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Master's Thesis Socrates A-R Megoulas

'Exercise during the first trimester of pregnancy and prevention of gestational diabetes - review '

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Athens, 01/2022

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my advisor Prof. Makarios Eleftheriades for his inspiration , support, motivation and immense knowledge.
Besides my advisor I would like to thank Prof.Stavroula Paschou, Prof.Irene Lambrinoudaki, Prof. Konstantinos Panoulis and Prof. Giorgos Valsamakis for their encouragement and kindness.
I thank Misses Argyro Vasileiou for her disponibility and support during the course evolution.
A special gratitude to my colleague Misses Amalia Savvidi for her dedication during the research process.
My Parents, my Family and I intend my wife and three children for their patience and understanding love .

DEDICATION

I dedicate this thesis to all pregnant women for their courage

and

to my grandfather Dr.Rene Boisseau.

ABSTRACT

Gestational diabetes mellitus or GDM is one of the most common complications during pregnancy and it is associated with severe outcomes for both the mother and the newborn. Its prevalence varies globally ranging from 9% in Africa, 12.6% in North America and 21% in Asia. Despite those high numbers, there is still debate around the diagnosis and treatment of GDM and still not enough data concerning its prevention. The first line prevention methods used currently are exercise combined with dietary alterations. However, whether exercise is effective for the prevention of GDM is not clear because the few randomized controlled trials (RCTs) investigating this issue show conflicting results. In this review we will analyze only the exercise during the first trimester as a method of prevention of GDM in both women with high risk of GDM and women with low risk of GDM. In order to do that we combined data already published in Randomized Control Articles during the last 10 years. After a filter method we ended up with 6 RCTs and collected information that led us to the conclusion that exercise in the first trimester can work as a prevention method for GDM. There are still many variables you have to manage in order to determine a specific percentage in which exercise in the first trimester reduces GDM, therefore more controlled and supervised research must be done in the future.

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INTRODUCTION

Gestational diabetes mellitus or GDM is one of the most common complications during pregnancy and it is associated with severe outcomes for both the mother and the newborn. Pregnancy is characterized by physiological, endocrine, and metabolic adaptations that create a pseudodiabetogenic state of progressive insulin resistance and declining insulin sensitivity. These maternal adaptations occur to sustain the continuous fetal requirements for nutrients and oxygen. As maternal blood glucose is the major energy supply for fetal growth and development, maternal supply versus fetal demand is met by insulin resistance at the level of the maternal skeletal muscle, which increases the availability of maternal blood glucose for fetal usage[1]. As insulin resistance progressively increases during pregnancy, the responsiveness of maternal b cells illustrates the plasticity necessary to maintain normal glucose regulation. Glucose intolerance may result from the inability of the pancreatic b cells to respond, a fact leading to hyperglycemia in the mother. First onset of high blood glucose concentrations representing glucose intolerance of variable severity that occurs during pregnancy is defined as gestational diabetes mellitus (GDM).

HISTORICAL ASPECTS OF GESTATIONAL DIABETES

Recognition of diabetes complicating pregnancy dates back to 1873[2] [3]. In 1910, it was proposed that patients with gestational glycosuria be grouped into two categories, namely, pregnant women suffering from true and persistent glycosuria and pregnant women who pass sugar in their urine only when their diet contains a large amount of sugar or starch [4]. Subsequently, in a series of 468 pregnant women, 5 were documented with glycosuria with only

one who was known to have pre-pregnancy diabetes [5]. The author suggested that in cases where glycosuria occurred during pregnancy, true diabetes might be “about to manifest itself”. From these early cases, it was recognized that there is a difference between diabetes diagnosed prior to pregnancy and diabetes diagnosed during pregnancy. Due to recognition of the possibility of diabetes affecting a pregnancy, studies were conducted to understand the effect of pregnancy on carbohydrate metabolism. The adverse effect of pregnancy on carbohydrate metabolism was first documented in 1946 [6]. Hoet from Belgium performed animal experiments to study carbohydrate metabolism during pregnancy [7]. The harmful effects of GDM on pregnancy outcomes were subsequently reported. In 1946, while reporting on the effects of hyperglycemia during pregnancy, the author documented the finding that fetal death can occur even before the woman has symptoms of diabetes [8]. Subsequently, in 1959, the association of maternal pre-diabetes with fetal macrosomia was published in Italy [9]. Two years later, O’Sullivan described GDM as “unsuspected and asymptomatic” diabetes, which is elicited in response to a glucose tolerance test during pregnancy [10]. At that time, the incidence of GDM was reported to be 1 in 116 [10]. Due to the recognition of the complications associated with GDM, a need for accurate and timely diagnosis was realized [11,12]. In 1924, a 50-g glucose load was administered to a pregnant patient with history of glycosuria, to determine if she had glucose intolerance [13]. The oral glucose tolerance test (OGTT) was described in 1932. In search of an ideal glucose screen, an intravenous glucose tolerance test and a prednisone-glucose tolerance test were studied [14,15]. In 1961, O’Sullivan screened all pregnant patients with a 50-g oral glucose load and when the one-hour venous blood sugar was ≥130 mg/dL, the patient was considered screen-positive. At that time, patients were also classified as screen-positive if the patient had a family history of diabetes, a prior fetal or neonatal death, congenital fetal anomaly, prematurity, toxemia in two or more pregnancies, or a history of a prior baby that weighed 9 pounds or greater. Patients screened as positive were administered a three-hour GTT [10]. By 1985, glucose screening was routinely being used in patients considered to be at “high risk” for GDM [16]. Due to the varying definitions, the reported incidence of GDM ranged from 0.31% to 18%. This led to the suggestion of using similar screening criteria by all centers, to help better understand the condition and its impact on pregnancy.

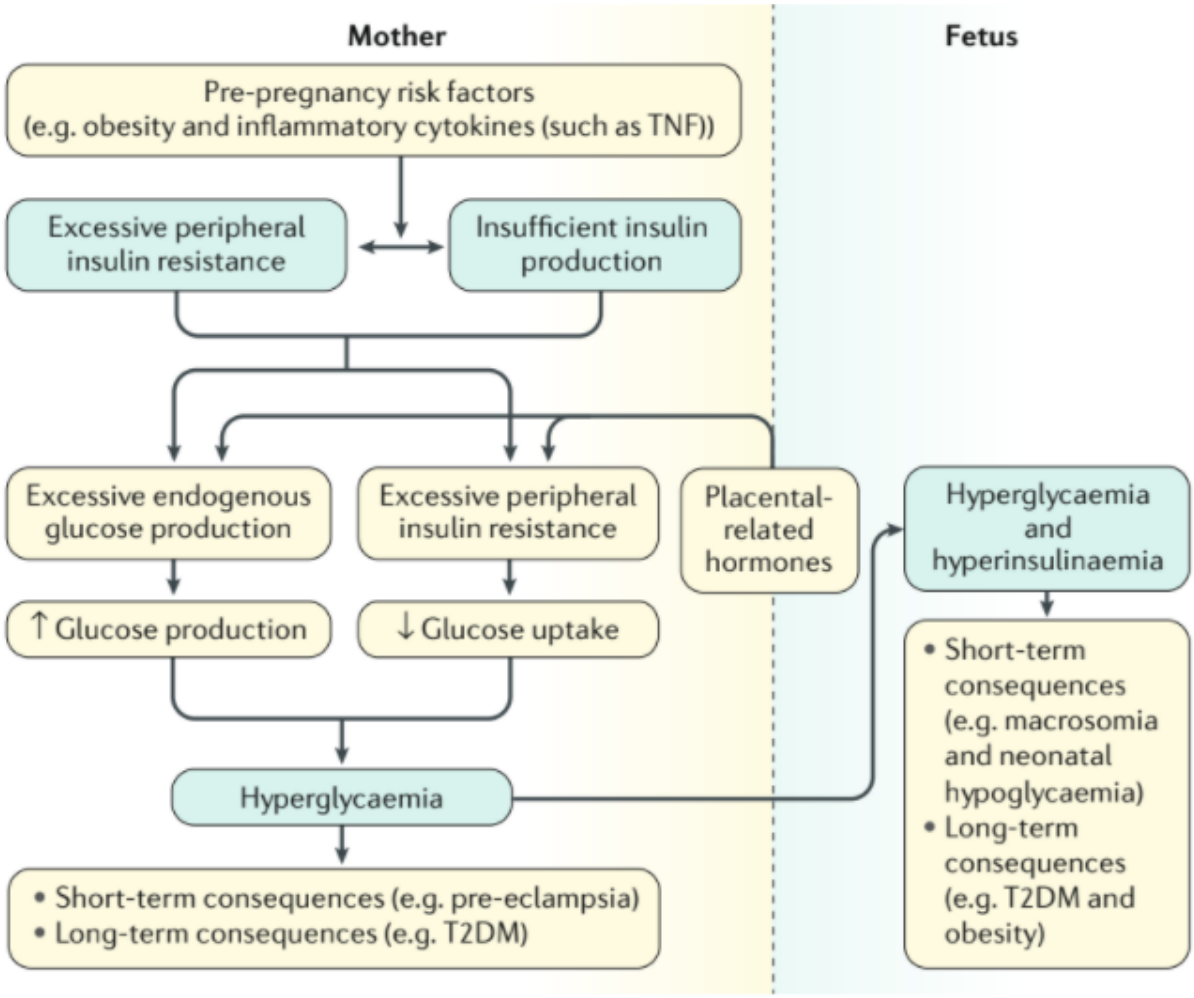
PREGNANCY AS A PSEUDODIABETOGENIC STATE

Glucose is needed to provide the energy for most cells within the body to function properly. Glucose can cross the cell membrane with the help of insulin, the key that unlocks the cell membrane and allows the passage of glucose from the bloodstream into the cell. Insulin is produced by beta cells of the pancreas and is released after food consumption, when there is an increase of glucose levels within the blood[17]. For this process to work, individuals need to be producing insulin or have a functioning pancreas sensitive to the insulin produced. During pregnancy, there is a normal physiologic variation to this process that results in a pseudodiabetogenic state of increasing insulin resistance and decreasing insulin sensitivity; this ensures adequate nutrients to the fetus [18]. This decrease in maternal sensitivity to insulin is triggered by human placental lactogen, which is increased in pregnancy. This diabetogenic hormone is at its greatest during the 24- to 28-week window, when GDM testing is recommended. The resulting maternal hyperglycemia triggers the pancreatic beta cells to release more insulin to counter the effects of the diabetogenic hormones and maintain maternal euglycemia. However, in some women, there may be pancreatic beta cell dysfunction or insufficiency due to the increased workload placed on the pancreas as it releases more insulin. This, in combination with increased insulin resistance, may lead to hyperglycemia and the development of GDM [19][20]

PATHOPHYSIOLOGY OF GDM

The remainder of this review will discuss molecular processes underlying the pathophysiology of GDM. GDM is usually the result of β-cell dysfunction on a background of chronic insulin resistance during pregnancy and thus both β-cell impairment and tissue insulin resistance represent critical components of the pathophysiology of GDM. In most cases, these impairments exist prior to pregnancy and can be progressive—representing an increased risk

of T2DM post-pregnancy [21]. A number of additional organs and systems contribute to, or are affected by, GDM. These include the brain, adipose tissue, liver, muscle, and placenta.



Pathophysiology of GDM. Women who develop gestational diabetes mellitus (GDM) during pregnancy have evidence of metabolic dysfunction before conception, such as pancreatic β-cell defects and increased insulin resistance. In high-income countries, many women who develop GDM are overweight or obese, which is associated with an inflammatory milieu. With the onset of pregnancy and associated metabolic changes (increased insulin resistance and demand for increased β-cell response becauseof placental factors), insulin is less effective in suppressing endogenous (primarily hepatic) glucose production and glucose uptake by peripheral skeletal muscle and adipose tissue, which results in clinical hyperglycaemia. Maternal hyperglycaemia results in increased placental transfer of glucose and (fetal) β-cell secretagogues, such as amino acids, to the fetus, leading to fetal hyperinsulinaemia. Fetal hyperinsulinaemia then results in fetal metabolic reprogramming that leads to short-term problems, such as fetal overgrowthand/or adiposity, and long-term problems, such as metabolic dysfunction in later life.T2DM, type 2 diabetes mellitus; TNF, tumour

necrosis factor.

β-Cell Dysfunction

The primary function of β-cells is to store and secrete insulin in response to glucose load. When β-cells lose the ability to adequately sense blood glucose concentration, or to release sufficient insulin in response, this is classified as β-cell dysfunction. β-cell dysfunction is thought to be the result of prolonged, excessive insulin production in response to chronic fuel excess [22]. However, the exact mechanisms underlying β-cell dysfunction can be varied and complex [23,24]. Defects can occur at any stage of the process: pro-insulin synthesis, post-translational modifications, granule storage, sensing of blood glucose concentrations, or the complex machinery underlying exocytosis of granules. Indeed, the majority of susceptibility genes that are associated with GDM are related to β-cell function, including potassium voltage-gated channel KQT-like 1 (*Kcnq1*) and glucokinase (*Gck*). Minor deficiencies in the β-cell machinery may only be exposed in times of metabolic stress, such as pregnancy [25].

β-cell dysfunction is exacerbated by insulin resistance. Reduced insulin-stimulated glucose uptake further contributes to hyperglycemia, overburdening the β-cells, which have to produce additional insulin in response. The direct contribution of glucose to β-cell failure is described as glucotoxicity [26]. Thus, once β-cell dysfunction begins, a vicious cycle of hyperglycemia, insulin resistance, and further β-cell dysfunction is set in motion.

Animal studies suggest that β-cell number is also an important determinant of glucose homeostasis. For example, Zucker fatty (ZF) rats that were subjected to 60% pancreatectomy mostly recover β-cell mass by one week post-surgery, but still develop hyperglycemia. In these cases, the short-term but dramatic reduction in β-cell mass overburdens the remaining β-cells, resulting in severely reduced glucose-stimulated insulin secretion and the depletion of internal insulin granule stores [27]. Sprague Dawley rats, which are usually very resistant to the development of diabetes, experience substantial loss of β-cell mass (50% reduction) by 15-weeks old when growth-restricted in utero via bilateral uterine artery ligation [28]. This loss of β-cell mass has been linked to epigenetic downregulation of pancreatic homeobox transcription factor (*Pdx1*), which is essential for normal β-cell differentiation in the embryo [29]. Prolactin is also essential for adequate β-cell proliferation, as demonstrated in mouse knockouts of the prolactin receptor ($PrlR^{-/-}$) [30]. In addition, glucotoxicity is also thought to result in β-cell apoptosis over time [26]. Pancreatic samples from T2DM patients can show a reduction of β-cell mass by 40–60% [31], but less than 24% loss after five years of disease has also been reported [32]. Reduced β-cell hyperplasia may also play a role in GDM, based on animal studies and limited post-mortem human studies [33]. Therefore, reduced β-cell mass, reduced β-cell number, β-cell dysfunction, or a mix of all three contribute to GDM, depending on the individual.

Chronic Insulin Resistance

Insulin resistance occurs when cells no longer adequately respond to insulin. At the molecular level, insulin resistance is usually a failure of insulin signaling, resulting in inadequate plasma membrane translocation of glucose transporter 4 (GLUT4)—the primary transporter that is responsible for bringing glucose into the cell to use as energy (Figure 1). The rate of insulin-stimulated glucose uptake is reduced by 54% in GDM when compared with normal pregnancy [34]. While insulin receptor abundance is usually unaffected, reduced tyrosine or increased serine/threonine phosphorylation of the insulin receptor dampens insulin signaling [35]. In addition, altered expression and/or phosphorylation of downstream regulators of insulin signaling, including insulin receptor substrate (IRS)-1, phosphatidylinositol 3-kinase (PI3K), and GLUT4, has been described in GDM [34]. Many of these molecular changes persist beyond pregnancy.

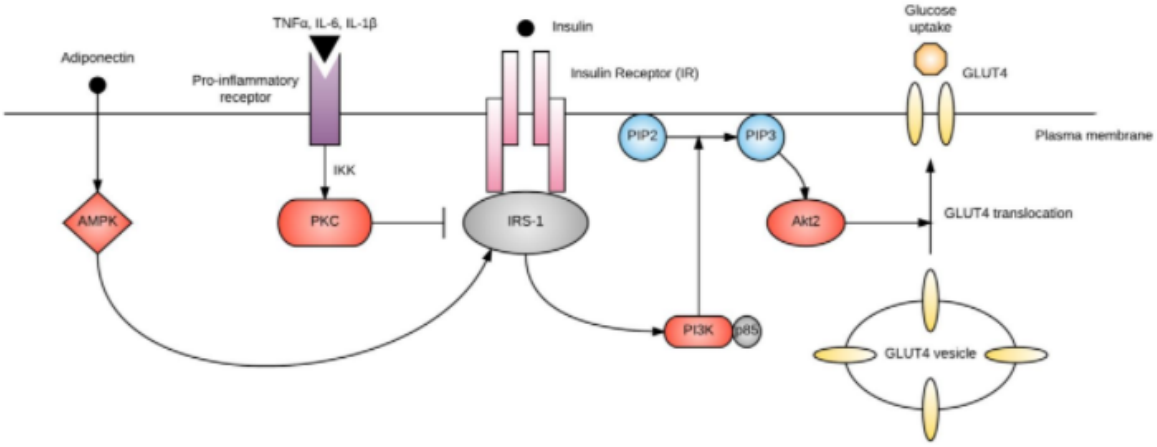


Figure 1. Simplified diagram of insulin signaling. Binding of insulin to the insulin receptor (IR) promotes IRS-1 activation through AMP-activated protein kinase (AMPK), while pro-inflammatory cytokines activate protein kinase C (PKC) via IκB kinase (IKK), which activates IRS-1. Adiponectin promotes IRS-1 activation through AMP-activated protein kinase inhibits IRS-1. IRS-1 activates phosphatidylinositol-3-kinase (PI3K), which phosphorylates phosphatidylinositol-4, 5-bisphosphate (PIP2) to phosphatidylinositol-3, 4, 5- phosphate (PIP3). PIP3 activates Akt2, which promotes GLUT4 translocation and glucose uptake into the cell. (AMPK), while pro-inflammatory cytokines activate protein kinase C (PKC) via IκB kinase (IKK), which inhibits IRS-1. IRS-1 activates phosphatidylinositol-3-kinase (PI3K), which phosphorylates phosphatidylinositol-4, 5-bisphosphate (PIP2) to phosphatidylinositol-3, 4, 5-phosphate (PIP3). PIP3 activates Akt2, which promotes GLUT4 translocation and glucose uptake into the cell.

Several of the previously discussed risk factors for GDM are thought to exert their effects by interfering with insulin signaling. For example, saturated fatty acids increase intracellular concentrations of diacylglycerol within myocytes, activating protein kinase C (PKC) and inhibiting tyrosine kinase, IRS-1 and PI3K [41]. Pro-inflammatory cytokines and adiponectin also modify this process, as discussed below. A diagram of the relationship between β-cell dysfunction, insulin resistance, and GDM is provided in Figure 2.

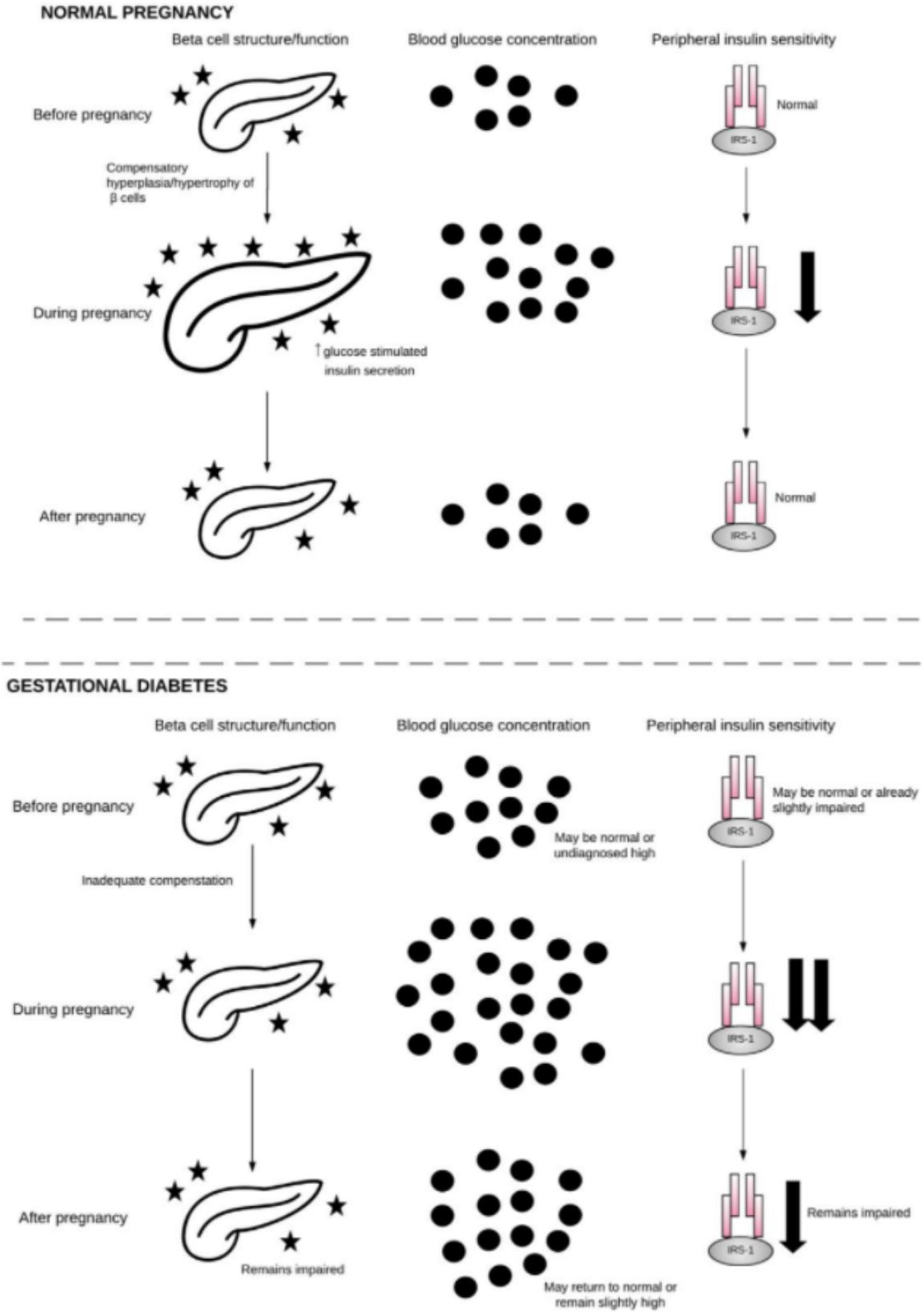


Figure 2. β-cell, blood glucose, and insulin sensitivity during normal pregnancy and GDM. normal

pregnancy, β-cells undergo hyperplasia and hypertrophy in order to meet the metabolic During normal pregnancy, β-cells undergo hyperplasia and hypertrophy in order to meet the metabolic demands of pregnancy. Blood glucose rises as insulin sensitivity falls. Following pregnancy, β-cells, demands of pregnancy. Blood glucose rises as insulin sensitivity falls. Following pregnancy, β-cells, blood glucose, and insulin sensitivity return to normal. During gestational diabetes, β-cells fail to blood glucose, and insulin sensitivity return to normal. During gestational diabetes, β-cells fail to compensate for the demands of pregnancy, and, when combined with reduced insulin sensitivity, this compensate for the demands of pregnancy, and, when combined with reduced insulin sensitivity, this results in hyperglycemia. Following pregnancy, β-cells, blood glucose, and insulin sensitivity results in hyperglycemia. Following pregnancy, β-cells, blood glucose, and insulin sensitivity may may return to normal or may remain impaired on a pathway toward GDM in future pregnancy or return to normal or may remain impaired on a pathway toward GDM in future pregnancy or T2DM. T2DM. Pancreas image obtained from The Noun Project under the terms and conditions of the Creative Pancreas image obtained from The Noun Project under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/), by artist Arif Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/), by artist Arif Fajar Vulianto. Fajar Vulianto.

Neurohormonal Networks

Neurohormonal dysfunction has been implicated in the pathogenesis of diseases of insulin resistance, such as that present in GDM. This network regulates appetite, active energy expenditure, and basal metabolic rate, and it is made up of a complex network of central (e.g., cortical centers that control cognitive, visual, and “reward” cues) and peripheral (e.g., satiety and hunger hormones) signals [37,38]. These contribute to GDM by influencing adiposity and glucose utilization. This network is highly regulated by the circadian clock, which may explain why pathological sleep disorders or those individuals undertaking shift work are correlated with GDM rates [39,40]. Neural networks controlling body weight are most likely set in early life, as demonstrated in animal studies. For example, rats that are both under- and over-fed in early life experience epigenetic alteration of the regulatory set-point of hypothalamic neurons [41,42]. This adds to the previously mentioned suggestion that predisposition to GDM may be set in the womb.

Some of the most important regulators of neurohormonal metabolic control are adipokines—cell signaling proteins that are secreted primarily by adipose tissue. These include leptin and adiponectin:

Leptin

Leptin is a satiety hormone secreted primarily by adipocytes in response to adequate fuel stores. It primarily acts on neurons within the arcuate nucleus of the hypothalamus to

decrease appetite and increase energy expenditure. Specifically, leptin inhibits appetite-stimulators neuropeptide Y (NPY) and agouti-related peptide (AgRP), and it activates the anorexigenic polypeptide pro-opiomelanocortin (POMC) [43]. When leptin was first discovered, it was lauded as a potential treatment for obesity [44]. However, it was soon revealed that the majority of obese individuals do not respond to leptin, and instead demonstrate leptin resistance. While leptin treatment is effective in obesity that is caused by leptin and leptin receptor genetic polymorphisms, these are rare (<5% of obese individuals) [45]. Therefore, obesity is associated with excessive plasma leptin concentration (hyperleptinemia) as a result of leptin resistance, and plasma leptin concentrations are generally proportional to the degree of adiposity [46]. Leptin resistance can occur either as a defect in blood-brain barrier leptin transport, or through intracellular mechanisms that are similar to insulin resistance [47]. Like insulin resistance, a degree of leptin resistance occurs in normal pregnancy, presumably to bolster fat stores beyond what would usually be required in the non-pregnant state. Leptin resistance is further increased in GDM, resulting in hyperleptinemia [48]. However, pre-pregnancy BMI is a stronger predictor of circulating leptin than GDM *per se* [49].

The placenta also secretes leptin during human pregnancy. In fact, the placenta is responsible for the majority of plasma leptin during pregnancy [50]. Placental leptin production is increased in GDM, probably as a result of placental insulin resistance, and this further contributes to hyperleptinemia. This is also thought to facilitate amino acid transport across the placenta, contributing to fetal macrosomia [51].

Adiponectin

Similar to leptin, adiponectin is a hormone that is primarily secreted by adipocytes. However, plasma adiponectin concentrations are inversely proportional to adipose tissue mass, with low concentrations in obese individuals. GDM is similarly associated with decreased adiponectin [52]. In contrast to leptin, there is a stronger association of adiponectin with insulin resistance than with adiposity [53]. This suggests that adiponectin plays an important role in the pathogenesis of GDM, independent of obesity. Adiponectin enhances insulin signaling and fatty acid oxidation, and it inhibits gluconeogenesis [54]. It does so by activating AMP-activated protein kinase (AMPK) within insulin-sensitive cells, which facilitates the action of IRS-1 (Figure 1), and by activating the transcription factor peroxisome proliferator-activated receptor alpha (PPARα) in the liver. Furthermore, adiponectin stimulates insulin secretion, by upregulating insulin gene expression and exocytosis of insulin granules from β-cells [55].

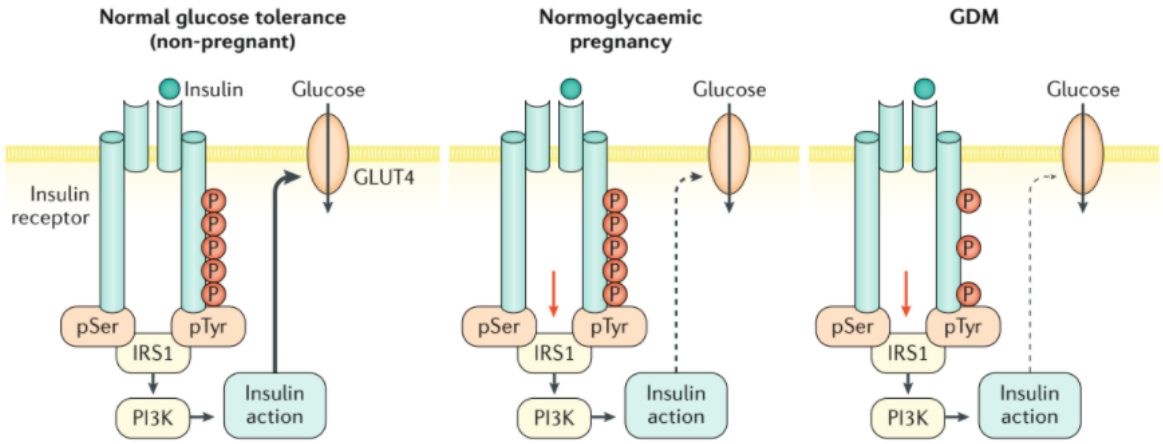
Adiponectin is also expressed at low concentration from the syncytiotrophoblast of the placenta where it is regulated by cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, interferon gamma (IFN-γ), and leptin [56]. The role of placental adiponectin in normal and GDM pregnancy is unclear [57]. However, emerging evidence suggests adiponectin impairs insulin signaling and amino acid transport across the placenta, limiting fetal growth. Therefore, adiponectin gene methylation in the placenta is associated with maternal glucose intolerance and fetal macrosomia [58].

Adipose Tissue

Originally believed to exist only as a passive depot of energy, the discovery of leptin in 1994 established adipose tissue as an essential endocrine organ. Adipose tissue both ensures that energy is partitioned safely and it actively secretes circulatory factors, including adipokines (the aforementioned leptin and adiponectin) and cytokines (such as TNF-α, IL-6, and IL-1β), which have wide-ranging metabolic effects.

Energy Storage

The storage capability of adipose tissue is essential for metabolic health. This is exemplified through two extremes: rare disorders in which white adipose tissue is absent lead to severe metabolic syndrome, whereas some obese individuals (with excessive white adipose tissue) do not develop metabolic syndrome at all [59]. Therefore, the ability to partition excess calories into adipose tissue rather than ectopically in the liver, muscle, or pancreas, appears to serve as a protective measure. Non-diabetic obese individuals exhibit adequate adipose tissue expansion in response to fuel surfeit, and therefore maintain healthy blood glucose concentrations, sufficient β-cell compensation, and avoid chronic insulin resistance [60,61]. In this way, key organs avoid glucose and fatty acid-induced tissue damage. As previously mentioned, early pregnancy is marked by an increase in adipose tissue mass, while later pregnancy promotes the mobilization of fats from adipose tissue in order to fuel fetal growth. Both of these processes are thought to be limited in GDM [62]. GDM is associated with reduced adipocyte differentiation and increased adipocyte size (hypertrophy), accompanied by downregulated gene expression of insulin signaling regulators, fatty acid transporters, and key adipogenic transcription factors, such as PPARγ [63]. The combination of insulin resistance and reduced adipocyte differentiation hinders the tissue's ability to safely dispose of excess energy, contributing to gluco- and lipo-toxicity in other peripheral organs. Indeed, both T2DM and GDM are associated with lipid deposition in muscle and liver [64,65].



Changes in insulin signalling in normoglycaemic and GDM pregnancies. Schematic representation of pregnancy-related changes in insulin signalling. Insulin signalling during pregnancy in women with normal glucose tolerance requires tyrosine autophosphorylation of the insulin receptor in skeletal muscle. This is the initial step in the insulin signalling cascade, allowing recruitment and activation of downstream effectors, such as insulin receptor substrate 1 (IRS1) and phosphatidylinositol 3-kinase (PI3K), resulting in translocation of glucose transporter type 4 (GLUT4) to the plasma membrane and thereby leading to increased glucose uptake into skeletal muscle55. In late pregnancy, skeletal muscle IRS1 content is lower (red arrow) than in non-pregnant women. In gestational diabetes mellitus (GDM) pregnancies, in addition to the decrease in IRS1, tyrosine autophosphorylation in the intracellular domain of the insulin receptor β-subunit is reduced, which results in 25% lower in vitro glucose uptake than in pregnant women with normal glucose tolerance

Adipose Tissue Inflammation

Obesity, T2DM and GDM are associated with an increased number of resident adipose tissue macrophages (ATM) that secrete pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β. The importance of a low-grade inflammatory state in the pathogenesis of insulin resistance has recently become apparent. Pro-inflammatory cytokines have been discovered to both impair insulin signaling and inhibit insulin release from β-cells. These factors induce insulin resistance either by diminishing insulin receptor (IR) tyrosine kinase activity, increasing serine phosphorylation of IRS-1, or through the STAT3-SOCS3 pathway, which degrades IRS-1 [35,66]. Circulating concentrations of pro-inflammatory cytokines are increased in GDM [57,67]. Plasma TNF-α, in particular, is strongly correlated with insulin resistance [68]. Similarly, placental gene expression of TNF-α, IL-1β and their receptors has been reported to be increased in GDM [68,69]. However, the relationship between pregnancy and inflammation is complex. For example, Lappas et al. (2010) reported that GDM placentae secrete *fewer* pro-inflammatory cytokines (3 of 16 studied: IL-1β, TNF-α and M1P1B) than healthy placentae (13 out of 16 studied) [70]. This suggests that, while chronic low-grade inflammation appears to be important in the pathogenesis of GDM, the relationship may not be straightforward.

Liver

GDM is associated with upregulated hepatic glucose production (gluconeogenesis). Gluconeogenesis is increased in the fasted state, and not adequately suppressed in the fed state [54]. This is not believed to be entirely the result of inaccurate glucose sensing due to insulin resistance, as the majority of glucose uptake by the liver (~70%) is not insulin dependent. Common factors between the insulin signaling pathway and the pathways controlling gluconeogenesis, such as PI3K, might contribute to these effects [71]. Increased protein intake and muscle breakdown may also stimulate the process by providing excess gluconeogenesis substrate [72]. Despite this, the liver does not seem to be a primary pathogenic driver of T2DM or GDM [73].

Skeletal and Cardiac Muscle

Traditionally, skeletal muscle insulin resistance was believed to play a causal role in T2DM. However, skeletal muscle insulin resistance now appears to be a consequence of hyperglycemia—a protective measure to prevent metabolic stress and steatosis [74]. Even following a short period of overfeeding, cardiac and skeletal muscle develop insulin resistance in order to divert the excess energy into adipose tissue [75]. This is an important distinction when considering potential treatments for GDM: attempts to directly reverse skeletal muscle insulin resistance, without reducing plasma glucose concentrations, could be detrimental [73].

Separate to insulin sensitivity, T2DM and GDM are associated with a reduced number and function of mitochondria within skeletal muscle cells [76]. This could be the result of genetics, early-life programming, or chronic inactivity. Therefore, decreased number and function of mitochondria is likely an additional contributor to reduced glucose utilization in GDM.

Gut Microbiome

There is emerging evidence that microbial organisms within the gut—the “gut microbiome”— might contribute to metabolic diseases, including GDM. The gut microbiome can be influenced by early-life events, such as preterm delivery and breastfeeding, and by events in later life, such as diet composition and antibiotic use. The gut microbiome has been consistently reported to differ between metabolically healthy and obese individuals, including during pregnancy [77]. Furthermore, a study of stool bacteria in women with a past case of GDM reported a lower proportion of the phylum *Firmicutes* and higher proportion of the family *Prevotellaceae* as compared with normoglycemic pregnancy [78]. Similar associations have been observed in obesity [79], T2DM [80], fatty liver disease [81], and elevated total plasma cholesterol [82]. *Firmicutes* metabolize dietary plant polysaccharides. This may explain some of the dietary risk factors for GDM that are discussed earlier. Both red meat and animal protein decrease levels of *Firmicutes*, while

high dietary fiber increases them [83]. However, the findings by Fugmann et al. (2015) remained after adjustment for dietary habits [78]. Therefore, *Firmicutes* appear to be relevant to pathogenesis of GDM independent of diet, although the mechanisms underlying this are unknown. *Prevotellaceae* are mucin-degrading bacteria that may contribute to increased gut permeability. Gut permeability is regulated by tight junction proteins, such as zonulin (ZO-1). Increased "free" plasma/serum ZO-1 is associated with type 1 diabetes (T1DM), T2DM [84], and GDM [85]. Increased gut permeability is thought to facilitate the movement of inflammatory mediators from the gut into the circulation, promoting systemic insulin resistance [84,86].

Oxidative Stress

Oxidative stress describes an imbalance between pro-oxidants and antioxidants in cells. Oxidative stress can lead to cellular damage by interfering with the state of proteins, lipids and DNA, and has been implicated in the pathogenesis of many diseases, including GDM [87]. Reactive oxygen species (ROS) are described as free radical and nonradical derivatives of oxygen, and include superoxide anion (O_2^-), hydroxyl radical (•OH) and hydrogen peroxide (H_2O_2) [88]. A hyperglycemic environment is associated with oxidative stress, and GDM women have been reported to overproduce free radicals and have impaired free-radical scavenging mechanisms [89]. ROS inhibit insulin-stimulated glucose uptake by interfering with both IRS-1 and GLUT4 [90]. ROS also slow glycogen synthesis in the liver and muscle. Pro-inflammatory cytokines, such as TNF-α, may also contribute to oxidative stress by increasing the expression and the activation of ROS precursors, like NADPH oxidase 4 (NOX4) [91].

Interestingly, iron supplementation in women already replete in iron is associated with GDM [92]. Several studies suggest that this relationship is the result of increased oxidative stress. Iron is a transitional metal and it can catalyze the reaction from O_{2-} and H_2O_2 to the extremely reactive •OH within mitochondria [93]. On the contrary, selenium and zinc are transitional metals that are necessary for the activity of some antioxidant enzymes, which may explain their inverse association with GDM [94].

Homocysteine—a non-protein α-amino acid that is formed by the demethylation of methionine—is also thought to contribute to GDM via oxidative stress. Exposure of β-cells to even small amounts of homocysteine results in dysfunction and impaired insulin secretion [95]. A recent meta-analysis examined the relationship between serum homocysteine concentration and GDM in ten eligible studies. The authors reported significantly higher homocysteine concentrations among women with GDM as compared with those without GDM [96]. B vitamins, including folic acid, B2, B6, and B12 are essential for homocysteine homeostasis, and this may be one reason why deficiencies and imbalances of these micronutrients are associated with GDM [97].

Placental Transport

The placenta contributes to insulin resistance during pregnancy via its secretion of hormones and cytokines. As the barrier between the maternal and fetal environments, the placenta itself is also exposed to hyperglycemia and its consequences during GDM. This can impact transport of glucose, amino acids, and lipids across the placenta:

Glucose—Glucose is the primary energy source for the fetus and the placenta, and therefore must be readily available at all times. For this reason, insulin is not required for the placental transport of glucose. Instead, glucose transport occurs via GLUT1, by carrier-mediated sodium-independent diffusion [98]. However, the placenta still expresses the insulin receptor, and insulin signaling can influence placental metabolism of glucose [99]. The receptiveness of the placenta to glucose uptake means that it is particularly sensitive to maternal hyperglycemia, and this directly contributes to increased fetal growth and macrosomia.

Protein—Amino acid transport across the placenta is also an important determinant of fetal growth. GDM is associated with increased System A and L activity [100]. These can also be modulated by pro-inflammatory cytokines, such as TNF-α and IL-6 [101]. Altered amino acid transport may also be one mechanism by which excess protein intake contributes to GDM.

Lipids—Finally, while GDM has traditionally been described as a disease of hyperglycemia, the rise in obesity-associated GDM has prompted a greater focus on the role of hyperlipidemia in GDM. The majority of placental gene expression alterations in GDM occur in lipid pathways (67%), as compared with glucose pathways (9%) [102]. Preferential activation of placental lipid genes is also associated with GDM compared with T1DM [102]. These data correlate with the results of the HAPO Study, which revealed independent effects of maternal obesity and glucose on excessive fetal growth [103]. Therefore, it appears that GDM influences the placental transport of glucose, amino acids, and fatty acids, and that all three must be considered when discussing the impact of GDM on placental function and fetal growth.

In addition to these alterations in placental transport, GDM has been associated with other changes in the placenta. Some recent studies have reported that GDM is associated with placenta global DNA hypermethylation [104]. Similarly, studies of the placental proteome have identified differences in the expression of proteins between GDM and non-GDM placentas [105]. However, more research is required before the role of placental epigenetic and proteomic modifications in GDM is fully understood [106]. There has also been recent interest in small noncoding single-stranded segments of RNA, called microRNAs (miRNAs), expressed in placental trophoblast cells. miRNAs are involved in a number of cellular processes, including proliferation, differentiation, and apoptosis. Emerging evidence suggests that exosomes containing miRNAs are shed from the placenta during gestation and released into the maternal circulation, which can in turn influence the functioning of other cells, potentially contributing to the pathogenesis of GDM [107,108]. Interestingly, exposure to endocrine disrupting chemicals (EDCs), including bisphenol A (BPA—found in food packaging materials and consumer products) has been associated with GDM, and it has been suggested that this could be because EDCs induce exosome signaling from the placenta [109]. Interestingly, EDCs including BPA

have also been associated with alterations in methylation, perhaps linking the two mechanisms [110]. A summary diagram of the pathophysiology of GDM is presented in Figure 3.

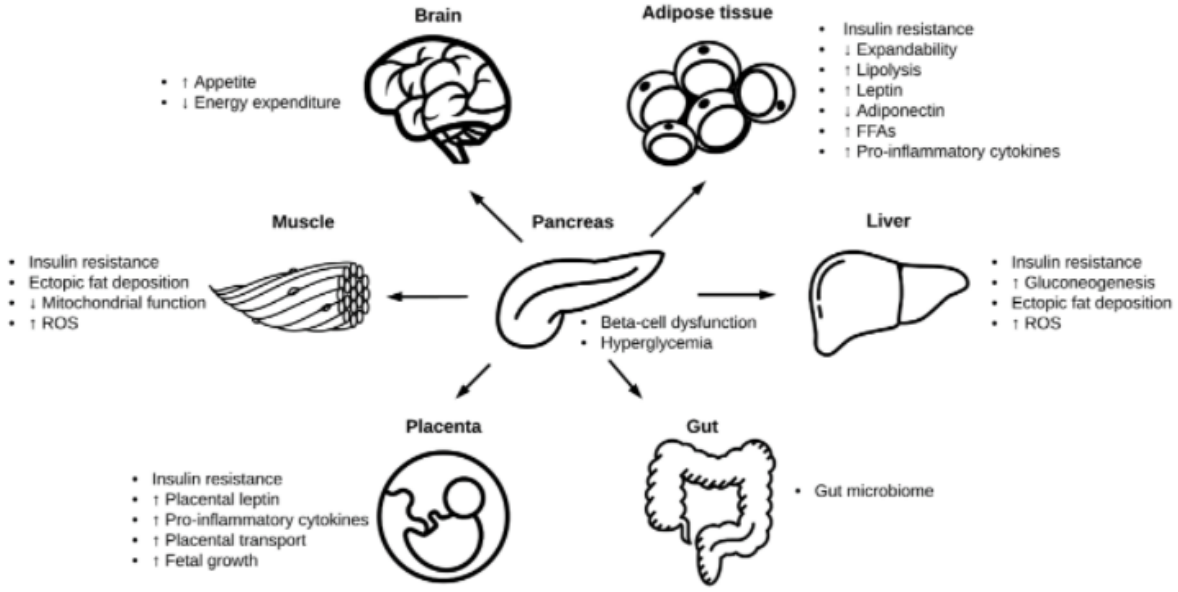


Figure 3. Organs involved in the pathophysiology of GDM (Images in this figure were obtained from Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/). Brain and Gut by Hunotika; Liver by Lavmik; Pancreas by Arif Fajar Vulianto; The Noun Project under the terms and conditions of the Creative Commons Attribution (CC BY)
Placenta by Charmeleon Design; Muscle by Misha Petrishchev).

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PREVALENCE

GDM's prevalence varies globally ranging from 9% in Africa, 12.6% in North America and 21% in Asia in 2017[111]. Despite those high numbers, there is still debate around the diagnosis and treatment of GDM and still not enough data concerning its prevention.

Among the eligible 77 studies meeting the search criteria, data from a total of 36 countries were included to derive country specific estimates for GDM prevalence. Some countries such as USA (n = 11), Canada (n = 4), Australia (n = 4), China (n = 4), and India (n = 3) have multiple

published prevalence studies based on various study populations and diagnostic criteria, whereas others (mostly developing countries in Africa and South/Central America) have few published estimates. If more than one estimate of GDM prevalence was available for one country, the country-specific prevalence of GDM was estimated by using the median of all available source data. Likewise, the region-specific prevalence of GDM was estimated by calculating the median prevalence of country specific estimates within each World Health Organization (WHO) region. Overall, Middle East and North Africa had the highest prevalence of GDM with a median estimate of 12.9 % (range 8.4–24.5 %), followed by Southeast Asia, Western Pacific, South and Central America, Africa, and North America and Caribbean (median prevalence 11.7, 11.7, 11.2, 8.9, and 7.0 %, respectively), whereas Europe had the lowest prevalence (median 5.8 %; range 1.8–22.3 %) (Fig. 4). Considering the fact that prevalence estimates are subject to the diagnosis criteria applied, we specified diagnosis criteria when describing country-specific estimates of GDM prevalence (Fig. 5). Considerable variations were observed both within and between countries. Within each country, the proportion of which the prevalence estimates were attributable to each major diagnostic criterion was indicated by different colors. Within the Western Pacific region, the prevalence estimates had a wide range from 4.5 % in Japan to 25.1 % in Singapore, to which different GDM diagnosis criteria were applied. The former was based on both the Japan Society of Gynecology and Obstetrics 1984 criteria [112] and the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [113], whereas the latter was solely based on the IADPSG criteria. Similarly, countries in Europe also had large variations in estimates of GDM prevalence, with Norway leading the prevalence (median 22.3 %; range 13.0–31.5 % using the WHO 1999 [114] and modified IADPSG criteria, respectively) and Ireland having the lowest prevalence of 1.8 % (using the National Institute for Health and Care Excellence criteria [115]). In contrast, countries in the North America and Carib bean region (i.e., Barbados, USA, Trinidad and Tobago, and Canada) had relatively the least variability in estimates of GDM prevalence, ranging from 6.5 % in Canada (mostly diagnosed by the Canadian Diabetes Association criteria [116]) to 11.9 % in Barbados (by the IADPSG criteria). In the Middle East and North Africa region which had on average the highest prevalence of GDM, the prevalence estimates ranged from 8.4 % in Iran to 24.5 % in United Arab Emirates, where as Qatar, Bahrain, and Israel had intermediate estimates (i.e., 16.3, 12.9, and 8.8 %, respectively). In Southeast Asia, Ma laysia had the highest prevalence of 18.3 %, followed by India (13.6 %), Bangladesh (9.7 %), and Sri Lanka (8.1 %). In South and Central America, data on GDM prevalence were only available in two countries (16.6 and 5.7 % in Cuba and Brazil, respectively). Likewise, only two countries in Africa had qual ified

and available data on prevalence of GDM (i.e., 8.2 % in Nigeria and 9.5 % in Tanzania), which used both the WHO and IADPSG criteria, respectively. Of particular note, caution is needed in interpreting the country- and region-specific estimates of GDM prevalence, due to several methodological issues as discussed below. IADPSG criteria emerged just recently. As such, recent studies by the NDDG National Diabetes Data Group, WHO World Health Organization, included International Classification of Diseases codes and local guidelines or criteria are more likely to apply the IADPSG criteria while estimating or reevaluating the prevalence of GDM. Thus, the synthesized prevalence estimates based on studies published during the past decade might reflect more about the prevalence defined by the new criteria than the previous ones, especially among countries which did not report their prevalence estimates until recently. In addition, when the prevalence by WHO regions was synthesized, no adjustment was made based on sample sizes and sampling methods. [117]

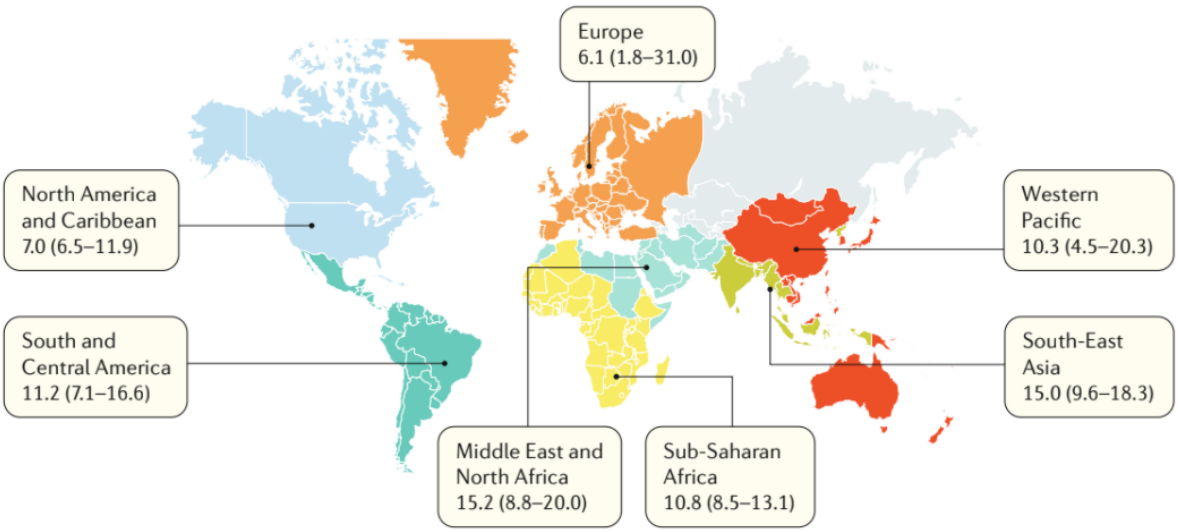

Figure 4. Median (interquartile range) prevalence (%) of GDM by WHO region, 2005–2018. (Map generated from WHO website at http://www.who.int/ about/regions/en/ [9])

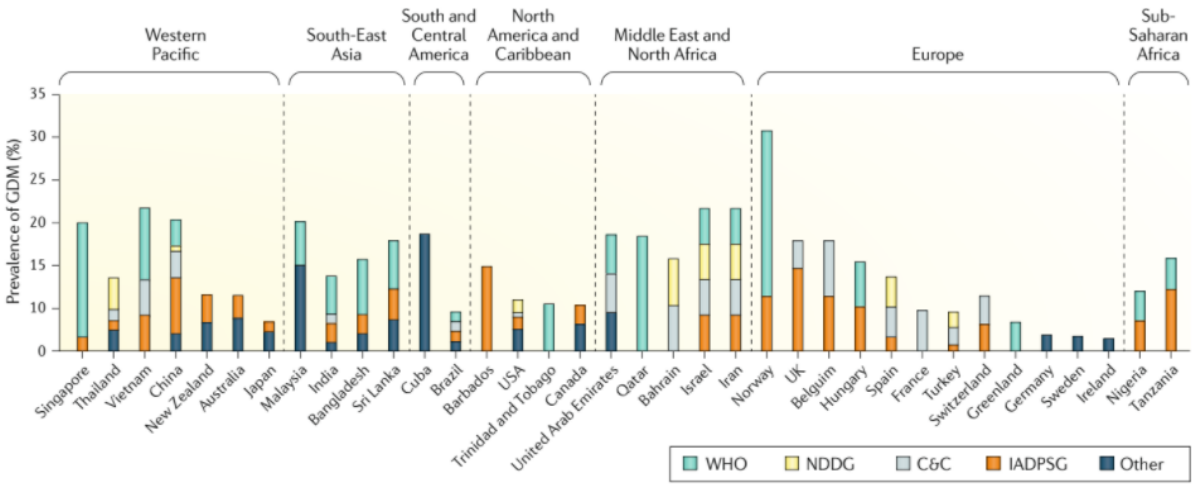

Figure 5. Country-specific prevalence of GDM according to different diagnostic criteria. Graph of prevalence of gestational diabetes mellitus (GDM) in selected countries according to the Carpenter–Coustan criteria (C&C), International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, National Diabetes Data Group (NDDG) criteria, WHO 2013 criteria and International Classification of Diseases codes and local guidelines or criteria (other). A literature search was conducted in PubMed, supplemented by cross-checking relevant references of eligible

studies on the prevalence of GDM from 1 January 2005 to 1 December 2018 to capture the contemporary burden of GDM.

Among the eligible studies that met the search criteria13, data from countries reported in the studies were included to derive country-specific estimates of GDM prevalence on the basis of different diagnostic criteria. The median of all available source data was used if more than one estimate of GDM prevalence was available for a country.

DIAGNOSIS

In 2010 the International Association of Diabetes and Pregnancy Groups (IADPSG) published the following new criteria for the diagnosis of GDM: at least one abnormal value (≥92, 180 and 153 mg/dl for fasting, one-hour and two-hour plasma glucose concentration respectively), after a 75 g oral glucose tolerance test (OGTT)[118]. Various organizations attempted to establish population-based protocols to diagnose GDM [119]. In 1999, the WHO recommended a screening test of a 75-g anhydrous glucose load, following an overnight fasting for 8–14 h, between 24 and 28 weeks' gestation. The protocols suggested by national and international

organizations such as the IADPSG, American Diabetes Association (ADA), and United Kingdom-based National Institute for Health and Care Excellence (NICE) and Canada were recently reviewed [120]. Both a single-step and a two-step screening process during pregnancy have been described. Based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, the IADPSG recommended a single-step 2-h glucose tolerance test. After an overnight fast, a 75-g glucose load is administered. The fasting 1-h and 2-h plasma glucose levels are checked. Despite the ADA endorsing the one-step 75-g glucose load GTT in 2011 based on the IADPSG criteria, the National Institute of Health in the USA recommended the two-step screening for GDM, which has been adopted by the American College of Obstetrics and Gynecology (ACOG) [121,122]. In the two-step approach, women first undergo a 1-h 50-g glucose screen, and if it is abnormal, a 3-h GTT with a 100-g glucose load is performed. If results are abnormal on the 3-h GTT, the patient is diagnosed with GDM. Based on the one-step IADPSG screening criteria, 17.8% of pregnant patients in the USA would test positive for GDM, which would nearly double the incidence of GDM in the USA [123]. The ACOG and other organizations in the USA have not adopted the one-step process due to a lack of evidence of impact on the pregnancy outcomes. The two-step testing at 24–28 weeks' gestation starts with an initial screen in a non-fasting state, with an oral 50-g glucose load followed by a 1-h plasma glucose level. The cutoff value for the 1-h glucose screen is 130 to 140 mg/dL. Screen-positive women undergo the 3-h oral GTT. Following an overnight fast, a 100-g oral glucose load is administered. Plasma glucose levels are checked in the fasting state and at 1 h, 2 h, and 3 h following the glucose load [121]. Details of the different screening protocols are documented in Table 1

Protocol-based guidelines for diagnosis of gestational diabetes on oral glucose tolerance test.

Guidelines	Gestational Age at Screening	Glucose Load	FBS	1 h	2 h	3 h
IADPSG 2010	24–28 weeks	75 g	<92 mg/dL	<180 mg/dL	<153 mg/dL	-
Canada Diabetes Association 2018	24–28 weeks	75 g	<95 mg/dL <5.3 mmol/L	<190 mg/dL <10.6 mmol/L	<162 mg/dL <9.0 mmol/L	-
NICE 2015	24–28 weeks	75 g	<101 mg/dL <5.6 mmol/L		<140 mg/dL <7.8 mmol/L	-
ACOG 2018	24–28 weeks	100 g	<95 mg/dL	<180 mg/dL	<155 mg/dL	<140 mg/dL

Table 1

Early glucose screening is normally completed at the first prenatal visit in women with risk factors that include obesity with a BMI of ≥30 Kg/m2, history of gestational diabetes in a prior pregnancy, known impaired glucose metabolism, hemoglobin A1C of ≥5.7%, first-degree relative with diabetes mellitus, high-risk ethnicity, history of polycystic ovarian syndrome, pre-existing hypertension or cardiovascular disease, or a prior large baby ≥4000 g [121]. The early screening helps detect patients with pre-pregnancy type II diabetes mellitus. Women who have a normal glucose screen in early pregnancy have the test repeated at 24–28 weeks' gestation. Plasma glucose levels are drawn in a fasting state, followed by a glucose load. The normal levels are as noted in the table. In the IADPSG, the Canada Diabetes Association, and the NICE guidelines, GDM is diagnosed when one or more plasma glucose levels are elevated above the normal levels. In the ACOG guidelines, patients with a positive 1-h glucose screen undergo the 3-h test and when two or more levels are elevated above the normal levels, GDM is diagnosed.

SCREENING

Organization	Recommended population
IADPSG	All women or high-risk women; decision based on local circumstances and the background frequency of abnormal glucose tolerance in local population
WHO	Screening should be determined by individual countries/health services based on prevalence of glucose intolerance in local population, resources, and competing priorities
ADA	Women with one or more risk factor for DM: • First-degree relative with DM • High-risk race/ethnicity • History of cardiovascular disease • Hypertension (140/90 mmHg or taking antihypertensive therapy) • High-density lipoprotein (HDL) <35 mg/dl (0.9 mmol/l); triglycerides >250 mg/dl (2.82 mmol/l) • Polycystic ovarian syndrome (PCOS) • Physical inactivity • Other clinical conditions associated with insulin resistance (e.g., acanthosis nigricans, severe obesity) Women with previous GDM should have screening for DM at least every 3 years
ACOG	Overweight or obese women (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) with one or more additional risk factor: • Physical inactivity • First-degree relative with DM • High-risk race or ethnicity • Previous macrosomic baby ≥4 kg • Previous GDM • Hypertension (140/90 mmHg or taking antihypertensive therapy) • HDL <35 mg/dl (0.9 mmol/l); triglycerides >250 mg/dl (2.82 mmol/l) • PCOS • HbA1c ≥5.7%, impaired glucose tolerance or impaired fasting glucose on previous testing • Other clinical conditions associated with insulin resistance (e.g., acanthosis nigricans, pre-pregnancy BMI >40 kg/m^2) • History of cardiovascular disease
SIGN, NICE	One or more risk factor for DM: • BMI >30 kg/m^2 • Previous macrosomic baby ≥4.5 kg • Previous GDM • First-degree relative with DM • Family origin with high prevalence of DM
Diabetes Canada	Women at high risk of undiagnosed T2DM

Table 2

Screening Early in Pregnancy

Early pregnancy screening, performed in the first trimester or at the initiation of antenatal care, is generally recommended to exclude pre-existing DM in women at high risk [122,123,128–130]. The populations in whom screening is recommended by national guideline bodies are summarized in Table 2. There is no consensus on the preferred early screening tool for pre-existing DM:

fasting plasma glucose, random plasma glucose, HbA1c, and 75-g 2-hour oral glucose tolerance test (OGTT) are each recommended as screening tools in one or more national Guidelines [122,123,130–132]. Results indicative of DM according to World Health Organization (WHO) diagnostic criteria outside pregnancy (i.e., fasting glucose 7 mmol/l, 2 hour 75-g OGTT, or random glucose 11.1 mmol/l or HbA1c 48 mmol/mol), should be considered to represent ‘diabetes in pregnancy’ and appropriate management initiated [129].

The ability to diagnose GDM in the first trimester as opposed to the second or third trimester of pregnancy remains controversial. The International Association of Diabetes in Pregnancy Study Groups (IADPSG) revoked their 2010 recommendation that fasting plasma glucose 5.1 mmol/l in early pregnancy should be considered diagnostic of GDM, following evidence that this was poorly predictive of OGTT outcomes in the third trimester [133]. For example, a retrospective cohort study in China, including data from 17 186 pregnant women, reported 37% of participants with fasting plasma glucose between 5.10 and 5.59 mmol/l at the first antenatal visit were subsequently diagnosed with GDM based on a 75-g OGTT between 24 and 28 weeks’ gestation [134]. Studies assessing the diagnostic utility of an OGTT between 12 and 15 weeks and 18 and 20 weeks’ gestation are ongoing [135,136].

Screening Later in Pregnancy

Screening for GDM later in pregnancy is performed between 24 and 28 weeks’ gestation using an OGTT. A ‘one-step’ 2-hour 75-g OGTT is endorsed by the IADPSG, WHO, and national guideline committees [122,123,128–130]. Alternative ‘two-step’ methods involving a glucose challenge test followed by an OGTT for those with a positive result are also recommended as an alternative [American Diabetes Association (ADA)] or preferable [American College of Obstetricians and Gynaecologists (ACOG), Diabetes Canada] screening method in the US and Canada . Whilst universal screening in the third trimester is advocated by several groups (IADPSG, ADA, ACOG, Diabetes Canada), guidelines in the UK suggest limiting screening to women with clinical risk factors for GDM [Scottish Intercollegiate Guidelines Network (SIGN), National Institute for Health and Care Excellence (NICE)] [122,123,128–130]. .

The diagnostic thresholds for GDM (Table 3) have evolved over recent decades and remain a source of active discussion. The IADPSG Consensus Panel issued updated diagnostic criteria in 2010 based on the results of the HAPO Study and these have been widely accepted by national and international organizations [128]. HAPO, an international cohort study involving a diverse group of more than 25 000 women, demonstrated a strong, continuous relationship between maternal glucose levels and primary outcomes, including increased birth weight [137]. This included glucose levels below those diagnostic of diabetes, which were not previously known to be harmful. Diagnostic thresholds for GDM were (somewhat arbitrarily) set at glucose values associated with estimated odds of 1.75 for birth weight, cord C-peptide, and percent infant body fat >90th percentiles, compared with the odds of these outcomes at mean glucose values for the entire study cohort [128]. The prevalence of GDM increased three- to fourfold at two European centers following the change from the two-step ADA (Carpenter-Coustan) screening approach to adopt the IADPSG criteria [138,139].

Guideline committee	Glucose load (g)	Fasting[a] mmol/l (mg/dl)	1-hour[a] mmol/l (mg/dl)	2-hour[a] mmol/l (mg/dl)	3-hour[a] mmol/l (mg/dl)	Refs
IADPSG/WHO/ADA/Diabetes Canada/SIGN[b]	75	≥5.1 (92)	≥10.0 (180)	≥8.5 (153)	–	[2,3,8,9,12]
NICE[b]	75	≥5.6 (101)	–	≥7.8 (140)	–	[10]
ADA (Carpenter-Coustan)[c]	100	≥5.3 (95)	≥10.0 (180)	≥8.6 (155)	≥7.8 (140)	[3]
ADA (NDDG)[c]	100	≥5.8 (105)	≥10.6 (190)	≥9.2 (165)	≥8.0 (145)	[3]
Diabetes Canada[d]	75	≥5.3 (95)	≥10.6 (190)	≥9.0 (162)	–	[12]

NDDG, National Diabetes Data Group.
[a]Plasma glucose levels: fasting, 1 hour, 2 hours, and 3 hours following oral glucose load.
[b]GDM diagnosed if one or more glucose value met or exceeded.
[c]Following an abnormal 50-g 1-hour glucose challenge test; GDM diagnosed if two or more plasma glucose levels met or exceeded.
[d]Following an abnormal 50 g 1-hour glucose challenge test; GDM diagnosed if one or more plasma glucose level met or exceeded.

Table 3

RISK FACTORS

The risk factors for GDM include obesity, family history of diabetes, high-risk ethnicity, increased maternal age, history of GDM, delivering a macrosomic infant, excessive gestational weight gain early in pregnancy (before glucose screening), sedentary behavior, low physical activity, and vitamin D deficiency.[140]Although, obesity is a risk factor, the majority of the GDM population comprises women of normal weights (based on pre-pregnant body mass index [BMI]) and this raises the need of physical activity as a prevention aid for all pregnancies.[141]Epidemiological

studies have identified a number of GDM risk factors (Box 1), such as advanced maternal age, ethnicity, previous history of gestational diabetes and family history of type 2 diabetes mellitus (T2DM). Although the traditional focus has been on risk factors detected during pregnancy, data support the important role of risk factors during the periconception and preconception periods in the development of GDM.[143,144]

Age

Advanced maternal age has been related to increased risk of GDM. In a large prospective study in the USA (>95% white ethnicity), women >40 years of age had a more than twofold increased risk of GDM compared with women <30 years of age (prevalence 9.8% versus 4.1%, respectively), even after adjustment for other major risk factors[145]. Women carrying a male fetus seem to have a higher risk of developing GDM[146], and some reports[147] suggest a higher risk of GDM in twin pregnancies, although this is not a universal finding[148].

Geography and ethnicity.

It should be noted that even when the same diagnostic criteria were applied, considerable variability in prevalence estimates of GDM was observed between different countries (Fig. 2), which indicates that variations in the distributions of inherent characteristics of study populations may contribute to the variability. Furthermore, in countries with multi-ethnic populations (such as Australia, the USA and Canada), notable differences in the prevalence of GDM between ethnicities have been observed. For example, in northern California, GDM prevalence was highest among women from the Philippines (10.9%) and Asians (10.2%) and lowest among non-Hispanic white (4.5%) and African American (4.4%) women[149]. In Australia[150], women of South Asian origin had more than fourfold higher risk of GDM than women of Australian or New Zealand origin, which is consistent with the higher prevalence of GDM among the general South-East Asian population. The reasons underlying the ethnic differences are likely to be multifactorial, including but not limited to the major risk factors for GDM (differences in body adiposity, lifestyle (diet and physical activity) and genetic susceptibility).

Modifiable lifestyle factors

Being overweight or obese before pregnancy (body mass index (BMI) ≥25kg m^{-2}) is the most significant GDM risk factor[151]. Cigarette smoking by pregnant women and whether their parents smoked are related to increased risk of GDM, independent of pre-pregnancy BMI and other risk factors[152]. Physical activity both during and before pregnancy reportedly reduces GDM risk[153,154]. In addition, a number of dietary factors affect GDM risk. To date, no concrete conclusions can be drawn about the role of specific dietary factors during pregnancy in the development of GDM[155]. However, there is suggestive evidence that low plasma levels of vitamin D[156] and vitamin C[157] in early pregnancy and increased dietary fat intake[158,159] during pregnancy increase the risk of developing GDM[160]. Large observational studies on pre-pregnancy diet identified various dietary factors that potentially increase GDM risk, independent of body adiposity and physical activity, including higher consumption of sugar sweetened beverages[161], potatoes[162], fried foods[163], haem iron[164] and animal fat[165] and protein[166]. Furthermore, a diet low in carbohydrates but high in animal fat and protein[167], as well as an overall 'western' dietary pattern (high intake of red meat, processed meat, refined grain products, sweets, french fries and pizza[168]) are associated with increased GDM risk. Potential healthful dietary factors include greater consumption of fiber[169,170] and nuts[171], a prudent dietary pattern characterized by a high intake of fruit, green leafy vegetables, poultry and fish[172], and a 'Mediterranean' diet[173]. Overall, findings from observational studies suggest that approximately 45% of GDM cases might be preventable by the adoption of a healthy diet before pregnancy, maintaining a BMI <25 kgm^{-2}, exercising for ≥30min minutes per day and avoiding cigarette smoking[174]. However, owing to the lack of data on these risk factors both before pregnancy and during pregnancy before the time of a GDM diagnosis, it is unclear whether these behaviors have a chronic effect on insulin sensitivity and pancreatic β-cell function or an acute effect due to continuing these behaviors during pregnancy. If the effects of these risk factors are chronic rather than acute, then prevention of GDM would require starting lifestyle interventions before pregnancy. Indeed, preventive efforts may need to be made at the population level to prevent childhood overweight and obesity, reduce excess adolescent weight gain and promote an optimal lifestyle pattern in both parents before pregnancy[175].

Emerging risk factors

In addition to diet and lifestyle factors, emerging data indicate a possible contribution of environmental and psychosocial factors to the risk of developing GDM. For example, higher exposure to persistent organic pollutants and endocrine disruptors, such as polybrominated diphenyl ethers[173] and perfluoro octanoic acid[174], has been associated with increased GDM risk. Furthermore, depression in the first and second trimester has been prospectively related to increased GDM risk.

COMPLICATIONS

Women with GDM are at higher risk of experiencing fetal demise, fetal malformation, preterm birth, macrosomia, polyhydramnios, infection, and cesarean section than the general population[175]. Furthermore, both women with GDM and their infants are more likely to become over weight or obese and develop type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD) and neuropsychological deficits later in life than the normal group. [176]There are many maternal and fetal complications that occur because of GDM and hyperglycemia. Women diagnosed with GDM are at a higher risk of cardiovascular disorders including gestational hypertension, preeclampsia, and eclampsia. Women with GDM who gain excessively not only have an additional risk of gestational hypertension disorders but also fetal overgrowth. There is an increased risk of cesarean delivery, postpartum hemorrhage, and vaginal laceration due to a larger baby. After pregnancy, b-cell dysfunction may persist after the GDM pregnancy and the combination of EGWG and retention of that excessive weight are strong contributors to long-term metabolic dysfunction. Without weight loss between subsequent pregnancies followed by excessive gain with each pregnancy, obesity may result. Obesity is associated with an increased risk of type 2 diabetes after a GDM pregnancy, likely due to a similar mechanism relating to metabolic dysregulation and decreased insulin sensitivity, in addition to an inadequate insulin response to glucose. After a GDM pregnancy women have increased dyslipidemia and blood pressure and are at increased risk for future cardiovascular disease. Furthermore, weight gain and obesity are indicators of the metabolic

syndrome and type 2 diabetes. It would appear that many of these risk factors are interrelated and have similar components of disease risk suggestive for future chronic disease in the mother, primarily the development of overt diabetes, the metabolic syndrome, and vascular dysfunction. Fetal overgrowth or macrosomia occurs in up to 45% of GDM pregnancies and these babies have a higher risk of childhood overweight and obesity and type 2 diabetes later in life. Large babies resulting from GDM pregnancies develop a unique pattern of overgrowth and fat distribution that affects central areas of the abdomen and the subscapular region. Overgrowth may lead to an increased risk of shoulder dystocia, clavicle fractures, and brachial plexus injuries and increases the risk for neonatal intensive care admission. Babies born to GDM mothers may have hypoglycemia at birth and these infants may require an intra venous supply of glucose to increase blood sugar values. Early insults to metabolism at birth may explain why these infants may be at risk for developing type 2 diabetes later in life. Furthermore, hypoglycemia at birth may lead to more serious complications to the developing central nervous system and cardio pulmonary disturbances with major long-term morbidities such as neurological damage, recurrent seizures, developmental delays, and personality disorders. Another long-term consequence of a GDM pregnancy includes development of the metabolic syndrome in the offspring.

Postpartum consequences of GDM.

In the postpartum period, within days of delivery of the placenta, there is a rapid and substantial 120% increase in insulin sensitivity and decrease in insulin response in comparison with late gestation[177]. A series of studies examining women with normal glucose tolerance and GDM in late pregnancy, involving skeletal muscle biopsies and clamp studies at 1 year postpartum, revealed that improvement in insulin resistance was associated with weight loss and increased skeletal muscle expression of IRβ and IRS1. The change in IRS1 levels was correlated with the change in insulin sensitivity (regression coefficient 0.84, $P<0.007$)59.In women with previous GDM in whom there was no significant improvement in insulin sensitivity, body weight or body composition measures and circulating and skeletal muscle TNF concentrations remained elevated 1 year postpartum. Although skeletal muscle IRβ and IRS1 levels improved, insulin-stimulated insulin receptor autophosphorylation and receptor tyrosine kinase activity did not improve. Levels of skeletal muscle 312Ser-IRS1 also did not improve and correlated with TNF expression[178]. These data are consistent with a state of chronic inflammation and insulin resistance in GDM and stress the importance of postpartum retention of excess weight gained during pregnancy as a significant risk factor for the development of

obesity and T2DM. Returning to prepregnancy body weight is associated with a substantial improvement in the overall metabolic condition, which supports the concept that pregnancy need not have a long-term detrimental effect on a woman's metabolic health[179]. However, weight gain postpartum that is associated with increased parity could increase the risk of T2DM owing to progressive insulin resistance and further deterioration of β-cell function63, which may be particularly important for women who developed GDM and have a greater lifetime risk of future metabolic problems.

Mechanisms of fetal consequences of GDM

The placenta is central in the maternal–fetal supply line, as it integrates maternal exposures and provides oxygen, macronutrients and micronutrients to the developing fetus. The interactions of these factors with the fetal genotype (including epigenotype) determine the fetal phenotype[180]. The placenta partitions maternal fuels to cover its own needs and at the same time to sustain fetal growth and thereby mediates the effects of maternal metabolic disturbances on the fetus. These metabolic changes encompass foremost hyperglycemia, which is both the means for diagnosing GDM and the principal therapeutic target. However, it is important to remember that the metabolic derangements also include elevated fatty acid and amino acid concentrations in the maternal circulation.

Placental nutrient transport.

The placenta is richly endowed with transporter molecules that ensure an adequate supply of glucose, lipids and amino acids when the mother is metabolically normal, although it does not protect the fetus from oversupply in GDM[181]. Transplacental glucose transfer becomes saturated only when the glucose concentration difference between the maternal and fetal circulation is ≥25mmoll–1. This high efficiency explains why glucose transfer is unaltered in GDM at the level of the placenta itself. Therefore, the glucose concentration gradient between the maternal and fetal circulation is the most important determinant of the amount of maternal glucose reaching the fetus. The gradient is determined not only by maternal glycaemia but also by the glucose level in the fetus. Fetal glycaemia is modified by fetal insulin levels, which are usually elevated in GDM. Fetal hyperinsulinemia facilitates glucose uptake into peripheral tissues and steepens the concentration gradient. In these conditions, the fetus also pulls

(‘steals’) glucose from the maternal circulation, the ‘fetal glucose steal’ phenomenon enon68, with the consequence that more maternal glucose reaches the fetal circulation. Placental transfer systems are much less efficient for fatty acids than for glucose, and therefore only ~3% of maternal fatty acids reach the fetal circulation . Efficient transfer is not needed, as the fetus can synthesize its own non-essential fatty acids using glucose as a precursor. Consequently, only 20% of the fatty acids in neonatal fat are derived from maternal sources[182]. Fatty acid transfer does not seem to be altered by GDM, except perhaps that of docosahexaenoic acid[183], which is important for the development of the brain and retina. The fetus depends on maternal supply of this essential fatty acid. GDM reduces the placental levels of the docosahexaenoic acid transporter NLS1 (encoded by MFSD2A) by ~30%[184]. NLS1 levels correlate with cord blood concentrations of docosahexaenoic acid. The reduced placental NLS1 levels may explain the lower cord blood levels of docosahexaenoic acid in women with GDM than in healthy women.At the end of pregnancy, only ~9–10% of the placental surface is involved in mediating nutrient transfer to the fetus[185], and this proportion is unaltered in GDM. Nutrients taken up across the vast majority of the placental surface instead enter metabolic pools in the placenta to sustain placental functions[186].Collectively, at the end of a GDM pregnancy, the placenta does not actively enhance the quantum of maternal nutrients reaching the fetal circulation and thus does not directly contribute to excessive fat accretion that leads to the characteristic phenotype of fetuses in GDM pregnancies. Buffering capacity of the placenta. Many of the changes in the placenta of women with GDM are adaptive responses to protect both the placenta and fetus, of which placental hypervascularization is the best studied example. Fetal aerobic metabolism is stimulated by hyperinsulinemia in GDM pregnancies, and elevated cord blood concentrations of erythropoietin and red blood cells reflect some degree of fetal hypoxia. The placenta responds to the increased fetal oxygen demand by increasing its capillary surface[187]. Low oxygen, hyperinsulinemia and changes in the levels of several other angiogenic factors in the fetal circulation in GDM stimulate placental angiogenesis [188,189]. Whereas these regulatory signals are derived from the fetus, others may come from the trophoblast and macrophages, both of which are essential cell types for placental function [190,191]. The number and function of these cell types may also be altered in GDM, including changes in the molecules they secrete, which contribute to regulation of placental vascularization. Overall, multiple signals give rise to placental hypervascularization in GDM.

Other examples of placental adaptations that ‘buffer’ the potentially adverse effects of the maternal environment in GDM on fetal growth and development include an enhanced

placental capacity to cope with increased cholesterol synthesis in placental endothelial cells. Multiple cellular and molecular mechanisms that facilitate cholesterol removal from the feto-placental circulation to avoid the formation of pre-atherosclerotic lesions (which would reduce blood flow) are upregulated in GDM[192,193]. The placenta seems to have evolved some capacity to buffer the intrauterine environment by adapting its functions to altered conditions in this environment, although this adaptive capacity is likely to be limited[194]. Thus, extreme perturbations of the maternal milieu, as in untreated GDM or GDM combined with obesity, may override the placental buffering capacity and thereby contribute to pathological effects in the fetus[195]. Some evidence exists to suggest that placental adaptive responses are more pronounced in female fetuses. As a fetal tissue, the placenta is under fetal control, especially in the second half of gestation, when fetal organs have formed. Consequently, the placenta is less vulnerable to an adverse maternal environment in this period than in early pregnancy, when the placenta is mostly under maternal control. For example, the placenta has poor antioxidative defenses (such as lower levels of the antioxidant enzyme catalase) in the first 10–12 weeks of pregnancy[196], resulting in the placenta being especially sensitive to oxidative and meta inflammatory stress, which often occurs in women with hyperglycemia, obesity and/or GDM[197,198] . Future studies should investigate whether and how early hypoglycemic events in women who will develop GDM later in pregnancy affect the growth and developmental trajectories of the placenta and, subsequently, the fetus[199].

Fetal phenotype and long-term effects.

Maternal glucose is the main macronutrient that sustains fetal growth. In pregnant women with T1DM, prolonged exposure of the fetal pancreas to hyperglycaemia from the early stages of pregnancy, which may also occur in GDM (but remain undetected until diagnosis), accelerated maturation of the stimulus–secretion coupling mechanism in pancreatic β-cells and results in early hyperinsulinemia, with ensuing fetal hyperglycemia. Some amino acids, such as arginine, also stimulate the fetal pancreas and contribute to hyperinsulinemia. Free fatty acids (FFAs) are released from maternal lipoproteins by lipolysis, but only a small proportion crosses the placenta and contributes to the fetal FFA pool. This pool mainly comprises FFAs produced by de novo lipogenesis in the fetal liver, using glucose as a precursor, which is present in excess in maternal overnutrition. Fetal insulin stimulates tri glyceride synthesis and, thus, fat storage in white adipo cytes in the fetus in a sex-dependent

manner, which is reflected by a stronger association of cord blood insulin with neonatal fat deposition in males than in females[200]. GDM also leads to long-term metabolic effects in offspring. The pathogenetic mechanisms underlying these abnormal metabolic characteristics are not known, but maternal hyperglycemia-induced changes in DNA methylation and microRNA (miRNA) content in fetal blood, skeletal muscle and adipose tissue [201-203] and other factors are most likely involved.

Clinical consequences

The first description of GDM arose from the observation that parous pregnant women with overt diabetes often had the same complications in pregnancies antedating their own diagnosis of diabetes as those in pregnant women with diabetes, which was speculated to be due to undetected prediabetic hyperglycaemia in previous pregnancies. The GDM diagnostic criteria were based on the long-term risk of maternal diabetes rather than the short-term risks of poor perinatal outcomes.

Short-term consequences for mother and offspring.

Later retrospective and prospective observational studies using these and similar diagnostic criteria clearly indicated that GDM was indeed associated with poor maternal and offspring outcomes. The short-term complications was intensely debated whether the poor outcomes associated with GDM were due to maternal hyperglycemia per se or other risk factors[204]. Subsequently, the large multinational landmark Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study[205] clearly documented that maternal hyperglycemia independently and in a graded linear way (without obvious cut-off points) increases the risk of pre-eclampsia, preterm delivery, cesarean section, large for gestational age (LGA) infants, shoulder dystocia, neonatal hypoglycaemia, hyperbilirubinemia and admission to neonatal special care unit. The absolute risk of these complications in women with GDM diagnosed using the IADPSG criteria ranges from 1.8% for shoulder dystocia to 16.6% for neonatal adiposity (absolute outcome frequencies are summarized in Table 4). Overall, fasting plasma glucose values from the OGTT were more strongly associated with poor outcomes than were the 1-hour and 2-hour values. Two large randomized controlled trials have clearly shown that treatment of GDM is effective in reducing or preventing maternal and fetal short-term

complications, in particular with reduction in LGA frequency to within the normal expected range and of pre-eclampsia by ~50%[206,207].

Long-term maternal consequences.

It has been known since the original diagnostic criteria for GDM by O'Sullivan 3 that women with elevated glucose levels in pregnancy are at an increased risk of subsequently developing diabetes (primarily T2DM). Risk estimates have been obtained for different populations and vary depending on the population studied and the GDM criteria used. A meta-analysis found a more than sevenfold increased risk of T2DM in women with GDM compared with women with normoglycemic pregnancies[208]. Thus, GDM is the best-known risk factor for T2DM[209]. Increasing BMI, GDM diagnosis early in pregnancy, higher glucose levels at the time of diagnosis during pregnancy, need for insulin treatment during pregnancy and IGT in the postpartum OGTT are some of the risk factors for subsequent diabetes in women with previous GDM [208-211]. In 2018, the HAPO Follow-Up Study (HAPO-FUS)[212] provided long-term data about maternal and infant outcomes in women who were diagnosed with GDM post hoc using IADPSG criteria but who were untreated in the index pregnancy. This study provided data about the natural history of untreated GDM (outcomes in the immediate perinatal period and after a mean of 11.4 years follow-up are summarized in Table 2). Untreated GDM clearly has substantial long-term risks for both mother and child. In some populations, risk of T1DM is also increased after GDM[213]. Furthermore, women with previous GDM have an increased risk of the metabolic syndrome and cardiovascular, kidney, liver and retinal disease.

Long-term offspring consequences.

Studies using animal models that are intended to simulate GDM have documented that the offspring of GDM mothers have increased risk of hyperglycemia, diabetes, obesity, cardiovascular disease and structural hypothalamic changes during their subsequent pregnancies and that these abnormal outcomes can be prevented by normalization of maternal blood glucose levels during pregnancy[214,215]. These adverse outcomes are similar to clinical observations in children from different populations that included women with

different types of diabetes mellitus, which noted an increased risk of diabetes and obesity in children of women with diabetes mellitus [216-217].

In a follow-up study from Denmark of the offspring (18–27 years of age) of women with GDM, 21% of the offspring had pre-diabetes or diabetes — an eightfold increased risk compared with the background population. Furthermore, the risk of overweight and the metabolic syndrome was higher (twofold and fourfold, respectively) and insulin sensitivity and secretion were reduced. In a study of nearly 100,000 pregnant women, children of women with GDM had increased fasting glucose levels, insulin resistance, adiposity and cardiovascular risk profile. The HAPO-FUS confirmed these findings but suggests that although maternal adiposity is a strong risk factor for offspring obesity, GDM remains a significant risk factor, even after adjustment for maternal BMI.

Although differing results have been reported about the effects of GDM on cognitive function in offspring, there is no solid evidence that maternal GDM independently causes impaired cognitive function. Some studies have found that the offspring of women with an early diagnosis of GDM have an increased risk of autism spectrum disorder, whereas the offspring of women with GDM needing medical treatment have Primer potential benefits from healthful diet and lifestyle changes have been inconsistent. Meta-analyses and systematic reviews have also reached divergent conclusions. Both the timing of intervention (early to mid or late pregnancy) and the intervention approaches themselves (yoga, aerobic exercises, resistance training and targeting different aspects of diet) were diverse in these studies. These methodological issues may have contributed to the markedly heterogeneous findings. A meta-analysis published in 2015 provides some evidence that lifestyle modification (diet, physical activity or both) initiated before the fifteenth gestational week can reduce the risk of GDM[218]. Antenatal dietary supplementation with myo-inositol (a derivative of secondary messengers involved in several signaling pathways, including the insulin pathway) for the prevention of GDM is a comparatively new intervention. In two small clinical trials, myo-inositol supplementation reduced the risk of GDM, whereas in a larger trial, supplementation with an inositol combination in early pregnancy did not prevent GDM in women with a family history of diabetes. However, of note, the overall quality of this evidence has been assessed as low or very low and the overall risk of bias is considered unclear.

Outcome	GDM[a] (%)	Non-GDM (%)	Statistical significance
Perinatal outcomes[b]			
Pre-eclampsia	9.1	4.5	$P<0.001$
Preterm delivery (<37 weeks)	9.4	6.4	$P<0.001$
Primary caesarean delivery	24.4	16.8	$P<0.001$
Shoulder dystocia or birth injury	1.8	1.3	$P<0.01$
Birthweight greater than ninetieth percentile	16.2	8.3	$P<0.001$
Neonate percentage body fat greater than ninetieth percentile	16.6	8.5	$P<0.001$
Cord blood C-peptide level greater than ninetieth percentile	17.5	6.7	$P<0.001$
Clinical neonatal hypoglycaemia	2.7	1.9	$P<0.001$
Admission to newborn intensive care	9.1	7.8	$P<0.01$
Long-term outcomes[c]			
Maternal diabetes	10.7	1.6	$P<0.001$
Maternal pre-diabetes	41.5	18.4	$P<0.001$
Offspring overweight or obesity	39.5	28.6	$P<0.001$
Offspring obesity	19.1	9.9	$P<0.001$
Offspring percentage body fat greater than eighty-fifth percentile	21.7	13.9	$P<0.001$
Offspring impaired fasting glucose (ADA threshold of $\geq 5.6\ mmol\ l^{-1}$)	9.2	7.4	Not significant
Offspring impaired glucose tolerance	10.6	5.0	$P<0.001$
Offspring diabetes	0.3	0.2	Not significant

Table 4

PREVENTION

The first line prevention methods used currently are exercise combined with dietary alterations. However, whether exercise is effective for the prevention of GDM is not clear because the few randomized controlled trials (RCTs) investigating this issue show conflicting results. In this review we will analyze only the exercise at the first trimester as a method of prevention of GDM in both women with high risk of GDM and women with low risk of GDM. Fig 6.

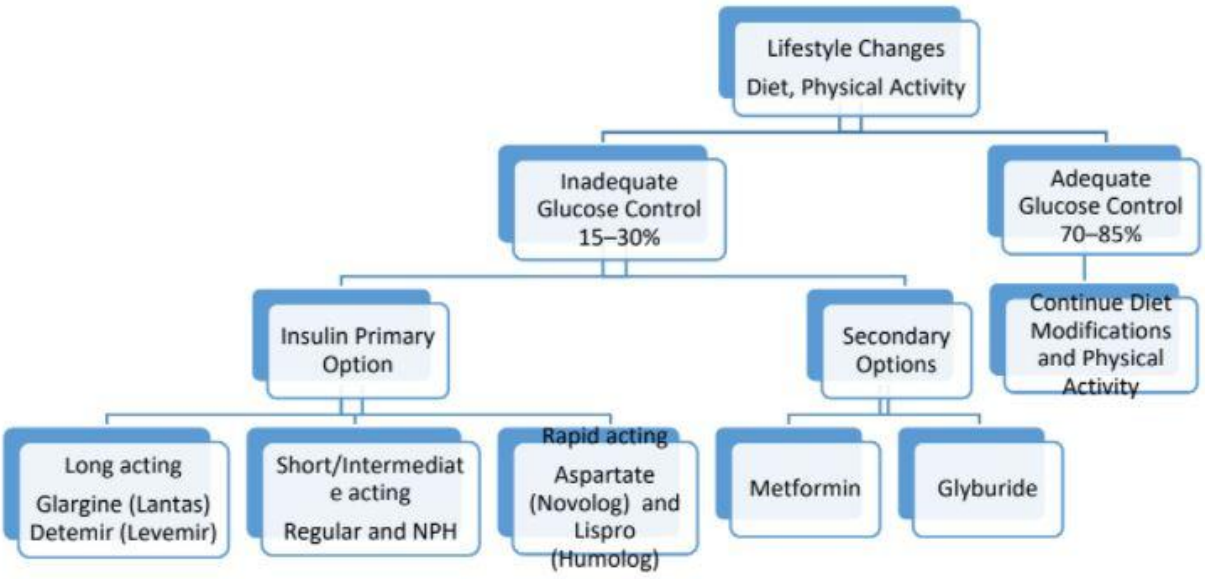

Figure 6. Management of hyperglycemia in gestational diabetes.

Physiologic role of exercise

There are several ways in which exercise may physiologically attenuate insulin resistance and lessen the risk of GDM. Exercise can affect the adipokine profile, which increases adiponectin, a protein that helps with cellular sensitivity to insulin [219]. Exercise also increases the presence of GLUT4, a glucose transporter that brings glucose from the bloodstream into the cell. GLUT4 helps decrease blood glucose levels and insulin resistance by not requiring as much insulin, giving the maternal pancreas relief. Exercise can also increase antioxidants and combat oxidative stress, a contributing factor for developing GDM. Exercise may also decrease the inflammatory markers associated with insulin resistance, which potentially means a reduction in GDM due to a reduction in maternal insulin resistance [219].

Role of exercise in prevention of GDM

Early systematic reviews of randomized controlled trials (RCTs) (up to April 2013) suggested that evidence was inconclusive, 29 or was shown to provide a slight protective effect (up to August 2014) 30 regarding the effectiveness of physical activity in reducing GDM risk. However, another systematic review and meta-analysis (RCTs up to May 2014) concluded that structured moderate physical activity decreased the risk of GDM (by 31%), reduced excessive maternal weight gain, and is safe for mother and fetus but could not suggest recommendations for exercise prescription.[220] It is interesting that when the same studies are being included in systematic reviews and meta-analysis that authors provide different conclusions. One major factor that must be considered in reviewing RCTs is adherence to the interventions being assessed. If the women in the intervention group do not adhere to the program being offered, the efficacy of the intervention remains in question and conclusions cannot be drawn. RCTs that are evaluated for adherence to the program and report attendance to the intervention are more likely to have a successful primary outcome. Furthermore, only RCTs that have a high adherence to the intervention being studied should be considered. A large RCT that examined maternal exercise using both aerobic and muscular conditioning on land and in the water with high compliance (Z80% attendance) reduced the incidence of GDM, decreased EGWG, and preserved glucose tolerance compared with standard care women.[221] The authors suggested that a structured exercise program should be offered at least 3 times per week, with a mixture of aerobic and muscle conditioning exercise, on land and in water, with sessions lasting at least 50 minutes with 10 minutes' warm up and 10 minutes' cool down, with an intensity of 60% predicted heart rate reserve (HHR) (12 to 14; somewhat strong on Borg's rating of perceived exertion scale) to reduce the incidence of GDM. A more recent study examining the exercise characteristics before and during pregnancy in women with and without GDM reported that regular exercise before and during pregnancy, especially up to and including second trimester, may prevent GDM.[222] This would suggest that women who actually participate in exercise are more likely to reap the rewards. RCTs should be studied in populations that are at risk for GDM rather than in populations that have no reported risk factors. To achieve the best decline in glucose concentrations when accompanied by MNT, pregnant women at risk for GDM should walk for 25 minutes per session at a vigorous intensity (70% of HHR) or walk for 35 to 40 minutes per session at a lower intensity (30% of HRR), 3 to 4 times per week.[223] On the basis

of these results it would appear that exercise intensity and duration may influence maternal glucose responses in women at risk for GDM and these results were different compared with women who were not at risk for GDM. These differing results for exercise effects on glucose excursion based on intensity and duration for those women with and without risk factors may explain why the systematic review literature shows conflicting results regarding the role of physical activity in reducing GDM risk.

SAFETY AND CONTRAINDICATIONS

Exercise during pregnancy is safe in the absence of any con- traindications and with avoidance of high-risk activities. Please refer to (Table 5) and (Table 6).[221.224]

Contraindications to exercise during pregnancy	
Absolute	Relative
Ruptured membranes Premature labor Placenta previa after 26–28 weeks of gestation Preeclampsia Incompetent cervix High-order multiple pregnancy	Intrauterine growth restriction

(Table 5)

Safety	
Safe	Avoid

For All	For women who participated prior to pregnancy	
Walking Swimming Stationary cycling Low-impact aerobics Yoga, pilates	Running or jogging Strength training Racquet sports	Contact sports (e.g., soccer, hockey) High falling risk (e.g., surfing, downhill skiing) Scuba diving Sky diving Hot yoga/pilates

(Table 6)

EXERCISE TIME

There are various recommendations concerning the premium exercise time per week, but according to the American College of Obstetricians and Gynecologists (ACOG) and the American College of Sports Medicine, pregnant women should participate in at least 150 min of moderate-intensity activity per week. The Canadian and UK guidelines suggest 15 min of exercise, three times a week, and a progressive increase of the duration to 30 min; frequency should be set at four times a week, even if the intensity is reduced. The guidelines from Denmark [225] and Norway [226,227], recom- mend that pregnant women exercise daily for at least 30 min at average intensity. The guidelines from Japan recommend aerobic exercise, to be done for over 60 min two to three times a week [228], while the guidelines from Spain recommend exercise two to three times a week, without, however, specifying the duration [225]. In summary, a frequency of two to four times a week and exercise duration of 30 min is, overall, considered to be efficacious and safe.

INTENSITY

Intensity constitutes the most difficult but most important parameter to consider when designing an exercise program for pregnancy. In general, intensity during a normal pregnancy does not need to be different from that for a non-pregnant state: the ACSM guidelines on physical condition can be followed: fast walking at 3–4 metabolic equivalent of task (MET) [229].
There is evidence that 16–28 MET exercising per week at a 60% intensity of heart rate reserve (HRR) reduces the risk of gestational diabetes and, possibly, pregnancy-induced hyper- tension and pre-eclampsia. A 28-MET per-week exercise program is equivalent to walking at a speed of 3.2 km/h for 11.2 h per week [30]. According to the ACOG, exercise at 60–70% of HRR or 50–60% of maximum consumption of oxygen (VO2max) is safe for most pregnant women. Women who were physically active before pregnancy can safely exercise at the highest levels of these values [230]. In a meta-analysis of high-intensity programs (81% of HRR), no complications were observed in the mother or the fetus [231]. Regarding exercise intensity, the Canadian and Norwegian guidelines recommend physical activities of high intensity and competitiveness, while the Australian guide- lines advise very close observation by a physician [232].
Given the variability of heart rate during pregnancy, the ACOG does not consider it necessary to record the heart rate of pregnant women on an exercise program. Intensity can be regulated by the Borg Scale, a frequently used quantitative measure of perceived exertion during physical activity and ex- ercise (desired levels 12–14, light to hard), or by the “talk test.” The latter was developed as an informal, subjective method of estimating appropriate cardiorespiratory exercise intensity. The method entails maintaining an intensity of exercise at which conversation is comfortable and not affected or limited by deep and frequent breaths necessary to meet the oxygen demands of working muscles [233].

TYPE

A summary of current guide- lines for exercise during pregnancy from eight countries re- ported a general recommendation that healthy pregnant women engage in 60–150 min per week of aerobic exercise with an upper limit of 30 min per day, and the addition of resistance exercise was recommended by five guidelines. Both aerobic and resistance exercises are considered safe and do not exert any adverse effects during pregnancy [234].

a)Resistance exercise

Data on resistance exercise is scarce. To prevent high blood pressure, it is generally suggested that isometric exercises should be avoided as well as exercises with heavy weights and numerous repetitions [234]. The Norwegian guidelines strictly warn against exercises with heavy loads. The Canadian guidelines suggest exercises with light weights and more repetitions and avoidance of exercises that require the supine position and holding one's breath with techniques such as the Valsalva maneuver. An interventional resistance program (1 set, 12 repetitions, several muscle groups, gestational week 28–38) reported that the fetal heart rate was not affected [235].

Stretching exercise Since during pregnancy hormonal changes cause considerable loosening or laxity of the ligaments, care must be taken with regard to stretching exercises. The latter should be practiced daily but must be personalized according to the needs and abilities of each woman while maintaining a wide range of movements [235].

b)Aerobic exercise

Every exercise that mobilizes large muscle groups in one continuous, rhythmic movement can be considered aerobic exercise. Characteristic examples are walking, running, jogging, dancing, swimming, bicycling, rowing, ski-ing, skating, and climbing [235]. Aerobic exercise is safe during pregnancy, but pregnant women must avoid sports requiring physical contact between players to minimize the risk of falls and blows to the abdomen [236].

Walking is one of the safest and most popular kinds of aerobic exercise during pregnancy and is the only form of exercise that does not need to be reduced during this period. In fact, during the third trimester, it can be increased as it helps to maintain and improve aerobic abilities without having any negative impact on the pregnant woman or her fetus [237].

Exercise in water is considered safe during pregnancy. Due to buoyancy, any musculoskeletal burdens due to weight gain are considerably decreased. Care must be taken as to the cleanliness and the temperature of the water, which should not be above 32 °C. In the case of a swimming pool, pregnant women should move slowly from the deep to the shallow end before coming out to avoid a sudden drop in blood pressure [238].

ORIGINALITY/VALUE OF RESEARCH

This paper is the first one that combines those RCTs in order to finally give an answer to a medical question that is not yet clear. We strongly believe this is an important topic, due to the constant rise of GDM cases, combined with no official guidelines for it's prevention. If more data from around the globe are collected, there is a chance to find a connection between exercise and prevention and therefore, help form prevention guidelines.

AIMS

The aim of this paper is to conduct a review of randomized controlled trials (RCTs) for assessing the effectiveness of physical exercise interventions during the first trimester of pregnancy to prevent gestational diabetes mellitus. Through the collection of the data from reliable medical databases we aspire to find common ground between different research performed with focus on exercise as a prevention for GDM. We are collecting data about the best duration of exercise, type of exercise, frequency of exercise at the control groups versus the GDM groups and comparing the results, in order to determine if there is a way to prevent GDM through exercise in the first trimester.

METHODS

This study was performed according to the Preferred Reporting Items for Systematic Reviews and MetaAnalysis (PRISMA) statement.

Data sources and searches

For this study we used the PubMed database with interest in Reviews and Meta-Analyses about exercise during pregnancy in women with Gestational Diabetes Mellitus (GDM), focussing our search at the first trimester. The keywords used at the search engine were “exercise in gestational diabetes” and the Filters used were: years= 2012-2022, types of articles= Reviews, Meta-Analyses. This gave us a total of 166 records. From those we excluded duplicates, articles including dietary alterations, type 2 diabetes or other pre-existing diabetes. The sources left were 25 and after reading those abstracts, we excluded 3 more sources. Continuously, we read the full text of these 22 sources and found 6 Research articles from their References that are specifically focused around Exercise as a prevention agent for GDM and those are the sources used for our Review . Figure 7.

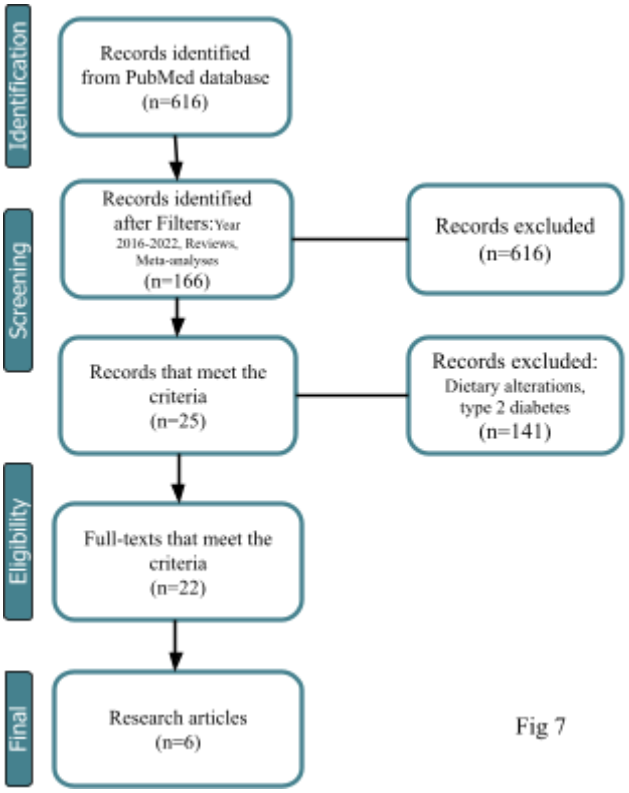

Fig 7

Data extraction and quality assessment

The two reviewers extracted the following data from each included article: (1) characteristics of participants (number, age, and obstetric characteristics); (2) intervention features (type, duration, frequency, and intensity of physical exercise intervention); (3) target of the study; (4) strengths and weakness of each RCT; and (5) results of outcomes: GDM (%) and MWG (kg). Risk of bias was evaluated according to the PRISMA Recommendation. The quality assessment was performed using the Jadad scale. This scale includes five items to be assessed as 'yes' or 'no', depending on whether the clinical trials met quality criteria in the following areas: randomisation, random.

RESULTS

Subjects

The total sample included 3.697 women were included and from them 1.556 were excluded due, so 2.141 were left: 1.091 in the intervention group (IG) and 1.050 in the control group (CG). Every woman had a healthy pregnancy, which was nullipara or multipara, with a singleton pregnancy and without maternal or fetal disease, and uncomplicated pregnancy evolution. The studies didn't mention the ethnicity of the participants. Two RCTs focused in obese women, starting with a BMI over 30[239,240], three RCTs chose women with at list one risk factor for GDM [241-243] and one RCT focused on women with normal BMI[244].

Exercise programmes

The RCTs used different exercise types, duration and frequency. As far as the types go, the categories were: Low Intensity Group and Vigorous Intensity Group, Toning and joint mobilization exercises and resistance exercises and lastly Aerobics and resistance exercises. As far as the duration goes, one RCT made 3 groups of 25min, 35min and 40 min, two of them chose a duration of 50min and 1 a duration of 150min per week. As far as the frequency is concerned they chose a 3 times per week programme.

Combined results

We combined the results of 6 RCTs focused on exercise in the first trimester of pregnancy as a prevention method of GDM. Most articles had divided patients in two groups: an exercise group or EG and a control group or CG. Only one article divided pregnancies in 4 groups according to GDM risk and exercise intensity. Four of the articles used OGTT 75gr as a diagnostic measure for the results of exercise in the pregnancies and one article used CGC (capillary glucose response). In Wang 2016 article 22% of EG got GDM, versus 40,6% in CG. In Wang 2015 17.16% of EG got GDM, versus 23.91% in CG. In Barakat 2014 2,6% of EG got GDM, versus 6,8% of the CG. In Koivusalo 2015 article 2.6% of EG got GDM, versus 6.8% of CG and in total moderate individualized lifestyle intervention reduced the incidence of GDM by 39% in high-risk pregnant women. Most articles preferred 50min of exercise 3 times per week and only 2 of the articles had supervised exercise. To conclude, all of the RCTs showed a lower prevalence of GDM in all groups of women that were studied. You can see the full results in (Table 7).

Final Sources	**Research**	**Subjectives**	**EG CG**	**OGTT 75gr**	**Results**	**Exercise**			**Supervised**
						Type	Duration	Frequency	
Wang2016	RCT	300 singleton pregnancies, **16weeks,** BMI=26 +/- kg/m2	2groups • EG =132/150 • CG =133/150	22% (29/132) 40.6% (54/133)	EG=less weight gain,low insulin resistance -> **reduced GDM**				+
Wang2015	RCT	1664 singleton pregnancies 6w-12w -> **299**	2groups • IG= 134 • CG =138	17.16%(23/134) 23.91%(33/138)	IG=less weight gain, lower positive rate of GDM				

		high risk							
Ruchat2012	RCT	46 singleton pregnancies 16weeks	4groups • LR 30% I = 12 • LR70% I =12 • R30%I =11 • R70%I =11	CGC(capillary glucose response)	Optimum exercise: • LR=25 min High or Low I • R=25min HI Or • R=35-40min LI	Low Intensity Group Vigorous Intensity Group	25min 35min 40min		+
Barakat 2014	RCT	456 pregnancies	2groups • EG =152 • CG =138		GDM • EG 2,6 % • CG 6,8 %	Toning and joint mobilization exercises and resistance exercises	50min	3 x week	
Ruiz et al (ming 2018)	RCT	962 pregnancies	2groups • EG =481 • CG =481			Aerobics and resistance exercises	50-55min	3	
Koivusalo2015	RCT	269 High Risk	IG=155 CG=138		IG = 13.9% CG= 21,6%	Moderate	150min/ week		

(Table 7)

CONCLUSION

The results from this study suggest that physical activity in pregnancy provides a slight protective effect against the development of GDM. Studies evaluating type, timing, duration, and compliance of physical activity regimens are warranted to best inform obstetric guidelines. Generally, the amount of physical activity during pregnancy is low. Thus, more concern needs to be paid to find a practical way to improve the level of physical activity during pregnancy. Furthermore, studies targeted on different ethnic groups are still needed to give more specific recommendations. There are still many variables you have to manage in order to determine a specific percentage in which exercise in the first trimester reduces GDM, therefore more controlled and supervised research must be done in the future.

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