are the most common types of birth defects. Regrettably, there are later complications childhood such as obesity and metabolic syndrome. Several studies propose that one of

the causes of childhood obesity is GDM. There has been mark of foetal programming of later adiposity amongst offspring exposed to present diabetes in utero. One study revealed that experience to maternal GDM was associated with an advanced BMI, a bigger waist circumference, more visceral and subcutaneous adipose tissue and a more centralized fat distribution pattern in 6 to 13-year-old multi-ethnic youth [74]. Furthermore, youth exposed to maternal GDM in utero had an overall higher average BMI growth from 27 months through 13 years of age and a higher BMI growth rapidity starting at age 10–13 years [75, 76]. These results recommend that the long-term effects of in utero GDM exposure are not always obvious in early childhood, but relatively arise during puberty, another sensitive period for the progress of obesity. Offspring of GDM mothers is also vulnerable to the beginning of metabolic syndromes such as augmented blood pressure, hyperglycaemia, obesity and abnormal cholesterol levels that occur together and increase the risk of CVD, stroke and diabetes[61]. Fortunately, the incidence of GDM in Japan has increased by 4.1 fold from 2.9% to 12.1%. By detecting abnormal maternal glucose metabolism at an early stage of pregnancy and accomplishing outstanding glycaemic control during pregnancy, it is possible to prevent perinatal maternal-infant complications [12].

Conclusions

The current study concluded that women with GDM is powerfully accompanying to adverse pregnancy outcome, with vibrant evidence that exposure to maternal diabetes in utero has short- and long-term adverse effects on the offspring. GDM has both maternal and foetal risks: for the mother the risk is mostly long term; the development to type 2 DM and metabolic syndrome. For the foetus there are both short- and long-term complications; IUFD, abnormal foetal growth primarily macrosomia with its effect on delivery and risk of shoulder dystocia and metabolic hematologic changes such as hypoglycaemia, hypokalaemia, hyperbilirubinemia, hypocalcaemia, polycythaemia and respiratory distress syndrome. The long-term complications for the foetus are adverse neurological and cognitive consequences and mostly early onset metabolic syndrome.

Recommendations And Further Research

The public authority, health and educational institutions should work together in undertaking GDM to give appropriate, great emergency to women with GDM during pregnancy.

- Future research is needed regarding prevention of GDM, treatment goals and effectiveness of interventions, guidelines for pregnancy care and prevention of long-term metabolic sequel for both the infant and the mother.
- Exploring the feasibility of other implications of GDM.
- Giving proposals to exercises that can forestall understudies' psychological problem to not more awful during the GDM.
- Discussing possible topics of research that could help improve clinical GDM treatment and prevention of foetal programming.

REFERENCES

1. Atlas D. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017. Available online at: <http://www.diabetesatlas.org>
2. Zhou B, Bentham J, Di Cesare M, Bixby H, Danaei G, Cowan MJ, Paciorek CJ, Singh G, Hajifathalian K, Bennett JE, Taddei C. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *The Lancet*. 2017 Jan 7;389(10064):37-55. doi: 10.1016/S0140-6736(16)00618-8
3. Goveia P, Cañon-Montañez W, Santos DD, Lopes GW, Ma RC, Duncan BB, Ziegelman PK, Schmidt MI. Lifestyle intervention for the prevention of diabetes in women with previous gestational diabetes mellitus: A systematic review and meta-analysis. *Frontiers in endocrinology*. 2018 Oct 5;9:583.
4. Monteiro LJ, Norman JE, Rice GE, Illanes SE. Fetal programming and gestational diabetes mellitus. *Placenta*. 2016 Dec 1;48:S5460.
5. American Diabetes Association (2018) Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. *Diabetes Care* 41, S13–S27
6. Farrar D, Simmonds M, Griffin S, Duarte A, Lawlor DA, Sculpher M, Fairley L, Golder S, Tuffnell D, Bland M, Dunne F. The identification and treatment of women with hyperglycaemia in pregnancy: an analysis of individual participant data, systematic reviews, meta-analyses and an economic evaluation. *Health technology assessment*. 2016 Nov 30:1-348.
7. Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, Lowe LP, Coustan DR, Hod M, Oats JJ, Persson B. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel–recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes care*. 2012 Mar 1;35(3):526-8.
8. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice*. 2019 Nov 1;157:107843.
9. Lavery JA, Friedman AM, Keyes KM, Wright JD, Ananth CV. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2017 Apr;124(5):804-13.
10. Gorgal R, Gonçalves E, Barros M, Namora G, Magalhães Â, Rodrigues T, Montenegro N. Gestational diabetes mellitus: A risk factor for non-elective cesarean section. *Journal of Obstetrics and Gynaecology Research*. 2012 Jan;38(1):154-9. [PMID: 21995455 DOI: 10.1111/-j.1447-0756.2011.01659.x]
11. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva Ad, Hod M, Kitzmiller JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; 33: 676-682 [PMID: 20190296 DOI: 10.2337/ dc09-1848]
12. Hashimoto K, Koga M. Indicators of glycemic control in patients with gestational diabetes mellitus and pregnant women with diabetes mellitus. *World journal of diabetes*. 2015 Jul 25;6(8):1045.
13. Clausen TD, Mathiesen ER, Hansen T, et al. Overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus or type 1 diabetes. *J Clin Endocrinol Metab* 2009;94:2464–70.
14. Kim SY, England JL, Sharma JA, et al. Gestational diabetes mellitus and risk of childhood overweight and obesity in offspring: a systematic review. *Exp Diabetes Res* 2011;2011:1–9.
15. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev* 2005;85:571–633.
16. Clausen TD, Mathiesen ER, Hansen T, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with

- gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care* 2008;31:340–6.
17. Li-Zhen L, Yun X, Xiao-Dong Z, Shu-Bin H, Zi-Lian W, Sandra DA, Bin L. Evaluation of guidelines on the screening and diagnosis of gestational diabetes mellitus: systematic review. *BMJ open*. 2019 May 1;9(5):e023014. doi:10.1136/bmjopen-2018-023014
 18. Macaulay S, Dunger DB, Norris SA. Gestational diabetes mellitus in Africa: a systematic review. *PLoS One* 2014; 9: e97871 [PMID: 24892280 DOI: 10.1371/journal.pone.0097871]
 19. Kampmann U, Madsen LR, Skajaa GO, Iversen DS, Moeller N, Ovesen P. Gestational diabetes: a clinical update. *World journal of diabetes*. 2015 Jul 25;6(8):1065.
 20. Coustan DR. Gestational diabetes mellitus. *Clinical chemistry*. 2013 Sep 1;59(9):1310-21.
 21. O'SULLIVAN JB. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes*. 1964 May 1;13:278-85.
 22. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. *Diabetologia*. 2019 Jun;62(6):905-14.
 23. Lacroix M, Kina E, Hivert MF. Maternal/fetal determinants of insulin resistance in women during pregnancy and in offspring over life. *Curr Diab Rep* 2013; 13: 238-244 [PMID: 23307191 DOI: 10.1007/s11892-012-0360-x]
 24. Sullivan SD, Umans JG, Ratner R. Gestational diabetes: implications for cardiovascular health. *Curr Diab Rep* 2012; 12: 43-52 [PMID: 22037824 DOI: 10.1007/s11892-011-0238-3]
 25. Shostrom, D.C.V.; Sun, Y.; Oleson, J.J.; Snetselaar, L.G.; Bao, W. History of Gestational Diabetes Mellitus in Relation to Cardiovascular Disease and Cardiovascular Risk Factors in US Women. *Front. Endocrinol*. 2017, 8, 144. [CrossRef] [PubMed]
 26. World Health Organization (WHO). Global Action Plan for the Prevention and Control of NCDs 2013–2020; WHO: Geneva, Switzerland, 2013.
 27. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The pathophysiology of gestational diabetes mellitus. *International journal of molecular sciences*. 2018 Nov;19(11):3342.
 28. Retnakaran R, Qi Y, Connelly PW, Sermer M, Zinman B, Hanley AJ. Glucose intolerance in pregnancy and postpartum risk of metabolic syndrome in young women. *J Clin Endocrinol Metab* 2010; 95: 670-677 [PMID: 19926711 DOI: 10.1210/jc.2009-1990]
 29. Retnakaran R (2018) Hyperglycemia in pregnancy and its implications for a woman's future risk of cardiovascular disease. *Diabetes Res Clin Pract* 145:193–199. <https://doi.org/10.1016/j.diabres.2018.04.008>
 30. Tobias DK, Stuart JJ, Li S et al (2017) Association of history of gestational diabetes with long-term cardiovascular disease risk in a large prospective cohort of US women. *JAMA Intern Med* 177(12): 1735–1742. <https://doi.org/10.1001/jamainternmed.2017.2790>
 31. Goueslard K, Cottenet J, Mariet AS et al (2016) Early cardiovascular events in women with a history of gestational diabetes mellitus. *Cardiovasc Diabetol* 15(1):15. <https://doi.org/10.1186/s12933-016-0338-0>
 32. Retnakaran R, Shah BR (2017) Role of type 2 diabetes in determining retinal, renal and cardiovascular outcomes in women with previous gestational diabetes. *Diabetes Care* 40(1):101–108. <https://doi.org/10.2337/dc16-1400>
 33. Bener A, Saleh NM & Al-Hamaq A. Prevalence of gestational diabetes and associated maternal and neonatal complications in a fast developing community: global comparisons. *International Journal of Women's Health* 2011 3 367–373. (doi:10.2147/IJWH.S26094)
 34. Fadl HE, Ostlund IKM, Magnuson AFK & Hanson USB. Maternal and neonatal outcomes and time trends of gestational diabetes mellitus in Sweden from 1991 to 2003. *Diabetic Medicine* 2010 27 436–441. (doi:10.1111/j.1464-5491.2010.02978.x)
 35. Baz B, Riveline JP, Gautier JF. Gestational diabetes mellitus: definition, aetiological and clinical aspects. *Eur J Endocrinol*. 2016 Feb 1;174(2):R43-51.
 36. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: preeclampsia. *Am J ObstetGynecol* 2010; 202: 255.e1-255.e7 [PMID: 20207245 DOI: 10.1016/j.ajog.2010.01.024]
 37. Retnakaran R, Qi Y, Sermer M, Connelly PW, Hanley AJ & Zinman B. b-cell function declines within the first year postpartum in women with recent glucose intolerance in pregnancy. *Diabetes Care* 2010 33 1798–1804. (doi:10.2337/dc10-0351)
 38. Xiang AH, Kjos SL, Takayanagi M, Trigo E & Buchanan TA. Detailed physiological characterization of the development of type 2 diabetes in Hispanic women with prior gestational diabetes mellitus. *Diabetes* 2010 59 2625–2630. (doi:10.2337/db10-0521)
 39. Ignell C, Shaat N, Ekelund M & Berntorp K. The impact of ethnicity on glucose homeostasis after gestational diabetes mellitus. *Acta Diabetologica* 2013 50 927–934. (doi:10.1007/s00592-013-04848)
 40. Retnakaran R, Qi Y, Connelly PW, Sermer M, Hanley AJ & Zinman B. The graded relationship between glucose tolerance status in pregnancy and postpartum levels of low-density-lipoprotein cholesterol and apolipoprotein B in young women: implications for future cardiovascular risk. *Journal of Clinical Endocrinology and Metabolism* 2010 95 4345–4353. (doi:10.1210/jc.2010-0361)
 41. Clausen TD, Mortensen EL, Schmidt L, Mathiesen ER, Hansen T, Jensen DM & Damm P. Cognitive function in adult offspring of women with gestational diabetes – the role of glucose and other factors. *PLoS ONE* 2013 8 1–8. (doi:10.1371/journal.pone.0067107)
 42. Abi Khalil C, Travert F, Fetita S, Rouzet F, Porcher R, Riveline J-P, Hadjadj S, Larger E, Roussel R, Vexiau P et al. Fetal exposure to maternal type 1 diabetes is associated with renal dysfunction at adult age. *Diabetes* 2010 59 2631–2636. (doi:10.2337/db10-0419)
 43. Chen D, Zhang A, Fang M, Fang R, Ge J, Jiang Y, Zhang H, Han C, Ye X, Huang H et al. Increased methylation at differentially methylated region of GNAS in infants born to gestational diabetes. *BMC Medical Genetics* 2014 15 1–7. (doi:10.1186/s12881-014-0108-3)
 44. Schwartz, N. et al. (2015) The prevalence of gestational diabetes mellitus recurrence—effect of ethnicity and parity: a metaanalysis. *Am. J. Obstet. Gynecol.* 213, 310–317
 45. Prakash GT, Das AK, Habeebullah S, Bhat V, Shamanna SB. Maternal and neonatal outcome in mothers with gestational diabetes mellitus. *Indian journal of endocrinology and metabolism*. 2017 Nov;21(6):854.
 46. Byrn, M.; Penckofer, S. The relationship between gestational diabetes and antenatal depression. *J. Obstet. Gynecol. Neonatal Nurs.* 2015, 44, 246–255. [CrossRef] [PubMed]
 47. Mitanchez D. Fetal and neonatal complications in gestational diabetes: perinatal mortality, congenital malformations, macrosomia, shoulder dystocia, birth injuries, neonatal complications. *Diabetes Metab* 2010;36:617–27.
 48. Hay Jr WW. Care of the infant of the diabetic mother. *Curr Diab Rep* 2012;12:4–15.
 49. Syed M, Javed H, Yakoob MY, Bhutta ZA. Effect of screening and management of diabetes during pregnancy on stillbirths. *BMC Public Health* 2011;11(Suppl. 3):S2.

50. Alberico S, Montico M, Barresi V, et al. The role of gestational diabetes, pre-pregnancy body mass index and gestational weight gain on the risk of newborn macrosomia: results from a prospective multicentre study. *BMC Pregnancy Childbirth* 2014;14:23
51. Ramos GA, Hanley AA, Aguayo J, Warshak CR, Kim JH, Moore TR. Neonatal chemical hypoglycemia in newborns from pregnancies complicated by type 2 and gestational diabetes mellitus — the importance of neonatal ponderal index. *J MaternFetal Neonatal Med* 2012;25:267–71.
52. Hopewell B, Steiner LA, Ehrenkranz RA, Bizzarro MJ, Gallagher PG. Partial exchange transfusion for polycythemia per viscosity syndrome. *Am J Perinatol* 2011;28: 557–64
53. Langer O. Obesity or diabetes: which is more hazardous to the health of the offspring? *J MaternFetal Neonatal Med* 2015;1–5.
54. Johns EC, Denison FC, Norman JE, Reynolds RM. Gestational diabetes mellitus: mechanisms, treatment, and complications. *Trends in Endocrinology & Metabolism*. 2018 Nov 1;29(11):74354.
55. Billionnet, C. et al. (2017) Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012. *Diabetologia* 60, 636–644
56. Feig, D.S. et al. (2014) Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996–2010. *Diabetes Care* 37, 1590–1596
57. Krishnaveni, G.V. et al. (2010) Intrauterine exposure to maternal diabetes is associated with higher adiposity and insulin resistance and clustering of cardiovascular risk markers in Indian children. *Diabetes Care* 33, 402–404
58. Wu, C.S. et al. (2012) Long-term health outcomes in children born to mothers with diabetes: a population-based cohort study. *PLoS One* 7, e36727
59. Kelstrup, L. et al. (2013) Insulin resistance and impaired pancreatic b-cell function in adult offspring of women with diabetes in pregnancy. *J. Clin. Endocrinol. Metab.* 98, 3793–3801
60. Damm, P. et al. (2016) Gestational diabetes mellitus and longterm consequences for mother and offspring: a view from Denmark. *Diabetologia* 59, 1396–1399
61. Kamana KC, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. *Annals of Nutrition and Metabolism*. 2015;66(Suppl. 2):14–20.
62. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: A World Health Organization Guideline. *Diabetes Res Clin Pract* 2014; 103: 341–363 [PMID: 24847517 DOI: 10.1016/j.diabres.2013.10.012]
63. Metzger BE, Persson B, Lowe LP, Dyer AR, Cruickshank JK, Deerochanawong C, Halliday HL, Hennis AJ, Liley H, Ng PC, Coustan DR, Hadden DR, Hod M, Oats JJ, Trimble ER. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. *Pediatrics* 2010; 126: e1545-e1552 [PMID: 21078733]
64. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva Ad, Hod M, Kitzmiller JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; 33: 676-682 [PMID: 20190296 DOI: 10.2337/ dc09-1848]
65. Gascho, C.L.L.; Leandro, D.M.K.; Ribeiro, E.; Silva, T.; Silva, J.C. Predictors of cesarean delivery in pregnant women with gestational diabetes mellitus. *Rev. Bras. Ginecol. Obstet.* 2017, 39, 60–65. [CrossRef] [PubMed]
66. Scifres, C.M.; Feghali, M.; Dumont, T.; Althouse, A.D.; Speer, P.; Caritis, S.N.; Catov, J.M. Large-for-Gestational-Age Ultrasound Diagnosis and Risk for Cesarean Delivery in Women With Gestational Diabetes Mellitus. *Obstet. Gynecol.* 2015, 126, 978–986. [CrossRef] [PubMed]
67. Tam, W.H.; Ma, R.C.W.; Ozaki, R.; Li, A.M.; Chan, M.H.M.; Yuen, L.Y.; Lao, T.T.H.; Yang, X.; Ho, C.S.; Tutino, G.E.; et al. In Utero Exposure to Maternal Hyperglycemia Increases Childhood Cardio metabolic Risk in Offspring. *Diabetes Care* 2017, 40, 679–686. [CrossRef] [PubMed]
68. Suehara S, Waguri M, Wakabayashi K, Nakanishi I. Frequency and congenital anomaly of pregnant women with diabetes mellitus and gestational diabetes mellitus. *Diabetes and Pregnancy* 2010; 10: 104-108
69. Wendland EM, Torloni MR, Falavigna M, Trujillo J, Dode MA, Campos MA, Duncan BB & Schmidt MI. Gestational diabetes and pregnancy outcomes – a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. *BMC Pregnancy and Childbirth* 2012 12 1–13. (doi:10.1186/1471-2393-12-23)
70. Ornoy A. Prenatal origin of obesity and their complications: Gestational diabetes, maternal overweight and the paradoxical effects of fetal growth restriction and macrosomia. *ReprodToxicol* 2011; 32: 205-212 [PMID: 21620955 DOI: 10.1016/j.reprotox.2011.05.002]
71. ACOG. Fetal macrosomia. 2000. ACOG practice bulletin no. 22. Available from: http://www.acog.org/Resources_And_Publications. William H. Barth, Jr. provided assistance. Reaffirmed 2013.
72. Kelstrup L, Damm P, Mathiesen ER, Hansen T, Vaag AA, Pedersen O, Clausen TD. Insulin resistance and impaired pancreatic β-cell function in adult offspring of women with diabetes in pregnancy. *J Clin Endocrinol Metab* 2013; 98: 3793-3801 [PMID: 23796568 DOI: 10.1210/jc.2013-1536]
73. Crume TL, Ogden L, Daniels S, Hamman RF, Norris JM, Dabelea D. The impact of in utero exposure to diabetes on childhood body mass index growth trajectories: the EPOCH study. *J Pediatr* 2011; 158: 941-946 [PMID: 21238981 DOI: 10.1016/j.jpeds.2010.12.007]
74. Crume TL, Ogden L, West NA, et al: Association of exposure to diabetes in utero with adiposity and fat distribution in a multiethnic population of youth: the Exploring Perinatal Outcomes among Children (EPOCH) study. *Diabetologia* 2011;54:87–92.
75. Crume TL, Ogden L, Daniels S, Hamman RF, Norris JM, Dabelea D: The impact of in utero exposure to diabetes on childhood body mass index growth trajectories: the EPOCH study. *J Pediatr* 2011;158:941–946.
76. Ashwal E, Hod M. Gestational diabetes mellitus: where are we now?. *Clinicachimica acta*. 2015 Dec 7;451:14-20.