Gestational Diabetes 1

Pathophysiology from preconception, during pregnancy, and beyond

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Lancet 2024; 404: 158–74

Published Online June 20, 2024 https://doi.org/10.1016/S0140-6736(24)00827-4

This is the first in a Series of three papers about gestational diabetes. All papers in the Series are available at www.thelancet.com/series/gestational-diabetes

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Gestational diabetes is the most common medical complication in pregnancy. Historically, gestational diabetes was considered a pregnancy complication involving treatment of rising glycaemia late in the second trimester. However, recent evidence challenges this view. Pre-pregnancy and pregnancy-specific factors influence gestational glycaemia, with open questions regarding roles of non-glycaemic factors in the aetiology and consequences of gestational diabetes. Varying patterns of insulin secretion and resistance in early and late pregnancy underlie a heterogeneity of gestational diabetes in the timing and pathophysiological subtypes with clinical implications: early gestational diabetes and insulin resistant gestational diabetes subtypes are associated with a higher risk of pregnancy complications. Metabolic perturbations of early gestational diabetes can affect early placental development, affecting maternal metabolism and fetal development. Fetal hyperinsulinaemia can affect the development of multiple fetal tissues, with short-term and long-term consequences. Pregnancy complications are prevented by managing glycaemia in early and late pregnancy in some, but not all women with gestational diabetes. A better understanding of the pathophysiology and heterogeneity of gestational diabetes will help to develop novel management approaches with focus on improved prevention of maternal and offspring short-term and long-term complications, from pre-conception, throughout pregnancy, and beyond.

Introduction

Gestational diabetes has classically been defined as maternal hyperglycaemia first discovered in pregnancy that does not meet the thresholds for overt diabetes in pregnancy (panel 1).[3,4] The diagnosis of gestational diabetes is based upon an oral glucose tolerance test (OGTT), although there remains partial consensus on who should undergo an OGTT, and the OGTT glucose thresholds for diagnosing gestational diabetes.[5] Overall, using WHO 2013 criteria[3] (based on the International Association of Diabetes and Pregnancy Study Groups [IADPSG] criteria), an estimated 14% of pregnancies are affected by gestational diabetes globally (although up to 40% of pregnancies can be affected within individual countries depending on screening methods used), making it the most common medical complication in pregnancy.[6–8]

In this first paper in this Series on gestational diabetes, we review the heterogeneity in the pathophysiology of maternal glycaemic dysregulation in gestational diabetes pregnancies, and the many maternal, placental, and fetal factors from early to late pregnancy that underlie pregnancy outcomes and programming for future health of mothers and offspring exposed to gestational diabetes. The second paper presents the epidemiology of gestational diabetes (early and late), screening and diagnosis, pregnancy complications, medical and obstetric management, and health economic considerations of screening and treating gestational diabetes.[9] The third paper focuses on transforming the current pregnancy-focused approach to a long-term, life-course perspective of gestational diabetes.[10]

The importance of gestational diabetes arises from its effects during and beyond pregnancy for both mother and offspring. A recent meta-analysis involving 156 cohorts (7 506 061 pregnancies) examined the adjusted association between gestational diabetes and pregnancy complications.[11] In studies where gestational diabetes was treated without insulin use, gestational diabetes was associated with increased risks of caesarean delivery (16%), preterm delivery (51%), and large for gestational age babies (57%), despite treatment largely from 24–28 weeks of gestation.[12–14] Furthermore, gestational diabetes pregnancies requiring insulin therapy were associated with a more than two-fold increased risk of neonatal intensive care unit admission.[11] Major studies have shown the effectiveness of gestational diabetes treatment,[12–14] as discussed in the second paper of this Series.[9] Gestational diabetes is clearly a major health problem and while the global costs of gestational diabetes are unclear, costs have been estimated at US$5·5 billion per year in China[15] and US$1·6 billion per year in the USA.[16]

Historically, gestational diabetes has been considered to be a pregnancy-induced condition which emerges in the late second trimester. More recently it has become

Search strategy and selection criteria

We performed a literature search on MEDLINE from database inception to Dec 31, 2023. We searched for existing reviews and original research studies (human and animal) that investigated the pathophysiology of glucose regulation in pregnancy. Our group of experts provided references of landmark papers in the field.

***Panel* 1: Terminology**

- Gestational diabetes refers to hyperglycaemia first diagnosed in pregnancy. This paper will not discuss (overt) diabetes in pregnancy—ie, hyperglycaemia first detected in pregnancy fulfilling the criteria for type 2 diabetes (glycated haemoglobin ≥6·5%, fasting glucose concentration ≥7·0 mmol/L, or 2 h glucose ≥11·1 mmol/L on a 75 g oral glucose tolerance test [OGTT]). At the first summit discussing gestational diabetes diagnosed early in pregnancy,[1] "early gestational diabetes" was the preferred term for gestational diabetes detected before 20 weeks of gestation (as defined by the International Association of Diabetes and Pregnancy Study Groups in 2016)[2] and "late gestational diabetes" for gestational diabetes identified at 24–28 weeks of gestation after negative screening for early gestational diabetes. If the early pregnancy glycaemic status or timing of the OGTT is unknown (ie, gestational diabetes cannot be differentiated into early or late), the term "gestational diabetes" is used.
- There are two approaches to screening and diagnosis of gestational diabetes. In the two-step approach, a screening test is first used to establish who will undergo a diagnostic OGTT, while in the one-step approach, a diagnostic OGTT is performed without earlier screening. In the one-step approach, an OGTT might be offered to all pregnant women or only in those with one or more risk factors for gestational diabetes.
- Macrosomia is used to define a baby that is large at birth independent of the gestational age, and large for gestational age is used to define a baby that is large for its gestational age. Different studies use various metrics—eg, macrosomia might indicate heavier at birth than 4·0 kg or 4·5 kg whereas large for gestational age might indicate above the 90th centile for the population or more than two standard deviations above the mean for the population. Fetal adiposity refers to fat mass independent of birthweight and gestational age.
- The terms woman and women are used throughout this review to refer to people who are pregnant or who recently gave birth.

clear that pregnancies affected by early hyperglycaemia less than overt diabetes (early gestational diabetes) are at greater risk of pregnancy complications and need for insulin treatment.[17–19] The risk of some pregnancy complications are reduced by treatment of early gestational diabetes before 20 weeks gestation, but especially if initiated by 14 weeks of gestation.[14] Among non-pregnant adults aged 20–49 years, an estimated 5–10% have impaired glucose tolerance (IGT) and 4–7% have impaired fasting glucose (IFG), indicating that many women of reproductive age enter pregnancy with previously undetected hyperglycaemia.[20] Moreover, a linear association exists between pregnancy complications and maternal glycaemia in both early and late pregnancy, at levels below the thresholds defining IGT and IFG.[21,22] This association reflects the sensitivity of fetal growth and development to continuous exposure to even mild elevations in glucose and other fuels (ie, glucose, lipids, protein, and amino acids).

Early and late gestational diabetes do not only correlate with perinatal complications,[21–23] but also with long-term cardio-metabolic risks in both mother and offspring.[24–26] There are opportunities to prevent future type 2 diabetes and cardiovascular disease among women with previous gestational diabetes, yet there are still many open questions regarding how to prevent excess adiposity and type 2 diabetes in the offspring who are exposed to gestational diabetes. Overall, a better understanding of the pathophysiological mechanisms underlying gestational diabetes and its effects on mother and child are essential to reduce the still elevated gestational diabetes-related perinatal complications observed despite current management approaches, and to potentially prevent long-term complications.

Physiology and pathophysiology of glycaemic regulation in pregnancy

There is increasing evidence of gestational diabetes heterogeneity in the timing of its diagnosis (early *vs* late) and in the underlying pathophysiology driving gestational diabetes; namely, insulin resistance and insulin deficiency.[14,27,28] Thus, a wider view of gestational diabetes is needed[29] to recognise this heterogeneity, including the importance and greater severity of early hyperglycaemia, the relevance of non-glycaemic metabolic factors, and individual characteristics (both phenotypic and genotypic) that might influence optimal management and both short-term and long-term risks for mother and offspring.

Physiological adaptation of insulin secretion and insulin resistance during pregnancy

Overall, both insulin secretion and insulin resistance increase during pregnancy, but the pattern differs across trimesters.[30] These metabolic adaptations of pregnancy affect all macronutrients (glucose, lipids, and amino acids). Maternal insulin resistance increases during pregnancy to theoretically partition more of these nutrients for the fetus. Despite the common belief that insulin secretion capacity rise is in response to the greater demands from elevated insulin resistance during pregnancy, strong evidence has shown that insulin secretion intrinsically increases in early pregnancy independent of the changes in insulin resistance, and before substantial increases in insulin resistance occurs in mid to late pregnancy.[31] Longitudinal studies show major differences in patterns of pregnancy insulin secretion and insulin resistance exist between women with normal glucose tolerance and those with early

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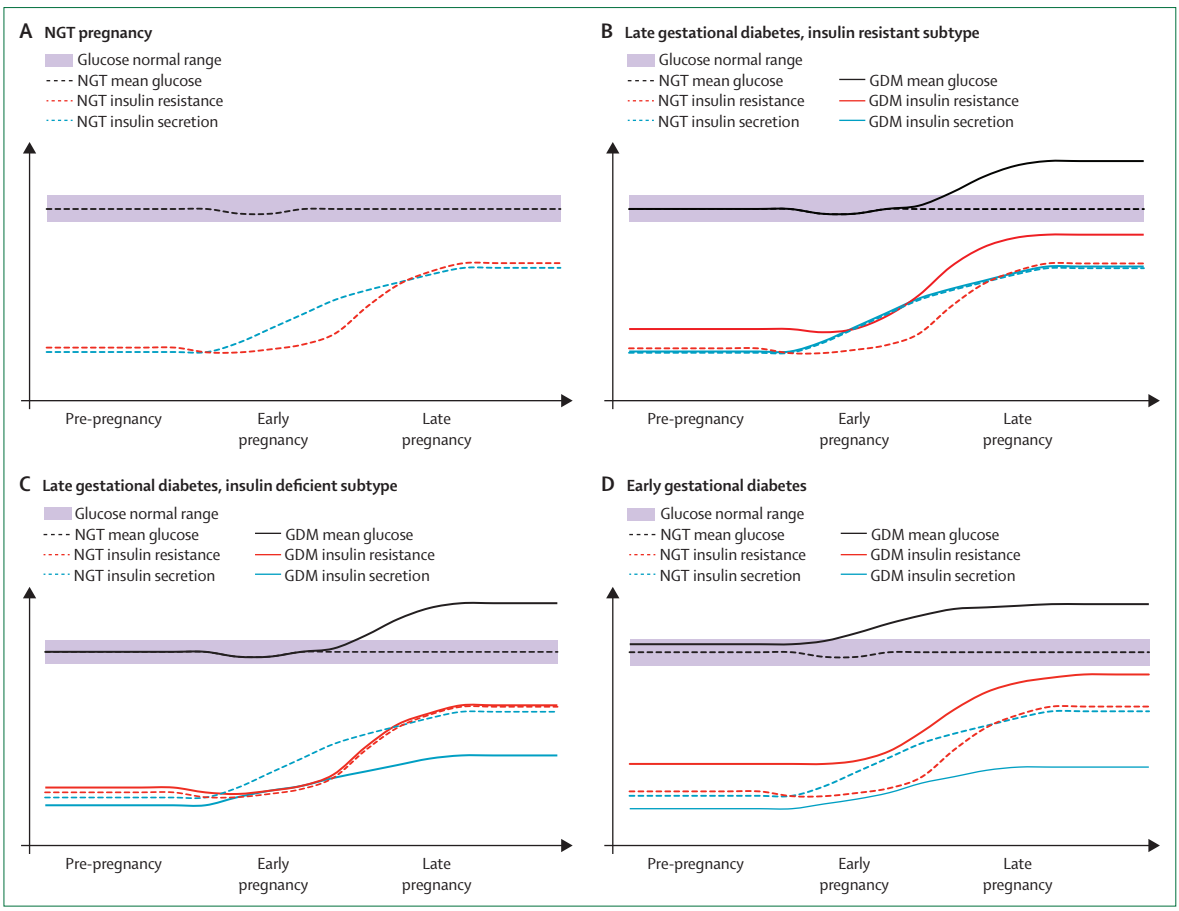

Figure 1: **Conceptual variations in insulin secretion and insulin resistance from pre-pregnancy to late pregnancy in normal physiology, and different subtypes of gestational diabetes**

(A) Changes through pregnancy in insulin resistance and insulin secretion in women who remain normoglycaemic (ie, the most physiological phenotype): insulin secretion (blue dotted line) increases in early pregnancy and continues to increase into later pregnancy; insulin resistance (red dotted line) starts rising in mid pregnancy; and insulin secretion and insulin resistance are within physiological balance and mean glucose stays within normal ranges (purple area) with a small decline of fasting glucose (black dotted line) in early pregnancy. (B) Changes through pregnancy in insulin resistance and insulin secretion in women who develop late insulin resistant gestational diabetes: insulin secretion rises starting in early pregnancy (similar to physiological variations); insulin resistance is higher in pre-pregnancy and rises in mid-pregnancy (ie, the superimposed pregnancy-induced insulin resistance plus the pre-pregnancy insulin resistance reach levels above the insulin secretion capacity); and hyperglycemia (black line) develops in late pregnancy. Changes in insulin resistance and insulin secretion in women who remain normoglycaemic during pregnancy are indicated by dotted lines. (C) Changes through pregnancy in insulin resistance and insulin secretion in women who develop late insulin deficient gestational diabetes: characterised by a smaller rise in insulin secretion and lower insulin secretion in late pregnancy compared with women who remain normoglycaemic throughout pregnancy; slightly higher insulin resistance pre-pregnancy (compared with BMI-matched women who remain normoglycaemic throughout pregnancy); and a rise in insulin resistance in late pregnancy (overall magnitude of increase similar to normoglycaemic): the lower capacity of insulin response leads to mismatch and hyperglycaemia (black line) in late pregnancy. Changes in insulin resistance and insulin secretion in women who remain normoglycaemic during pregnancy are indicated by dotted lines. (D) Changes through pregnancy in insulin resistance and insulin secretion in women who have early gestational diabetes: insulin secretion capacity might be impaired pre-pregnancy and pregnancy is characterised by a suboptimal rise in insulin secretion (both early and late); insulin resistance is substantially higher pre-pregnancy and as women are entering pregnancy leading to an insulin secretion-insulin resistance mismatch in early pregnancy and a diagnosis of gestational diabetes, but many women likely have abnormal glycemia (black line) pre-pregnancy that is undiagnosed, or not meeting diabetes diagnosis threshold for outside of pregnancy. Changes in insulin resistance and insulin secretion in women who remain normoglycaemic during pregnancy are indicated by dotted lines. NGT=normal glucose tolerant.

gestational diabetes or who develop late gestational diabetes, which also differ depending on pre-pregnancy factors—eg, pre-existing maternal overweight, obesity, or mild hyperglycaemia.[32,33] These differences are illustrated in figure 1, which compares insulin secretion and insulin resistance in women with normal glucose tolerance throughout pregnancy with those affected by recognised gestational diabetes subtypes, which underpin the heterogeneity of gestational diabetes.

Heterogeneity in the pathophysiology of gestational diabetes

The main pathophysiological process causing hyperglycaemia in gestational diabetes is a failure of insulin secretion, or relative insulin deficiency, to compensate for insulin resistance, which might be pre-existing in addition to the insulin resistance elevation during mid to late pregnancy.[34,35] The importance of this insulin deficiency and insulin resistance interaction in

determining glycaemia can be reflected by the disposition index (the result of insulin secretion by insulin sensitivity), which is used in research to combine both concepts.[34] Studies have sub-classified women into pathophysiological subtypes according to the predominant pathophysiological driver: insulin resistant gestational diabetes, insulin deficient gestational diabetes, or gestational diabetes with both defects (mixed gestational diabetes). In both early and late gestational diabetes, these subgroups were identified in ethnically and geographically diverse populations.[27,36–40] The most common subtype is insulin resistant gestational diabetes, typically accounting for 50–60% of women with gestational diabetes, with insulin deficient-gestational diabetes accounting for 15–30% irrespective of an early or late gestational diabetes diagnosis. Gestational diabetes-related pregnancy complications are more frequent in the insulin resistant gestational diabetes subtype, with the insulin deficient gestational diabetes subtype (treated) having similar complication rates as women without gestational diabetes,[40,41] independent of maternal pre-pregnancy BMI, in both early and late gestational diabetes.[29,37,40] The consistency of findings regarding these pathophysiological subtypes across populations and regions of the world argue for their relevance; future studies are needed to investigate whether different clinical approaches targeted to each subtype would result in better outcomes, as novel precision medicine promises.

Pre-pregnancy and pregnancy factors contributing to insulin resistance

Multifactorial pre-pregnancy and pregnancy factors contribute to insulin resistance, with pre-pregnancy and pregnancy insulin resistance being strongly related.[42,43] There is a 40–50% increase in insulin resistance with advancing gestation, in both women with normal glucose tolerance and gestational diabetes, with rapid insulin resistance reversal after delivery.[44] Most women who develop gestational diabetes have higher pre-pregnancy insulin resistance,[42,43] although the severity can differ according to gestational diabetes subtype (figure 1). Genetic variants known to increase insulin resistance outside of pregnancy (eg, genetic variants of glucokinase regulator gene) have been associated with higher maternal glycaemia and gestational diabetes in large genome-wide association studies across multiple populations and multi-cohort meta-analyses.[45–47] Non-genetic factors that increase insulin resistance before pregnancy (eg, central adiposity, physical inactivity, or unhealthy diet) can also contribute to the risk of insulin resistant gestational diabetes.

The contribution of fetoplacental factors during pregnancy (eg, fetoplacental hormones or cytokines) to maternal insulin resistance are yet to be fully characterised, but could act directly on maternal tissues (muscle, liver, and adipocytes) or indirectly via altered maternal metabolism of lipids, glycerol, or amino acids, as previously reported.[48–50] For example, proinflammatory markers (eg, TNF-α) are strongly related to insulin resistance in pregnancy,[51] and there is a 40% increase in maternal glycerol turnover during pregnancy, reflecting lipid insulin resistance.[43] Higher maternal blood lipid concentrations (mostly triglyceride-rich lipoproteins) have been associated with the risk of gestational diabetes or related complications.[27,50]

Pregnancies affected by gestational diabetes show altered carbohydrate, lipid, and protein metabolism. The metabolomic profile also differs by gestational diabetes subtype, suggesting that fuel metabolism (reflected by circulating levels of small molecules) contributes to the heterogeneity of gestational diabetes: insulin resistant-gestational diabetes is distinguished by higher triglycerides and branched-chain amino-acids, whereas the metabolome of insulin deficient gestational diabetes shows higher medium-chain and long-chain acylcarnitines.[52] It is unclear whether these differences reflect the consequences of gestational diabetes or are part of its underlying pathophysiology, including whether if these metabolic changes predate pregnancy.

Pre-pregnancy and pregnancy factors contributing to insulin deficiency

Pre-pregnancy factors can also be important contributors to insulin deficient gestational diabetes. For example, many of the genetic loci with a role in insulin secretion or islet β-cell biology are common to gestational diabetes and type 2 diabetes.[45,47] Other insulin-deficient conditions that exist outside of pregnancy might be revealed for the first time during pregnancy because of universal gestational diabetes screening and would resemble the insulin deficient gestational diabetes phenotype, such as stage two of type 1 diabetes,[53] possible alloimmune islet responses,[54] monogenic diabetes,[55] or pancreatic injuries (eg, past pancreatitis).

Pregnancy-specific factors also influence insulin secretion independent of changes in insulin resistance. Before the physiological rise in insulin resistance occurs in mid to late pregnancy, insulin secretion increases in the first trimester (figure 1), and correlates with maternal circulating leptin, known to be highly expressed and released from the placenta.[31] Glucose-stimulated insulin secretion is augmented by fatty acids, however, the role of maternal lipids in altering islet β-cell function in early pregnancy is not known.[56] In animal studies, prolactin enhances islet β-cell proliferation and function, and human β-cells exhibit the prolactin receptor, which can be stimulated by both prolactin and human placental lactogen.[57] If we could identify and prove causal any of these placental-specific factors that modulate insulin secretion, we could envision new therapies for gestational diabetes.

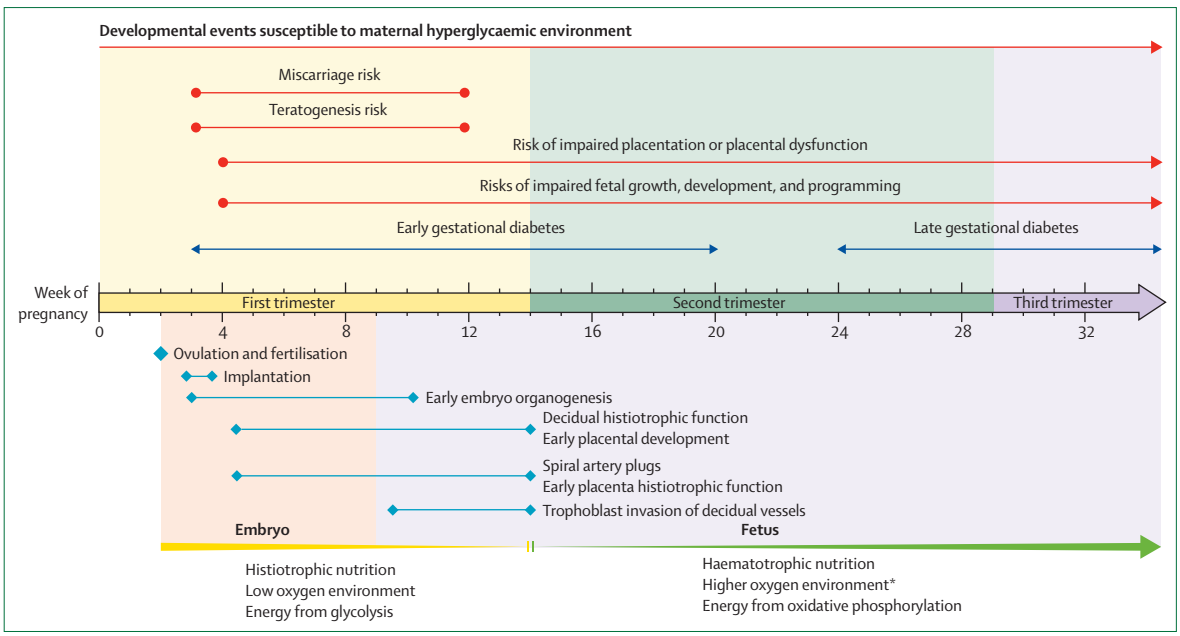

Figure 2: **Developmental events susceptible to a hyperglycaemic environment**
The effect of the hyperglycaemic environment depends on the developmental stage of embryo, fetus, and placenta, and will affect nutrition differently at stages of histotrophic and haemotrophic nutrition.[60,61] Increased risks of miscarriage and embryo dysmorphogenesis in gestational diabetes likely depend on the effects of early gestational diabetes in the first weeks of pregnancy.[62,63] Impaired fetal development and growth and placental changes could be induced by early gestational diabetes in the last weeks of the first trimester[64] and during the second trimester of pregnancy.[65] Fetal programming of the offspring's diseases might arise as a result of fetal and placental impairments and adaptations due to both early and late gestational diabetes.[66,67] Weeks of pregnancy are indicated as post-last menstrual period. *Higher than in first trimester.

Role of the placenta in the context of gestational diabetes

Beyond the role of maternal and fetal factors in determining the effect of gestational diabetes, lies the placenta. The placenta is a multifunctional organ involved in oxygen and nutrient transport, hormone production, immune regulation, and reverse transport of fetal waste, all of which are essential to support fetal development and growth.[58,59] Although most nutrient transfer across the placenta occurs late in pregnancy, its structure and function depends highly on its development early in pregnancy, which can be susceptible to early maternal hyperglycaemia (figure 2).[60–70]

Specific effects of early gestational diabetes on placental development and function are unknown as human placental tissue at this stage in pregnancy is difficult to obtain. Hence, our current understanding relies on triangulation from general placental biology, evidence obtained in pregnancies of women with type 1 diabetes or obesity, animal models, and in vitro results. There is a large gap in evidence on the roles of the placenta in early gestational diabetes and the consequences of modest hyperglycaemia on placental development in early pregnancy.

After blastocyst implantation, there is an intimate interaction between the decidua (the modified mucosal lining of the uterus) and the forming embryo-placental unit. Decidual glands produce abundant glycogen, lipids, and glycoproteins (eg, glycodelin and mucin-1), as part of unique secretions providing nutrients to the embryo and early placenta (histiotrophic nutrition).[71,72] During this period, glycogen-derived glucose in the placenta is primarily metabolised by glycolysis, providing energy for biosynthetic processes and cell proliferation (figure 2).[60,73] From animal models of diabetes in pregnancy and human studies of women with type 1 diabetes or obesity,[60,61,74–77] we suspect that maternal metabolic impairments early in gestation (eg, hyperglycaemia and hyperinsulinaemia) compromise decidual function and histiotrophic nutrition by enhancing decidual protein glycation, increasing glycogen deposition and altering the profile of decidual immune cells. Hypothetically, given the epigenetic malleability at this stage of pregnancy, potential early gestational diabetes-associated changes in placental DNA methylation might affect placental developmental trajectories throughout pregnancy.[78] Although causality is difficult to establish, associations of cell-specific placental methylation in early pregnancy with placental developmental phenotypes later in pregnancy could support this speculation.

Early embryonic development occurs in a low-oxygen environment,[79,80] which protects the embryo and placenta from oxygen free radical mediated cell and tissue damage including teratogenesis. The greater pro-oxidant or pro-inflammatory intrauterine milieu, evident in women with gestational diabetes and likely present in early gestational diabetes,[62,63,81,82] might explain the association of early gestational diabetes with an increased rate of

malformations and a history of miscarriage.[83–85] In-depth characterisation of the intrauterine milieu in early gestational diabetes in relation to malformations or miscarriage would be a first step to support this notion.

By completion of the first trimester of pregnancy, extravillous cytotrophoblast cells have invaded and remodelled decidual vessels (figure 2). As a result, fully oxygenated maternal blood reaches the intervillous space and the fetoplacental unit.[79] Changes in spiral artery remodelling associated with hyperglycaemia[64,86] and hyperinsulinaemia can influence oxygen and nutrient supply during early developmental stages.[79,80] Haemotrophic nutrition initiates and provides a stable environment for adequate fetal growth and development from the second trimester. A disturbance in these processes due to maternal early hyperglycaemia might have consequences for placental function and fetal growth dynamics throughout gestation.

Early in pregnancy, placenta-derived signals such as hormones and extracellular vesicles induce adaptive responses in maternal physiology to support the development of the embryo, fetus, and placenta, and to accommodate the needs of the fetoplacental unit for further growth. In turn, maternal signals affect placental development and contribute to the continual shaping of placental growth and functional trajectories throughout pregnancy (figure 3).[87–94,96–102,104,105] This mother–placenta interplay progressively changes within the first trimester and then further throughout gestation: it is tightly balanced at each stage of pregnancy and highly sensitive to the maternal metabolic environment. The early gestational diabetes environment might have the potential to influence this interplay by changing the release of placental hormones and exosomes to the maternal circulation with consequences for maternal adaptation to pregnancy (figure 3).

By the end of pregnancy, multiple gestational diabetes-associated alterations are found in the placental structure and function.[106–110] These changes often represent placental adaptations, which are at least partly driven by fetal signals to the fetoplacental endothelium, for fetal protection.[102] Best understood is hypervascularisation, mostly found in terminal villi, a structural change to facilitate oxygen transfer to the fetus in situations of metabolically-induced oxygen deficit of the fetus.[103] This hypervascularisation is also stimulated by fetal insulin,[99] the levels of which are responsive to maternal glucose, and is therefore increased in many pregnancies complicated by gestational diabetes. Fetal insulin can also facilitate removal of excessively synthesised cholesterol from the fetoplacental unit.[102] If the duration or extent of fetal oxygen deficit exceeds the placental capacity to increase its vascularisation, then the fetus could be at risk for severe compromise, including stillbirth.[103] Placental accumulation of triglycerides, glycogen, and collagen at term reflects the influence of nutrient overabundance characterising maternal metabolic derangements in diabetes.[99,111] Other fetal

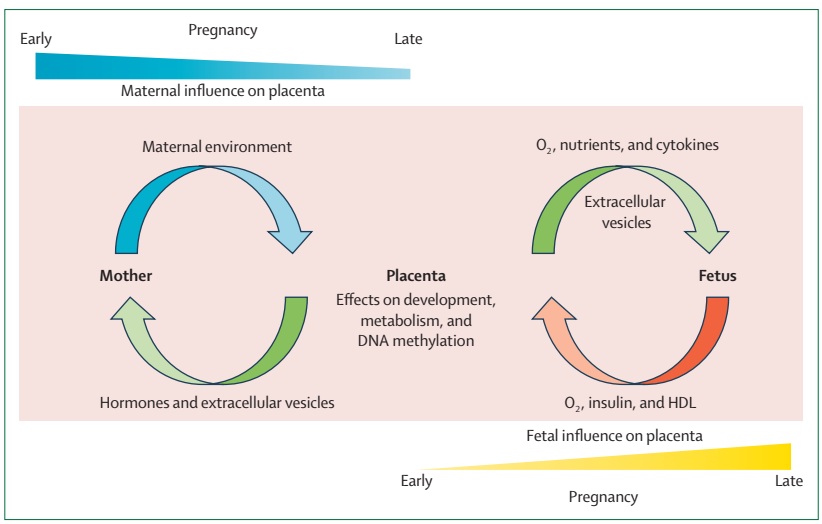

Figure 3: **Maternal–placental and fetoplacental signalling loops**
The placenta is exposed to the maternal and fetal circulations, via the trophoblast and endothelial layers, respectively. The trophoblast compartment secretes hormones and releases extracellular vesicles to the maternal circulation. Based mostly on rodent and in vitro experiments, these placenta-derived signals can stimulate β-cell expansion (eg, human placental lactogen,[87,88] hepatocyte growth factor,[89] or kisspeptin),[90] affect insulin release (eg, human chorionic gonadotropin[91,92] or microRNA miR-320b),[93] increase insulin resistance (eg, placenta variant of growth hormone,[94] insulin-like growth factor binding proteins,[95] and microRNAs),[96,97] and can also stimulate hepatic glucose release (eg, placensin).[98] The resulting changes in the glucose–insulin axis with mostly elevated maternal insulin levels can induce placental human chorionic gonadotropin secretion, which can again affect maternal insulin release, thus constituting one of the maternal–placental signalling loops. Fetal signals communicate with the placenta foremost by interactions with the endothelium to induce protective changes. In diabetes, fetal hyperinsulinaemia can stimulate hypervascularisation[99,100] and glycogen deposition[101] in the placenta and facilitate the removal of excessively synthesised cholesterol from the fetoplacental unit.[102] Further likely fetal signals are oxygen (pO_2),[103] high density lipoproteins and their associated proteome,[104] oxysterols,[105] and others that are yet to be identified.

signals include high-density lipoproteins and their associated proteome,[104] and oxysterols.[105] Epigenetic alterations and multiple affected signalling pathways, including those regulated by insulin, insulin-like growth factors, cytokines, mammalian target or rapamycin, and peroxisome proliferator-activated receptor activators are involved in the aetiology of placental developmental alterations related to maternal hyperglycaemia.[78,85,95,112–114]

Collectively, any early disturbance of placental growth and development by the gestational diabetes-associated maternal exposome might influence fetal development and growth. Specific consequences depend on the level of glycaemia throughout pregnancy. Reduced fetal growth early in pregnancy in women diagnosed later with gestational diabetes[115,116] could be the result of reduced placental growth if findings can be extended to gestational diabetes from placenta studies performed in women with type 1 diabetes and obesity.

Late in pregnancy, gestational diabetes is associated with manifold changes in placental structure and function that can be regarded as adaptations to the compromised in utero environment to maintain placental support of fetal development and growth. Should these adaptive (ie, protective) responses be inadequate, the fetus will be adversely affected, which, among other factors, might further explain the

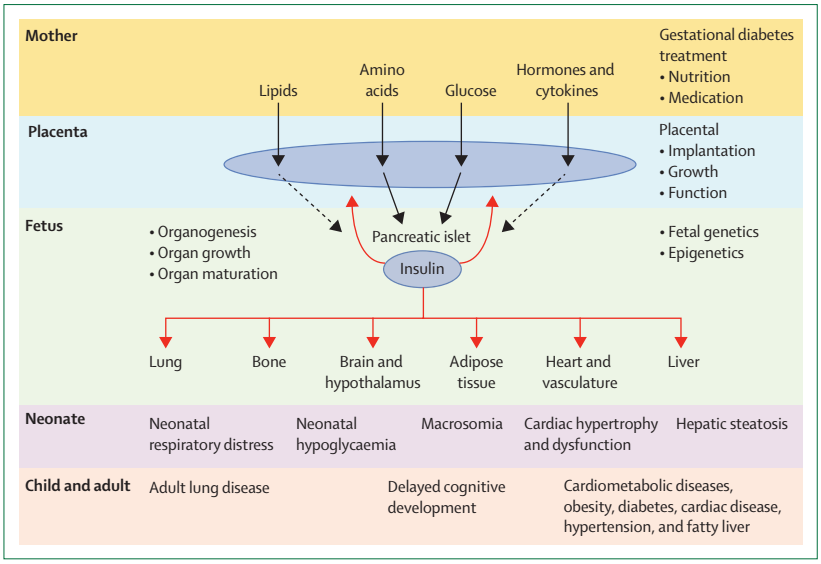

Figure 4: **Central role of fetal insulin in gestational diabetes pregnancy for determining fetal outcomes**
Fetal outcome in gestational diabetes pregnancy is determined by maternal, placental, and fetal factors. However, fetal insulin has a central role as it affects all body system development and growth. Fetal hyperinsulinaemia can develop from 14 weeks of gestation in response to increased maternal mixed nutrient supply and is dependent on fetal genetic factors (eg, islet β-cell genes involved in monogenic diabetes). Fetal hyperinsulinaemia can affect placental growth and function, lung surfactant synthesis, fat accretion, cardiac growth and function, vascular development, hepatic metabolism and erythropoiesis, bone growth, and post-natal feeding regulation via its effects on the brain and hypothalamus. These effects of fetal insulin influence pregnancy outcomes for the neonate and can have long-lasting effects into childhood and adult life.

increased risk for stillbirth in women with gestational diabetes.[117]

Growth of the fetus in the context of gestational diabetes

The historical view is that gestational diabetes does not begin to affect the fetus until late pregnancy, influencing predominantly metabolic and anthropometric development (eg, fetal adiposity including macrosomia, large for gestational age, and neonatal hypoglycaemia).[118,119] Randomised controlled trials (RCTs) that treat gestational diabetes diagnosed at more than 24 weeks of gestation are consistent with this view, as treatment reduced the risk of large for gestational age offspring by 40–50%.[12,13,120,121] However, in early gestational diabetes there might also be an effect on the development of other organ systems, such as lung development as suggested in the Treatment of Booking Gestational Diabetes Mellitus (TOBOGM) study,[14] but potentially all organ systems (eg, cardiovascular[122–124] and brain).[125–127] The mechanisms underlying these clinical risks in early gestational diabetes are not yet fully known.

Factors that can affect the developing fetus in a pregnancy complicated by gestational diabetes include: those that are non-modifiable (eg, the fetal genome, sex, and epigenetic factors carried in the gametes)[128,129] and those modifiable through intervention, such as the impacts of the maternal hormonal and metabolic milieu on placental function and fetal nutrient supply, early organ development, organ maturation and growth.[59,118,119,130]

Fetal endocrine pancreas development is undoubtedly of crucial importance for the development of all organs and overall fetal growth (figure 4). In both early and late gestational diabetes, the extent of fetal fat accretion correlates strongly with fetal insulinaemia,[131] such that it is widely accepted that fetal hyperinsulinaemia is a driver of accelerated fetal fat accretion in later pregnancy. Relevant to early gestational diabetes, precursors of fat lobules can be identified as early as at 14 weeks of gestation.[131] Liver size and the cardiac interventricular septum thickness in gestational diabetes are also associated with fetal fat accretion, implicating fetal hyperinsulinaemia in abnormal development of these organs.[132] Neonatal hyperinsulinaemia at birth, due to impaired suppression of insulin secretion as blood glucose concentrations fall, is the primary cause of neonatal hypoglycaemia.[133,134] Key to this discussion, therefore, is at what gestational age does intrauterine pancreatic islet dysfunction begin and how crucial is it to intervene early to prevent it?

Insulin in the fetal circulation is first detected from 12 weeks and its concentration rises throughout the remainder of pregnancy.[135,136] Often not realised, the fetal islet β-cell in early gestation is usually poorly responsive to glucose as a secretagogue, being highly responsive to amino acids in utero;[137,138] the switch to glucose responsiveness does not occur until mid to late pregnancy. However, in studies among pregnant women with pre-existing diabetes, fetal islet β-cells become glucose-responsive as early as post-menstrual week 16.[35,136,137] Indeed, fetal hyperinsulinaemia, reflected by amniotic fluid insulin concentrations, has been found at 14 weeks of post-menstrual age, increasing the risk for large for gestational age newborns in pregnancies without pre-existing diabetes.[138,139] Therefore, fetal islet dysfunction could begin early in the second trimester in early gestational diabetes.[138]

Also important to consider is the role that the fetus has in determining pregnancy outcomes. Once fetal hyperinsulinaemia has developed, it drives fetal glucose disposal increasing the downward glucose gradient from the mother, across the placenta, to the fetus, and creating a fetal glucose steal. The result of increased delivery of maternal glucose to the fetus is fetal overgrowth,[135] more so in male fetuses as they develop less insulin resistance for protection from the effects of hyperinsulinaemia.[139–141] Studies of monogenic diabetes during pregnancy support the role of fetal genetics and fetal insulin on fetal growth, with fetal insulin responsible for up to 50% of birthweight variance.[129,142]

Paradoxically, in some women with gestational diabetes, fetal growth restriction occurs that increases the risk of major neonatal morbidity, such as severe neonatal hypoglycaemia and hypoxic-ischaemic encephalopathy,[143,144] and potentially poorer long-term cardiometabolic health as well.[145,146] Fetal growth restriction in gestational diabetes

appears to be more common in lean women, in those with inadequate gestational weight gain, or without fasting hyperglycaemia, suggesting it might be associated with the insulin deficient gestational diabetes subtype.[147,148] Overzealous macronutrient restriction in these women could contribute to the fetal growth restriction.[149] There might also be genetic determinants in women diagnosed with gestational diabetes that place the fetus at risk of hypoinsulinaemia, such that aggressive lifestyle treatment could actually worsen the outcome for the fetus.[129] Earlier diagnosis of gestational diabetes would allow greater ultrasound scrutiny of fetal growth trajectories, enabling early pick-up of a slow-growing fetus, but will also pick up changing trajectories (eg, slow early growth with later catch-up or accelerated early growth with later slowing), as these scenarios could also increase the long-term risk of metabolic complications.[115,150]

Infants of women with gestational diabetes are at increased risk of neonatal unit admission for respiratory distress and transient tachypnoea of the newborn, characterised by increased fetal lung fluid volume at birth, or respiratory distress syndrome due to lung surfactant deficiency and atelectasis.[151,152] The mechanisms underlying these clinical risks in gestational diabetes are not yet fully known. Lung surfactant, which consists mostly of phospholipids and a smaller amount of proteins, is produced in type II epithelial cells from around 24 weeks of gestation, although considerable pools of surfactant do not appear until 35 weeks of gestation.[153] Fetal hyperglycaemia and hyperinsulinaemia impair surfactant function by altering the composition of surfactant phospholipids and by reducing surfactant proteins synthesis.[154,155] This effect on fetal surfactant production is mediated, in part, by an inhibitory effect of fetal insulin on the respiratory epithelial response to cortisol, which is a fetal hormone that has a key role in coordinating pulmonary maturation before term birth. Other potential mechanisms by which gestational diabetes might affect fetal lung development and maturation include: (1) the potential effect of early hyperglycaemia on the canalicular phase of lung development between 16–25 weeks of gestation;[156] (2) the effect of trophoblast-derived exosomes in gestational diabetes pregnancies to impede fetal lung terminal airway branching, as demonstrated in rodent studies;[157] and (3) delayed switching of fetal lung fluid physiology from chloride-driven fluid secretion to sodium-driven absorption.[154,155,158] These processes can be compounded by the adverse effects of preterm and non-labour birth on lung fluid clearance, which are more common in pregnancies complicated by gestational diabetes.

Among infants exposed to gestational diabetes, those born before 34 weeks of gestation are more likely to have respiratory distress syndrome as a cause of respiratory distress, whereas those who are born 34–38 weeks of gestation often have features of both respiratory distress

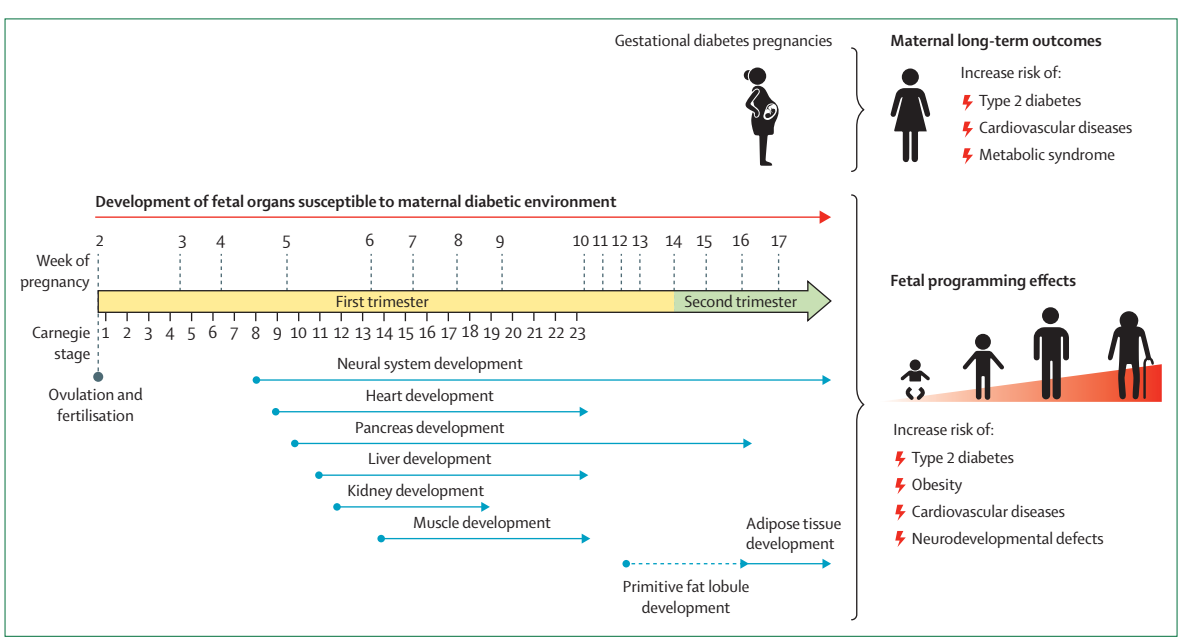

Figure 5: **Maternal and fetal long-term outcomes of gestational diabetes pregnancies**
Gestational diabetes increases the risks of maternal metabolic and cardiovascular disease, possibly due to factors already present pre-pregnancy and in early gestational diabetes.[159,160] Early gestational diabetes is likely involved in fetal programming. Fetal organs start their development at the embryonic stages and are susceptible to an early diabetes environment that can affect their structure, cellularity, signalling responses, and epigenetic marks and lead to the programming of offspring long-term health. The endocrine pancreas, liver, muscle and adipose tissues, organs respectively involved in insulin secretion, metabolic regulation, and insulin resistant responses, are likely susceptible to an early pregnancy diabetic environment, which could induce changes and mediate, at least in part, the increased long-term risk of offspring metabolic diseases.[131,161] A maternal diabetes environment early in pregnancy might also alter heart and kidney development, and therefore mediate long-term cardiovascular diseases.[66,162,163] Weeks of pregnancy are indicated as post-last menstrual period.

syndrome and transient tachypnoea of the newborn. At full term (>39 weeks of gestation), classical features of transient tachypnoea of the newborn predominate. Regardless of the primary pathophysiology, the functional consequences for the newborn are a delay in the establishment of a stable functional residual capacity and normal pulmonary compliance causing tachypnoea, grunting, and hypoxaemia.[151] The RCTs of gestational diabetes treatment after 24 weeks of gestation showed a low incidence of respiratory distress syndrome (in both treated and untreated groups), and no effect of gestational diabetes treatment.[12,13,121] However, in the TOBOGM study, diagnosis and treatment of gestational diabetes before 20 weeks of gestation (compared with later treatment), reduced neonatal respiratory distress (absolute risk reduction of 7%), suggesting greater benefit for fetal lung development if early gestational diabetes is treated (preferably before 14 weeks of gestation), although confirmation of this finding is required.[14]

Fetal programming of long-term outcomes

Offspring metabolic outcomes

Several studies have shown that in utero exposure to gestational diabetes increases the risk of glucose intolerance, overweight or obesity, metabolic syndrome, and higher blood pressure in the offspring later in life (figure 5).[24,164–169] The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) follow-up study that evaluated 4832 offspring at a mean of 11·4 years postpartum, showed that the prevalence of obesity was significantly higher in children of women with gestational diabetes (diagnosed at 28 weeks of pregnancy) compared with those without, with an adjusted odds ratio of 1·58 (95% CI 1·24–2·01).[164] Furthermore, the HAPO study showed a continuous and independent association between maternal glucose concentrations during pregnancy and greater adiposity and risk of impaired glucose tolerance in the offspring.[24,167] Similarly, a large cohort of 33 482 mother–offspring pairs showed that maternal hyperglycaemia in pregnancy, including categories lower than gestational diabetes thresholds (when using a two-step screening strategy), was associated with increased odds for offspring overweight or obesity by late adolescence.[170] Moreover, the HAPO study also highlighted the importance of maternal weight status in pregnancy as a strong risk factor for childhood excess adiposity,[171] confirming other observational studies. This intergenerational risk of excess adiposity and dysglycaemia could be due to shared genetics, shared familial environment, or to programming due to an intrauterine metabolic environment created by excess glucose and other fuels. An observational study using a data-driven clustering of metabolic phenotyping (insulin resistance or lipids profile) at 17 weeks of gestation suggested that offspring from the pregnancy subgroup characterised by high insulin resistance or by high free fatty acids showed greater adiposity at age 5 years beyond the risk attributed to gestational diabetes exposure.[172]

It remains unclear whether treatment of early or late gestational diabetes can reduce the long-term risk of metabolic complications in offspring. So far, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and Maternal Fetal Medicine Units (MFMU) follow-up studies overall did not show an improvement in the metabolic profile of the offspring of mothers who were treated for gestational diabetes compared with offspring of mothers in the control group.[173,174] Specifically, in the MFMU 5–10-year follow-up study among 500 children,[174] treatment of gestational diabetes diagnosed after 24 weeks of gestation was not associated with a reduction in childhood obesity. However, a sub-analysis suggested that treatment was associated with a lower risk of impaired fasting glucose and lower insulin resistance in girls of mothers in the treatment group, compared with those of mothers in the control group (adjusted risk ratio for impaired fasting glucose 0·24; 95% CI 0·07–0·82). Although these data suggest that sex might influence the effect of gestational diabetes treatment on the long-term metabolic risk in the offspring, some caution is required until these data are confirmed in other RCT follow-up studies. A recent meta-analysis did not show a treatment effect of gestational diabetes on the long-term metabolic outcomes in the offspring.[175] However, the report highlighted restricted follow-up time and a significant loss to follow-up in currently available studies. The effect of early diagnosis and treatment of gestational diabetes on offspring long-term metabolic outcomes is currently unknown.

Potential explanations for the partial long-term effect of gestational diabetes treatment in the intervention RCTs include: (1) gestational diabetes treatment in late pregnancy improves only short-term outcomes (in pregnancy and at delivery), (2) hyperglycaemia present before the initiation of treatment can already programme long-term outcomes, (3) other pregnancy metabolic factors (adipokines, growth factors, and lipids) contribute to long-term programming, (4) family-shared environmental and lifestyle factors override any potential benefits, or (5) offspring follow-up of RCTs of gestational diabetes treatment are too short or restricted by substantial loss to follow-up. Mendelian randomisation studies showed that maternal hyperglycaemia is causally linked to higher birth weight,[176] and future Mendelian randomisation studies could help establish potential causality between gestational diabetes and long-term outcomes. Other studies such as long-term follow-up of initial RCTs, with links to existing registries or administrative databases, could help address some of the gaps in the data on long-term offspring outcomes related to gestational diabetes treatment, for both early and late treatment.

Offspring neurodevelopmental outcomes

Thus far, observational studies have found that associations between gestational diabetes diagnosed after 24 weeks of gestation and neurocognitive impairment in

the offspring are mostly explained by established predictors of cognitive function (eg, socioeconomic status and maternal BMI), but fully matched prospective cohort studies at school age are absent and there is a need for further studies of the long-term effects of neonatal hypoglycaemia.[177–179] However, some evidence suggests that early gestational diabetes is associated with adverse neurobehavioral outcomes in children. For example, the risk of autism was greater in offspring exposed to gestational diabetes diagnosed before week 26 of pregnancy (adjusted hazard ratio 1·42; 95% CI 1·15–1·74), but not significantly greater in gestational diabetes diagnosed after 26 weeks.[180] Moreover, using patterns of glucose levels based on random capillary blood glucose assessed at multiple time during pregnancy, offspring exposed to high glucose only in early pregnancy (ie, <20 weeks) were specifically at higher risk of autism and attention-deficit hyperactivity disorder, compared with the always low glucose group.[181] In other studies, neonates who experienced neonatal hypoglycaemia (various definitions from <1·1 to <2·6 mmol/L), not specifically due to gestational diabetes, were more likely to have neurodevelopment impairment in early childhood (age 2–5 years), with a reported two-fold to three-fold increased risk for visual motor impairment and executive dysfunction, and a two-fold increased risk of literacy and numeracy problems in later childhood (age 6–11 years).[179,182]

Potential mechanisms underlying offspring disease susceptibility over the lifespan

In utero metabolic programming could be explained by gestational diabetes-induced structural and functional changes of the infant's organ systems during fetal development.[96,183] Fetal organs start developing in the fifth week of pregnancy, thus making early pregnancy a crucial period for programming of offspring diseases (figure 5).[66,131,159–163] Experimental animal models clearly show how sensitive the embryo and early fetoplacental development are to maternal metabolic impairments, and how multiple organs can be affected by changes in cellularity, morphology, or function.[161,184] Major changes in early gene expression, signalling pathways, inflammatory responses, and cell death are related to long-term organ dysfunction.[67,85,184]

The molecular mechanism purported to be most involved in the fetal programming of increased long-term risk of chronic diseases is epigenetics.[112] Epigenetic marks are highly dynamic in the embryo, parallelling the differentiation of the fetal tissues and organs. DNA methylation, histone post-translation modifications, and non-coding RNAs are sensitive to metabolic changes.[185] In humans, maternal hyperglycaemia or gestational diabetes have been associated with epigenetic marks in the offspring, mostly of DNA methylation in placenta, cord blood, or in blood later in life.[78,85,186–189] In the UK Pregnancies Better Eating and Activity Trial (UPBEAT) RCT, the association between gestational diabetes and cord blood DNA methylation markers was attenuated in the group randomised to a diet and exercise intervention (starting at 15–19 weeks of gestation), suggesting that lifestyle intervention during pregnancy might reduce gestational diabetes-related epigenetic programming.[190] It remains to be shown whether gestational diabetes-associated DNA methylation differences detected at birth are associated with long-term outcomes. The importance of timing of pregnancy exposure to hyperglycaemia (early *vs* late) on epigenetic programming for later offspring health is still unknown; one study compared cord blood DNA methylation collected in newborns exposed to early or late gestational diabetes with pregnancies of normal glucose tolerance and did not identify significant DNA methylation markers in either group, likely due to power issues.[191]

Maternal long-term outcomes and potential gestational diabetes and pregnancy mechanisms

Meta-analyses have shown that women with a history of gestational diabetes have a seven to ten-fold increased risk of developing type 2 diabetes later in life compared with women without gestational diabetes.[192–194] Women with a history of gestational diabetes progress to type 2 diabetes more rapidly than women with similarly elevated glucose levels outside of pregnancy.[195] The HAPO follow-up study showed that untreated women with gestational diabetes had a significantly higher prevalence of a composite of type 2 diabetes or pre-diabetes than women without gestational diabetes (52·2% *vs* 20·1%) by 10–14 years postpartum.[164] Recent systematic reviews have confirmed that women with gestational diabetes, based on the IADPSG criteria, have a similarly increased risk for postpartum glucose intolerance as gestational diabetes based on other diagnostic criteria.[193,194] Hyperglycaemia below the gestational diabetes threshold is also associated with higher risk of type 2 diabetes (in a dose–response mode) over more than 10 years of follow-up.[26]

Women with a history of gestational diabetes are also at increased risk for developing the metabolic syndrome and cardiovascular disease, including coronary heart disease and stroke.[25,196,197] A recent meta-analysis confirmed that gestational diabetes identifies women with a two-fold higher risk of cardiovascular disease evident in the first decade after pregnancy compared with women without gestational diabetes, independent of type 2 diabetes development.[25] Women without gestational diabetes, but with an elevated glucose challenge test after 24 weeks of gestation are also at increased risk of cardiovascular disease.[198] Moreover, population-based cohort studies have shown that gestational diabetes diagnosed after 24 weeks of gestation is independently associated with a higher risk of incident heart failure compared with no gestational diabetes, especially with co-occurrence with hypertensive disorders of pregnancy.[199]

Cohort studies are now emerging that follow-up women with previous early gestational diabetes, but these have not all involved a full two or three-timepoint OGTT in early pregnancy. One French study comparing women with a single early pregnancy fasting glucose of 5·1–6·9 mmol/L (n=192) with those with gestational diabetes using IADPSG criteria on an OGTT at 24–28 weeks (n=135) found no difference in the proportion with dysglycaemia 4–18 weeks postpartum (25% *vs* 21% respectively).[200] A Swiss study compared women with early gestational diabetes diagnosed with either a fasting glucose (5·6–6·9 mmol/L) or glycated haemoglobin (5·7–6·4%; n=76) with those with gestational diabetes using IADPSG criteria on an OGTT at 24–28 weeks (n=1185).[159] At 6–8 weeks postpartum, those with early gestational diabetes had a more atherogenic lipid profile, a 1·8-fold higher prevalence of (waist-based) metabolic syndrome (62% *vs* 34%), 3·1-fold higher prevalence of pre-diabetes (47·5% *vs* 15·3%), and 7·4-fold higher prevalence of type 2 diabetes (11·9% *vs* 1·6%) compared with those with late gestational diabetes. In a 5-year follow-up study from Norway (n=985),[201] first trimester estimates of β-cell function based on an OGTT (insulin secretion sensitivity index-2, similar to the disposition index) predicted pre-diabetes at 5-years postpartum.

In terms of pathophysiology, pregnancy is a unique window, with its physiological challenge highlighting defects in insulin resistance or insulin secretion, along with other metabolic abnormalities, that at-risk women carry before and after pregnancy, underpinning their underlying trajectory and progression towards type 2 diabetes and cardiovascular (figure 5).[35,160] This is certainly the case for women with pre-pregnancy impaired fasting glucose or impaired glucose tolerance as they are more likely to have early gestational diabetes. Assessment of glucose tolerance 12 months postpartum in gestational diabetes subtypes showed that the rate of pre-diabetes and diabetes were similar in insulin resistant gestational diabetes (30·9%) and insulin deficient gestational diabetes (27·6%), and both higher than in non-gestational diabetes pregnancy (10·4%).[160]

It is unclear whether pregnancy itself or gestational diabetes pregnancy can cause, or accelerate, the development of later maternal type 2 diabetes, or whether these conditions are entirely manifestations of a shared pathophysiological pathway, such as insulin resistance and impairment in insulin secretion. Such acceleration is hinted at by the observation that multiparity is associated with an increased risk of later maternal diabetes; however, any pregnancy-related pathogenic factors that could increase diabetes risk after pregnancy remain unknown.[202,203] A follow-up study comparing women (n=21) with and without an interval pregnancy (with a return to pre-pregnancy weight) showed no differences in

***Panel* 2: Gaps in knowledge in the pathophysiology of gestational diabetes**

Key gaps in knowledge for the new paradigm that gestational diabetes is a heterogenous condition with foundations for it commencing before pregnancy, often present in early pregnancy, which might benefit from targeted treatment, and that gestational diabetes consequences should be considered to follow a life course trajectory

Physiology and pathophysiology of glycaemic regulation in pregnancy

- Understanding the degree of insulin resistance and defects in insulin secretion present before pregnancy or in early pregnancy in women with early and late gestational diabetes, and the non-glycaemic factors contributing to the pathophysiological changes
- Better understanding of the heterogeneity of the pathophysiology of gestational diabetes, including among diverse ethnic groups

Pathophysiology of fetal hyperinsulinaemia

- Understanding the mechanisms (including timing) by which fetal islet β-cell nutrient-secretion coupling is altered in gestational diabetes pregnancies causing fetal hyperinsulinaemia

Role of the placenta in the context of gestational diabetes

- Understanding placental structural and functional development in the metabolic and inflammatory environment associated with early gestational diabetes and its pathophysiological subtypes, and how it influences a maternal glucose–insulin axis and fetal growth and development

Neonatal outcomes in the context of gestational diabetes

- Understanding the mechanisms behind the reduction in respiratory distress with early gestational diabetes treatment

Long-term maternal outcomes and fetal programming

- Understanding the mechanisms involved in long-term maternal and offspring outcomes, including epigenetics
- More long-term follow-up studies of maternal and offspring outcomes in diverse populations, for both early and late gestational diabetes exposure and treatment during pregnancy
- Long-term studies of whether early gestational diabetes might be an even greater risk marker of future long-term adverse outcomes in mothers and offspring compared with late gestational diabetes

maternal metabolic profile 1 year post-pregnancy using a hyperinsulinaemic–euglycaemic clamp, intravenous glucose tolerance test, indirect calorimetry, and body composition analysis suggesting no direct effect of a single pregnancy on future diabetes risk.[204] A study of 666 Latin American women with a history of gestational diabetes reported that an additional pregnancy (with or without gestational diabetes) increased the adjusted risk ratio of type 2 diabetes to 3·34 (95% CI 1·80–6·19; unadjusted for weight gain),[205] keeping in mind that weight gain was itself independently associated with an increased risk of type 2 diabetes with an adjusted risk ratio of 1·95 (95% CI 1·63–2·33) for each 10 lb (4·5 kg) gained during the approximate 7·5 year follow-up.[205] Thus, it was unclear whether the increased risk of type 2 diabetes was due to the additional pregnancy or weight gain in this specific study.[205] A potential role for altered metabolic and proinflammatory factors associated with a gestational diabetes pregnancy, and miRNAs in exosomes from placental dysfunction, is suggested by their lasting adverse effect on maternal organs (eg, pancreas, liver, and heart);[206] an observation supported by animal studies,[207] but with a need for confirmation in humans.

Conclusion

Contrary to the widely held historical view that gestational diabetes commences in late pregnancy, there is basic science and clinical evidence that gestational diabetes sets its pathophysiological foundations before pregnancy and that gestational diabetes can be present in early pregnancy, with the effects extending well beyond pregnancy via heterogenous metabolic pathways. Indeed, as more women enter pregnancy with obesity and some degree of abnormal glucose or insulin regulation, gestational diabetes is becoming a more complex disease. Women are more frequently presenting with insulin resistance and hyperglycaemia in early pregnancy, which even below type 2 diabetes glycaemic thresholds are likely to carry higher risks of congenital anomaly and miscarriage. Women are also presenting with a higher degree of hyperglycaemia (although less than overt diabetes), consistent with pre-existing dysglycaemia, which more frequently requires pharmacological treatment during pregnancy. Although gestational diabetes and type 2 diabetes in pregnancy are distinct diagnoses with different treatment strategies, this approach masks the facts that blood glucose is a continuous variable and is associated with a spectrum of risks in pregnancy from conception to delivery. Indeed, early gestational diabetes and type 2 diabetes share many common risk factors and could be considered as different levels of severity of the same pathophysiological process. Both conditions also have insulin-resistant and insulin-deficient subtypes. To address these population level changes and the new insights into early gestational diabetes, better strategies are now needed to fully understand (panel 2), and manage, the pre-pregnancy and early pregnancy changes in the mother and fetus, articulated with the rest of pregnancy and beyond birth.

Contributors

DS was responsible for the conceptualisation of all papers in this Series. All authors contributed to the original draft of different sections of this paper. M-FH, PC, CJN, GD, and AJ contributed to the conceptualisation of figures and all authors reviewed and edited the overall manuscript before submission.

Declaration of interests

KB received research funding and study devices from Medtronic for the investigator-initiated CRISTAL study; study devices from Dexcom for the investigator-initiated GLORIA-study; study medication from Novo Nordisk for the investigator-initiated SERENA study; consulting fees from AstraZeneca and Lilly; and serves on the speakers bureau for Novo Nordisk, AstraZeneca, and Mundipharma. DS received study devices on loan from Tandem for the CIRCUIT study; and speaker fees from Ascensia and Sanofi. M-FH, PC, HB, CJDM, CLM, GD, AJ, JI, CJN, UR, and AS declare no competing interests.

Acknowledgments

We thank Irune Pirrone (PhD student) for their assistance with graphical design.

References

1 Sweeting A, MacMillan F, Simmons D, TOBOGM Summit attendees. The first International Association of Diabetes and Pregnancy Study Groups summit on the diagnosis of gestational diabetes in early pregnancy: TOBOGM Summit report. *Aust N Z J Obstet Gynaecol* 2024; published online April 18. https://doi.org/10.1111/ajo.13823.

2 McIntyre HD, Sacks DA, Barbour LA, et al. Issues with the diagnosis and classification of hyperglycemia in early pregnancy. *Diabetes Care* 2016; **39:** 53–54.

3 No authors listed. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization guideline. *Diabetes Res Clin Pract* 2014; **103:** 341–63.

4 Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop–conference on gestational diabetes mellitus. *Diabetes Care* 1998; **21** (suppl 2)**:** B161–67.

5 Simmons D, Sweeting A. Defining gestational diabetes: not just about cutoffs. *Lancet Diabetes Endocrinol* 2023; **11:** 303–04.

6 Wang H, Li N, Chivese T, et al. IDF diabetes atlas: Estimation of global and regional gestational diabetes mellitus prevalence for 2021 by International Association of Diabetes in pregnancy study group's Criteria. *Diabetes Res Clin Pract* 2022; **183:** 109050.

7 Scheuer CM, Jensen DM, McIntyre HD, et al. Applying WHO2013 diagnostic criteria for gestational diabetes mellitus reveals currently untreated women at increased risk. *Acta Diabetol* 2023; **60:** 1663–73.

8 Saeedi M, Cao Y, Fadl H et al. Increasing prevalence of gestational diabetes mellitus when implementing the IADPSG criteria: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2021; **172:** 108642.

9 Sweeting A, Hannah W, Backman H, et al. Epidemiology and management of gestational diabetes. *Lancet* 2024; published online June 20. https://doi.org/10.1016/S0140-6736(24)00825-0.

10 Simmons D, Gupta Y, Hernandez TL, et al. Call to action for a life course approach. *Lancet* 2024; published online June 20. https://doi.org/10.1016/S0140-6736(24)00826-2.

11 Ye W, Luo C, Huang J, et al. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ* 2022; **377:** e067946.

12 Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009; **361:** 1339–48.

13 Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005; **352:** 2477–86.

14 Simmons D, Immanuel J, Hague WM, et al. Treatment of gestational diabetes mellitus diagnosed early in pregnancy. *N Engl J Med* 2023; **388:** 2132–44.

15 Xu T, Dainelli L, Yu K, et al. The short-term health and economic burden of gestational diabetes mellitus in China: a modelling study. *BMJ Open* 2017; **7:** e018893.

16 Dall TM, Yang W, Gillespie K, et al. The economic burden of elevated blood glucose levels in 2017: diagnosed and undiagnosed diabetes, gestational diabetes mellitus, and prediabetes. *Diabetes Care* 2019; **42:** 1661–68.

17 Immanuel J, Simmons D. Screening and treatment for early-onset gestational diabetes mellitus: a systematic review and meta-analysis. *Curr Diab Rep* 2017; **17:** 115.

18 Hannah W, Bhavadharini B, Beks H, et al. Global burden of early pregnancy gestational diabetes mellitus (eGDM): a systematic review. *Acta Diabetol* 2022; **59:** 403–27.

19 Sweeting AN, Ross GP, Hyett J, et al. Gestational diabetes mellitus in early pregnancy: evidence for poor pregnancy outcomes despite treatment. *Diabetes Care* 2016; **39:** 75–81.

20 Magliano D, Boyko E, Balkau B, et al. IDF diabetes atlas, 10th edn. Brussels: International Diabetes Federation, 2021.

21 Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; **358:** 1991–2002.

22 Riskin-Mashiah S, Younes G, Damti A, Auslender R. First-trimester fasting hyperglycemia and adverse pregnancy outcomes. *Diabetes Care* 2009; **32:** 1639–43.

23 Dunne F, Newman C, Alvarez-Iglesias A, et al. Early metformin in gestational diabetes: a randomized clinical trial. *JAMA* 2023; **330:** 1547–56.

24 Lowe WL Jr, Scholtens DM, Kuang A, et al. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal gestational diabetes mellitus and childhood glucose metabolism. *Diabetes Care* 2019; **42:** 372–80.

25 Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. *Diabetologia* 2019; **62:** 905–14.

26 Bardugo A, Bendor CD, Rotem RS, et al. Glucose intolerance in pregnancy and risk of early-onset type 2 diabetes: a population-based cohort study. *Lancet Diabetes Endocrinol* 2023; **11:** 333–44.

27 Francis EC, Powe CE, Lowe WL Jr, et al. Refining the diagnosis of gestational diabetes mellitus: a systematic review and meta-analysis. *Commun Med* 2023; **3:** 185.

28 Meek CL, Simmons D. Timing of gestational diabetes diagnosis: a novel precision approach to hyperglycaemia in pregnancy? *Diabet Med* 2023; **40:** e15191.

29 Tobias DK, Merino J, Ahmad A, et al. Second international consensus report on gaps and opportunities for the clinical translation of precision diabetes medicine. *Nat Med* 2023; **29:** 2438–57.

30 Catalano PM, Tyzbir ED, Wolfe RR, et al. Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. *Am J Physiol* 1993; **264:** E60–67.

31 Powe CE, Huston Presley LP, Locascio JJ, Catalano PM. Augmented insulin secretory response in early pregnancy. *Diabetologia* 2019; **62:** 1445–52.

32 Lain KY, Catalano PM. Metabolic changes in pregnancy. *Clin Obstet Gynecol* 2007; **50:** 938–48.

33 Thaweethai T, Soetan Z, James K, Florez JC, Powe CE. Distinct insulin physiology trajectories in euglycemic pregnancy and gestational diabetes mellitus. *Diabetes Care* 2023; **46:** 2137–46.

34 Buchanan TA, Xiang AH. Gestational diabetes mellitus. *J Clin Invest* 2005; **115:** 485–91.

35 Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. *Lancet* 2011; **378:** 169–81.

36 Benhalima K, Van Crombrugge P, Moyson C, et al. Characteristics and pregnancy outcomes across gestational diabetes mellitus subtypes based on insulin resistance. *Diabetologia* 2019; **62:** 2118–28.

37 Immanuel J, Simmons D, Harreiter J, et al. Metabolic phenotypes of early gestational diabetes mellitus and their association with adverse pregnancy outcomes. *Diabet Med* 2021; **38:** e14413.

38 Liu Y, Hou W, Meng X, et al. Heterogeneity of insulin resistance and beta cell dysfunction in gestational diabetes mellitus: a prospective cohort study of perinatal outcomes. *J Transl Med* 2018; **16:** 289.

39 Pan Q, Yang Y, Cao H, et al. Contribution of insulin resistance and β cell dysfunction to gestational diabetes stratified for pre-pregnant body mass index. *Reprod Sci* 2024; **31:** 1151–58.

40 Powe CE, Allard C, Battista MC, et al. Heterogeneous contribution of insulin sensitivity and secretion defects to gestational diabetes mellitus. *Diabetes Care* 2016; **39:** 1052–55.

41 Selen DJ, Edelson PK, James K, et al. Physiological subtypes of gestational glucose intolerance and risk of adverse pregnancy outcomes. *Am J Obstet Gynecol* 2022; **226:** 241e.1–14.

42 Alvarado FL, O'Tierney-Ginn P, Catalano P. Contribution of gestational weight gain on maternal glucose metabolism in women with GDM and normal glucose tolerance. *J Endocr Soc* 2020; **5:** bvaa195.

43 Rojas-Rodriguez R, Price LL, Somogie J, et al. Maternal lipid metabolism is associated with neonatal adiposity: a longitudinal study. *J Clin Endocrinol Metab* 2022; **107:** e3759–68.

44 Waters TP, Kim SY, Sharma AJ, et al. Longitudinal changes in glucose metabolism in women with gestational diabetes, from late pregnancy to the postpartum period. *Diabetologia* 2020; **63:** 385–94.

45 Elliott A, Walters RK, Pirinen M, et al. Distinct and shared genetic architectures of gestational diabetes mellitus and type 2 diabetes mellitus. *medRxiv* 2023; published online Feb 23. https://doi.org/10.1101/2023.02.16.23286014 (preprint).

46 Hayes MG, Urbanek M, Hivert MF, et al. Identification of HKDC1 and BACE2 as genes influencing glycemic traits during pregnancy through genome-wide association studies. *Diabetes* 2013; **62:** 3282–91.

47 Pervjakova N, Moen GH, Borges MC, et al. Multi-ancestry genome-wide association study of gestational diabetes mellitus highlights genetic links with type 2 diabetes. *Hum Mol Genet* 2022; **31:** 3377–91.

48 Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM. Tumor necrosis factor alpha inhibits signaling from the insulin receptor. *Proc Natl Acad Sci USA* 1994; **91:** 4854–58.

49 Nair S, Ormazabal V, Lappas M, et al. Extracellular vesicles and their potential role inducing changes in maternal insulin sensitivity during gestational diabetes mellitus. *Am J Reprod Immunol* 2021; **85:** e13361.

50 Barbour LA, Hernandez TL. Maternal non-glycemic contributors to fetal growth in obesity and gestational diabetes: spotlight on lipids. *Curr Diab Rep* 2018; **18:** 37.

51 Kirwan JP, Hauguel-De Mouzon S, Lepercq J, et al. TNF-alpha is a predictor of insulin resistance in human pregnancy. *Diabetes* 2002; **51:** 2207–13.

52 Lee K, Kuang A, Bain JR, et al. Metabolomic and genetic architecture of gestational diabetes subtypes. *Diabetologia* 2024; **67:** 895–907.

53 Lapolla A, Dalfrà MG, Fedele D. Diabetes related autoimmunity in gestational diabetes mellitus: is it important? *Nutr Metab Cardiovasc Dis* 2009; **19:** 674–82.

54 Oztekin O. New insights into the pathophysiology of gestational diabetes mellitus: possible role of human leukocyte antigen-G. *Med Hypotheses* 2007; **69:** 526–30.

55 Dickens LT, Letourneau LR, Sanyoura M, et al. Management and pregnancy outcomes of women with GCK-MODY enrolled in the US monogenic diabetes registry. *Acta Diabetol* 2019; **56:** 405–11.

56 Kim JH, Delghingaro-Augusto V, Chan JY, et al. The role of fatty acid signaling in islet beta-cell adaptation to normal pregnancy. *Front Endocrinol* 2022; **12:** 799081.

57 Rawn SM, Huang C, Hughes M, et al. Pregnancy hyperglycemia in prolactin receptor mutant, but not prolactin mutant, mice and feeding-responsive regulation of placental lactogen genes implies placental control of maternal glucose Homeostasis. *Biol Reprod* 2015; **93:** 75.

58 Maltepe E, Fisher SJ. Placenta: the forgotten organ. *Annu Rev Cell Dev Biol* 2015; **31:** 523–52.

59 Desoye G. The human placenta in diabetes and obesity: friend or foe? The 2017 Norbert Freinkel Award lecture. *Diabetes Care* 2018; **41:** 1362–69.

60 Chen Z, Dean M. Endometrial glucose metabolism during early pregnancy. *Reprod Fertil* 2023; **4:** e230016.

61 Gou R, Zhang X. Glycolysis: a fork in the path of normal and pathological pregnancy. *FASEB J* 2023; **37:** e23263.

62 Wu Y, Liu B, Sun Y, et al. Association of maternal prepregnancy diabetes and gestational diabetes mellitus with congenital anomalies of the newborn. *Diabetes Care* 2020; **43:** 2983–90.

63 Li Q, Wang H, Sun L, et al. The mediating role of inflammation in the association between pregnancy loss history and gestational diabetes mellitus. *Diabetol Metab Syndr* 2023; **15:** 132.

64 Björk O, Persson B, Stangenberg M, Václavínková V. Spiral artery lesions in relation to metabolic control in diabetes mellitus. *Acta Obstet Gynecol Scand* 1984; **63:** 123–27.

65 Ehlers E, Talton OO, Schust DJ, Schulz LC. Placental structural abnormalities in gestational diabetes and when they develop: a scoping review. *Placenta* 2021; **116:** 58–66.

66 Hufnagel A, Dearden L, Fernandez-Twinn DS, Ozanne SE. Programming of cardiometabolic health: the role of maternal and fetal hyperinsulinaemia. *J Endocrinol* 2022; **253:** R47–63.

67 Higa R, Leonardi ML, Jawerbaum A. Intrauterine programming of cardiovascular diseases in maternal diabetes. *Front Physiol* 2021; **12:** 760251.

68 Björk O, Persson B. Placental changes in relation to the degree of metabolic control in diabetes mellitus. *Placenta* 1982; **3:** 367–78.

69 Majali-Martinez A, Weiss-Fuchs U, Miedl H, et al. Type 1 diabetes mellitus and the first trimester placenta: hyperglycemia-induced effects on trophoblast proliferation, cell cycle regulators, and invasion. *Int J Mol Sci* 2021; **22:** 10989.

70 Rice GE, Scholz-Romero K, Sweeney E, et al. The effect of glucose on the release and bioactivity of exosomes from first trimester trophoblast cells. *J Clin Endocrinol Metab* 2015; **100:** E1280–88.

71 Burton GJ, Cindrova-Davies T, Turco MY. Review: histotrophic nutrition and the placental-endometrial dialogue during human early pregnancy. *Placenta* 2020; **102:** 21–26.

72 Jones CJ, Choudhury RH, Aplin JD. Tracking nutrient transfer at the human maternofetal interface from 4 weeks to term. *Placenta* 2015; **36:** 372–80.

73 Guo XY, Shu J, Fu XH, et al. Improving the effectiveness of lifestyle interventions for gestational diabetes prevention: a meta-analysis and meta-regression. *BJOG* 2019; **126:** 311–20.

74 Antoniotti GS, Coughlan M, Salamonsen LA, Evans J. Obesity associated advanced glycation end products within the human uterine cavity adversely impact endometrial function and embryo implantation competence. *Hum Reprod* 2018; **33:** 654–65.

75 Groen B, Links TP, van den Berg PP, de Vos P, Faas MM. The role of autoimmunity in women with type 1 diabetes and adverse pregnancy outcome: a missing link. *Immunobiology* 2019; **224:** 334–38.

76 Roberti SL, Gatti CR, Capobianco E, Higa R, Jawerbaum A. Peroxisome proliferator-activated receptor pathways in diabetic rat decidua early after implantation: regulation by dietary polyunsaturated fatty acids. *Reprod Biomed Online* 2023; **46:** 659–72.

77 Duval F, Dos Santos E, Maury B, et al. Adiponectin regulates glycogen metabolism at the human fetal–maternal interface. *J Mol Endocrinol* 2018; **61:** 139–52.

78 Hjort L, Novakovic B, Cvitic S, et al. Placental DNA methylation in pregnancies complicated by maternal diabetes and/or obesity: state of the art and research gaps. *Epigenetics* 2022; **17:** 2188–208.

79 Burton GJ, Jauniaux E. The human placenta: new perspectives on its formation and function during early pregnancy. *Proc Biol Sci* 2023; **290:** 20230191.

80 Hoch D, Gauster M, Hauguel-de Mouzon S, Desoye G. Diabesity-associated oxidative and inflammatory stress signalling in the early human placenta. *Mol Aspects Med* 2019; **66:** 21–30.

81 Pinto Y, Frishman S, Turjeman S, et al. Gestational diabetes is driven by microbiota-induced inflammation months before diagnosis. *Gut* 2023; **72:** 918–28.

82 Heim KR, Mulla MJ, Potter JA, et al. Excess glucose induce trophoblast inflammation and limit cell migration through HMGB1 activation of Toll-Like receptor 4. *Am J Reprod Immunol* 2018; **80:** e13044.

83 Jawerbaum A, González E. Diabetic pregnancies: the challenge of developing in a pro-inflammatory environment. *Curr Med Chem* 2006; **13:** 2127–38.

84 Kalagiri RR, Carder T, Choudhury S, et al. Inflammation in complicated pregnancy and its outcome. *Am J Perinatol* 2016; **33:** 1337–56.

85 Lappas M, Hiden U, Desoye G, Froehlich J, Hauguel-de Mouzon S, Jawerbaum A. The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. *Antioxid Redox Signal* 2011; **15:** 3061–100.

86 Qin Y, McCauley N, Ding Z, et al. Hyperglycemia results in significant pathophysiological changes of placental spiral artery remodeling and angiogenesis, further contributing to congenital defects. *Front Biosci* 2021; **26:** 965–76.

87 Lombardo MF, De Angelis F, Bova L, et al. Human placental lactogen (hPL-A) activates signaling pathways linked to cell survival and improves insulin secretion in human pancreatic islets. *Islets* 2011; **3:** 250–58.

88 Retnakaran R, Ye C, Kramer CK, et al. Evaluation of circulating determinants of beta-cell function in women with and without gestational diabetes. *J Clin Endocrinol Metab* 2016; **101:** 2683–91.

89 Simpson S, Smith L, Bowe J. Placental peptides regulating islet adaptation to pregnancy: clinical potential in gestational diabetes mellitus. *Curr Opin Pharmacol* 2018; **43:** 59–65.

90 Bowe JE, Hill TG, Hunt KF, et al. A role for placental kisspeptin in β cell adaptation to pregnancy. *JCI Insight* 2019; **4:** e124540.

91 Donovan BM, Nidey NL, Jasper EA, et al. First trimester prenatal screening biomarkers and gestational diabetes mellitus: a systematic review and meta-analysis. *PLoS One* 2018; **13:** e0201319.

92 Parkash J, Lei Z, Rao CV. The presence of human chorionic gonadotropin/luteinizing hormone receptors in pancreatic β-cells. *Reprod Sci* 2015; **22:** 1000–07.

93 Wang Y, Yuan Y, Shen S, Ge Z, Zhu D, Bi Y. Placenta-derived exosomes exacerbate beta cell dysfunction in gestational diabetes mellitus through delivery of miR-320b. *Front Endocrinol* 2024; **14:** 1282075.

94 McIntyre HD, Serek R, Crane DI, et al. Placental growth hormone (GH), GH-binding protein, and insulin-like growth factor axis in normal, growth-retarded, and diabetic pregnancies: correlations with fetal growth. *J Clin Endocrinol Metab* 2000; **85:** 1143–50.

95 Hivert MF, White F, Allard C, et al. Placental IGFBP1 levels during early pregnancy and the risk of insulin resistance and gestational diabetes. *Nat Med* 2024; published online April 16. https://doi.org/10.1038/s41591-024-02936-5.

96 Elliott HR, Sharp GC, Relton CL, Lawlor DA. Epigenetics and gestational diabetes: a review of epigenetic epidemiology studies and their use to explore epigenetic mediation and improve prediction. *Diabetologia* 2019; **62:** 2171–78.

97 Légaré C, Desgagné V, Poirier C, et al. First trimester plasma microRNAs levels predict Matsuda Index-estimated insulin sensitivity between 24th and 29th week of pregnancy. *BMJ Open Diabetes Res Care* 2022; **10:** e002703.

98 Yu Y, He JH, Hu LL, et al. Placensin is a glucogenic hormone secreted by human placenta. *EMBO Rep* 2020; **21:** e49530.

99 Hiden U, Maier A, Bilban M, et al. Insulin control of placental gene expression shifts from mother to foetus over the course of pregnancy. *Diabetologia* 2006; **49:** 123–31.

100 Lassance L, Miedl H, Absenger M, et al. Hyperinsulinemia stimulates angiogenesis of human fetoplacental endothelial cells: a possible role of insulin in placental hypervascularization in diabetes mellitus. *J Clin Endocrinol Metab* 2013; **98:** e1438–47.

101 Jones CJ, Desoye G. Glycogen distribution in the capillaries of the placental villus in normal, overt and gestational diabetic pregnancy. *Placenta* 1993; **14:** 505–17.

102 Desoye G, Wells JCK. Pregnancies in diabetes and obesity: the capacity-load model of placental adaptation. *Diabetes* 2021; **70:** 823–30.

103 Desoye G, Carter AM. Fetoplacental oxygen homeostasis in pregnancies with maternal diabetes mellitus and obesity. *Nat Rev Endocrinol* 2022; **18:** 593–607.

104 Augsten M, Hackl H, Ebner B, et al. Fetal HDL/apoE: a novel regulator of gene expression in human placental endothelial cells. *Physiol Genomics* 2011; **43:** 1255–62.

105 Sun Y, Kopp S, Strutz J, et al. Gestational diabetes mellitus modulates cholesterol homeostasis in human fetoplacental endothelium. *Biochim Biophys Acta Mol Cell Biol Lipids* 2018; **1863:** 968–79.

106 Carrasco-Wong I, Moller A, Giachini FR, et al. Placental structure in gestational diabetes mellitus. *Biochim Biophys Acta Mol Basis Dis* 2020; **1866:** 165535.

107 Dahlstrom JE, Nolan CJ, Desoye G. Maternal diabetes and obesity. In: Baergen RN, Burton GJ, Kaplan CG, eds. Benirschke's pathology of the human placenta, 7th edn. Switzerland: Springer Nature; 2022: 555–75.

108 Desoye G, Cervar-Zivkovic M. Diabetes mellitus, obesity, and the placenta. *Obstet Gynecol Clin North Am* 2020; **47:** 65–79.

109 Desoye G, Hauguel-de Mouzon S. The human placenta in gestational diabetes mellitus. The insulin and cytokine network. *Diabetes Care* 2007; **30** (suppl 2)**:** S120–26.

110 Gauster M, Desoye G, Tötsch M, Hiden U. The placenta and gestational diabetes mellitus. *Curr Diab Rep* 2012; **12:** 16–23.

111 Higa R, Jawerbaum A. Intrauterine effects of impaired lipid homeostasis in pregnancy diseases. *Curr Med Chem* 2013; **20:** 2338–50.

112 Hjort L, Novakovic B, Grunnet LG, et al. Diabetes in pregnancy and epigenetic mechanisms-how the first 9 months from conception might affect the child's epigenome and later risk of disease. *Lancet Diabetes Endocrinol* 2019; **7:** 796–806.

113 Jawerbaum A, Capobianco E. Review: effects of PPAR activation in the placenta and the fetus: implications in maternal diabetes. *Placenta* 2011; **32** (suppl 2): S212–17.

114 Lizárraga D, García-Gasca A. The placenta as a target of epigenetic alterations in women with gestational diabetes mellitus and potential implications for the offspring. *Epigenomes* 2021; **5:** 13.

115 van Poppel MNM, Damm P, Mathiesen ER, Ringholm L, Zhang C, Desoye G. Is the biphasic effect of diabetes and obesity on fetal growth a risk factor for childhood obesity? *Diabetes Care* 2023; **46:** 1124–31.

116 Desoye G, Ringholm L, Damm P, Mathiesen ER, van Poppel MNM. Secular trend for increasing birthweight in offspring of pregnant women with type 1 diabetes: is improved placentation the reason? *Diabetologia* 2023; **66:** 33–43.

117 McElwee ER, Oliver EA, McFarling K, et al. Risk of stillbirth in pregnancies complicated by diabetes, stratified by fetal growth. *Obstet Gynecol* 2023; **141:** 801–09.

118 Freinkel N. Banting Lecture 1980. Of pregnancy and progeny. *Diabetes* 1980; **29:** 1023–35.

119 McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. *Nat Rev Dis Primers* 2019; **5:** 47.

120 Fadl HE, Gärdefors S, Hjertberg R, et al. Randomized controlled study in pregnancy on treatment of marked hyperglycemia that is short of overt diabetes. *Acta Obstet Gynecol Scand* 2015; **94:** 1181–87.

121 Crowther CA, Samuel D, McCowan LME, Edlin R, Tran T, McKinlay CJ. Lower versus higher glycemic criteria for diagnosis of gestational diabetes. *N Engl J Med* 2022; **387:** 587–98.

122 Yu Y, Arah OA, Liew Z, et al. Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: population based cohort study with 40 years of follow-up. *BMJ* 2019; **367:** l6398.

123 Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis. *J Dev Orig Health Dis* 2020; **11:** 599–616.

124 Aguilera J, Semmler J, Anzoategui S, Zhang H, Nicolaides KH, Charakida M. Cardiac function in gestational diabetes mellitus: a longitudinal study from fetal life to infancy. *BJOG* 2021; **128:** 272–79.

125 Adane AA, Mishra GD, Tooth LR. Diabetes in pregnancy and childhood cognitive development: a systematic review. *Pediatrics* 2016; **137:** e20154234.

126 Faleschini S, Doyon M, Arguin M, et al. Maternal hyperglycemia in pregnancy and offspring internalizing and externalizing behaviors. *Matern Child Health J* 2023; **27:** 1765–73.

127 Griffith RJ, Harding JE, McKinlay CJD, Wouldes TA, Harris DL, Alsweiler JM. Maternal glycemic control in diabetic pregnancies and neurodevelopmental outcomes in preschool aged children. A prospective cohort study. *Early Hum Dev* 2019; **130:** 101–08.

128 Hanson MA, Skinner MK. Developmental origins of epigenetic transgenerational inheritance. *Environ Epigenet* 2016; **2:** dvw002.

129 Hughes AE, De Franco E, Freathy RM, Fetal Insulin and Growth Consortium, Flanagan SE, Hattersley AT. Monogenic disease analysis establishes that fetal insulin accounts for half of human fetal growth. *J Clin Invest* 2023; **133:** e165402.

130 Loegl J, Hiden U, Nussbaumer E, et al. Hofbauer cells of M2a, M2b and M2c polarization may regulate feto-placental angiogenesis. *Reproduction* 2016; **152:** 447–55.

131 Desoye G, Herrera E. Adipose tissue development and lipid metabolism in the human fetus: the 2020 perspective focusing on maternal diabetes and obesity. *Prog Lipid Res* 2021; **81:** 101082.

132 Brumbaugh DE, Tearse P, Cree-Green M, et al. Intrahepatic fat is increased in the neonatal offspring of obese women with gestational diabetes. *J Pediatr* 2013; **162:** 930–6.e1.

133 Alsweiler JM, Harris DL, Harding JE, McKinlay CJD. Strategies to improve neurodevelopmental outcomes in babies at risk of neonatal hypoglycaemia. *Lancet Child Adolesc Health* 2021; **5:** 513–23.

134 Metzger BE, Persson B, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. *Pediatrics* 2010; **126:** e1545–52.

135 Desoye G, Nolan CJ. The fetal glucose steal: an underappreciated phenomenon in diabetic pregnancy. *Diabetologia* 2016; **59:** 1089–94.

136 Reiher H, Fuhrmann K, Noack S, et al. Age-dependent insulin secretion of the endocrine pancreas in vitro from fetuses of diabetic and nondiabetic patients. *Diabetes Care* 1983; **6:** 446–51.

137 Otonkoski T, Andersson S, Knip M, Simell O. Maturation of insulin response to glucose during human fetal and neonatal development. Studies with perifusion of pancreatic isletlike cell clusters. *Diabetes* 1988; **37:** 286–91.

138 Nolan CJ, Desoye G. Disentangling fetal insulin hypersecretion and insulin resistance. *Trends Endocrinol Metab* 2024; published online May 1. https://doi.org/10.1016/j.tem.2024.04.008.

139 Carpenter MW, Canick JA, Hogan JW, Shellum C, Somers M, Star JA. Amniotic fluid insulin at 14-20 weeks' gestation: association with later maternal glucose intolerance and birth macrosomia. *Diabetes Care* 2001; **24:** 1259–63.

140 Eder M, Csapo B, Wadsack C, et al. Sex differences in the association of cord blood insulin with subcutaneous adipose tissue in neonates. *Int J Obes* 2016; **40:** 538–42.

141 Logan KM, Gale C, Hyde MJ, Santhakumaran S, Modi N. Diabetes in pregnancy and infant adiposity: systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2017; **102:** F65–72.

142 van Poppel MNM, Nolan CJ, Desoye G. Pancreas agenesis and fetal growth: a semi-quantitative analysis. *Endocr Connect* 2024; **13:** e230500.

143 Bailey MJ, Rout A, Harding JE, Alsweiler JM, Cutfield WS, McKinlay CJD. Prolonged transitional neonatal hypoglycaemia: characterisation of a clinical syndrome. *J Perinatol* 2021; **41:** 1149–57.

144 Chen J, Xiao H, Yang Y, et al. Demographic and clinical features of small-for-gestational-age infants born to mothers with gestational diabetes mellitus. *Front Pediatr* 2021; **9:** 741793.

145 Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. *Lancet* 1993; **341:** 938–41.

146 Neimark E, Wainstock T, Sheiner E, Fischer L, Pariente G. Long-term cardiovascular hospitalizations of small for gestational age (SGA) offspring born to women with and without gestational diabetes mellitus (GDM)[‡]. *Gynecol Endocrinol* 2019; **35:** 518–24.

147 Catalano PM, Mele L, Landon MB, et al. Inadequate weight gain in overweight and obese pregnant women: what is the effect on fetal growth? *Am J Obstet Gynecol* 2014; **211:** 137.e1–7.

148 Drever HJ, Davidson SJ, Callaway LK, Sekar R, Jersey SJDE. Factors associated with higher risk of small-for-gestational-age infants in women treated for gestational diabetes. *Aust N Z J Obstet Gynaecol* 2023; **63:** 714–20.

149 Apostolopoulou A, Tranidou A, Chroni V, et al. Association of maternal diet with infant birthweight in women with gestational diabetes mellitus. *Nutrients* 2023; **15:** 4545.

150 Prentice PM, Olga L, Petry CJ, et al. Reduced size at birth and persisting reductions in adiposity in recent, compared with earlier, cohorts of infants born to mothers with gestational diabetes mellitus. *Diabetologia* 2019; **62:** 1977–87.

151 Edwards MO, Kotecha SJ, Kotecha S. Respiratory distress of the term newborn infant. *Paediatr Respir Rev* 2013; **14:** 29–36.

152 Mortier I, Blanc J, Tosello B, Gire C, Bretelle F, Carcopino X. Is gestational diabetes an independent risk factor of neonatal severe respiratory distress syndrome after 34 weeks of gestation? A prospective study. *Arch Gynecol Obstet* 2017; **296:** 1071–77.

153 Zimmermann LJ, Janssen DJ, Tibboel D, Hamvas A, Carnielli VP. Surfactant metabolism in the neonate. *Biol Neonate* 2005; **87:** 296–307.

154 Dekowski SA, Snyder JM. The combined effects of insulin and cortisol on surfactant protein mRNA levels. *Pediatr Res* 1995; **38:** 513–21.

155 McGillick EV, Morrison JL, McMillen IC, Orgeig S. Intrafetal glucose infusion alters glucocorticoid signaling and reduces surfactant protein mRNA expression in the lung of the late-gestation sheep fetus. *Am J Physiol Regul Integr Comp Physiol* 2014; **307:** R538–45.

156 Rehman S, Bacha D. Embryology, pulmonary. In: StatPearls. Treasure Island, FL: StatPearls Publishing, 2023.

157 Chen P, Gu M, Wan S, et al. Gestational diabetes mellitus impedes fetal lung development through exosome-dependent crosstalk between trophoblasts and lung epithelial cells. *Int J Nanomedicine* 2023; **18:** 641–57.

158 Marunaka Y, Niisato N, O'Brodovich H, Post M, Tanswell AK. Roles of Ca2+ and protein tyrosine kinase in insulin action on cell volume via Na+ and K+ channels and Na+/K+/2Cl- cotransporter in fetal rat alveolar type II pneumocyte. *J Membr Biol* 1999; **168:** 91–101.

159 Quansah DY, Gross J, Gilbert L, et al. Cardiometabolic and mental health in women with early gestational diabetes mellitus: a prospective cohort study. *J Clin Endocrinol Metab* 2022; **107:** e996–1008.

160 Retnakaran R, Ye C, Hanley AJ, Connelly PW, Sermer M, Zinman B. Subtypes of gestational diabetes and future risk of pre-diabetes or diabetes. *EClinicalMedicine* 2021; **40:** 101087.

161 Jawerbaum A, White V. Review on intrauterine programming: consequences in rodent models of mild diabetes and mild fat overfeeding are not mild. *Placenta* 2017; **52:** 21–32.

162 Inzani I, Ozanne SE. Programming by maternal obesity: a pathway to poor cardiometabolic health in the offspring. *Proc Nutr Soc* 2022; **81:** 227–42.

163 Tain YL, Hsu CN, Chan JY. PPARs link early life nutritional insults to later programmed hypertension and metabolic syndrome. *Int J Mol Sci* 2015; **17:** 20.

164 Lowe WL Jr, Scholtens DM, Lowe LP, et al. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. *JAMA* 2018; **320:** 1005–16.

165 Nijs H, Benhalima K. Gestational diabetes mellitus and the long-term risk for glucose intolerance and overweight in the offspring: a narrative review. *J Clin Med* 2020; **9:** 599.

166 Kaseva N, Vääräsmäki M, Matinolli HM, et al. Pre-pregnancy overweight or obesity and gestational diabetes as predictors of body composition in offspring twenty years later: evidence from two birth cohort studies. *Int J Obes* 2018; **42:** 872–79.

167 Lowe WL Jr, Lowe LP, Kuang A, et al. Maternal glucose levels during pregnancy and childhood adiposity in the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study. *Diabetologia* 2019; **62:** 598–610.

168 Grunnet LG, Hansen S, Hjort L, et al. Adiposity, dysmetabolic traits, and earlier onset of female puberty in adolescent offspring of women with gestational diabetes mellitus: a clinical study within the Danish national birth cohort. *Diabetes Care* 2017; **40:** 1746–55.

169 Tam WH, Ma RC, Yang X, et al. Glucose intolerance and cardiometabolic risk in adolescents exposed to maternal gestational diabetes: a 15-year follow-up study. *Diabetes Care* 2010; **33:** 1382–84.

170 Bendor CD, Bardugo A, Rotem RS, et al. Glucose intolerance in pregnancy and offspring obesity in late adolescence. *Diabetes Care* 2022; **45:** 1540–48.

171 Josefson JL, Catalano PM, Lowe WL, et al. The joint associations of maternal BMI and glycemia with childhood adiposity. *J Clin Endocrinol Metab* 2020; **105:** 2177–88.

172 Francis EC, Kechris K, Jansson T, Dabelea D, Perng W. Novel metabolic subtypes in pregnant women and risk of early childhood obesity in pffspring. *JAMA Netw Open* 2023; **6:** e237030.

173 Gillman MW, Oakey H, Baghurst PA, Volkmer RE, Robinson JS, Crowther CA. Effect of treatment of gestational diabetes mellitus on obesity in the next generation. *Diabetes Care* 2010; **33:** 964–68.

174 Landon MB, Rice MM, Varner MW, et al. Mild gestational diabetes mellitus and long-term child health. *Diabetes Care* 2015; **38:** 445–52.

175 García-Patterson A, Balsells M, Solà I, Gich I, Corcoy R. Impact of gestational diabetes mellitus treatment on medium/long-term outcomes after pregnancy: a systematic review and meta-analysis. *Diabet Med* 2023; **40:** e14998.

176 Tyrrell J, Richmond RC, Palmer TM, et al. Genetic evidence for causal relationships between maternal obesity-related traits and birth weight. *JAMA* 2016; **315:** 1129–40.

177 Clausen TD, Mortensen EL, Schmidt L, et al. Cognitive function in adult offspring of women with gestational diabetes–the role of glucose and other factors. *PLoS One* 2013; **8:** e67107.

178 Heldarskard GF, Spangmose AL, Henningsen AA, et al. Academic performance in adolescents born to mothers with gestational diabetes–a national Danish cohort study. *J Clin Endocrinol Metab* 2021; **106:** e4554–64.

179 Shah R, Harding J, Brown J, McKinlay C. Neonatal glycaemia and neurodevelopmental outcomes: a systematic review and meta-analysis. *Neonatology* 2019; **115:** 116–26.

180 Xiang AH, Wang X, Martinez MP, et al. Association of maternal diabetes with autism in offspring. *JAMA* 2015; **313:** 1425–34.

181 Chen S, Persson M, Wang R, et al. Random capillary glucose levels throughout pregnancy, obstetric and neonatal outcomes, and long-term neurodevelopmental conditions in children: a group-based trajectory analysis. *BMC Med* 2023; **21:** 260.

182 Edwards T, Alsweiler JM, Gamble GD, et al. Neurocognitive outcomes at age 2 years after neonatal hypoglycemia in a cohort of participants from the hPOD randomized trial. *JAMA Netw Open* 2022; **5:** e2235989.

183 Ruchat SM, Hivert MF, Bouchard L. Epigenetic programming of obesity and diabetes by in utero exposure to gestational diabetes mellitus. *Nutr Rev* 2013; **71** (suppl 1)**:** S88–94.

184 Ornoy A, Reece EA, Pavlinkova G, Kappen C, Miller RK. Effect of maternal diabetes on the embryo, fetus, and children: congenital anomalies, genetic and epigenetic changes and developmental outcomes. *Birth Defects Res C Embryo Today* 2015; **105:** 53–72.

185 Ding Q, Gao Z, Chen K, Zhang Q, Hu S, Zhao L. Inflammation-related epigenetic modification: the bridge between immune and metabolism in type 2 diabetes. *Front Immunol* 2022; **13:** 883410.

186 Cardenas A, Gagné-Ouellet V, Allard C, et al. Placental DNA methylation adaptation to maternal glycemic response in pregnancy. *Diabetes* 2018; **67:** 1673–83.

187 Howe CG, Cox B, Fore R, et al. Maternal gestational diabetes mellitus and newborn DNA methylation: findings from the pregnancy and childhood epigenetics consortium. *Diabetes Care* 2020; **43:** 98–105.

188 Taschereau A, Thibeault K, Allard C, et al. Maternal glycemia in pregnancy is longitudinally associated with blood DNAm variation at the FSD1L gene from birth to 5 years of age. *Clin Epigenetics* 2023; **15:** 107.

189 Tobi EW, Juvinao-Quintero DL, Ronkainen J, et al. Maternal glycemic dysregulation during pregnancy and neonatal blood DNA methylation: meta-analyses of epigenome-wide association studies. *Diabetes Care* 2022; **45:** 614–23.

190 Antoun E, Kitaba NT, Titcombe P, et al. Maternal dysglycaemia, changes in the infant's epigenome modified with a diet and physical activity intervention in pregnancy: secondary analysis of a randomised control trial. *PLoS Med* 2020; **17:** e1003229.

191 Kasuga Y, Kawai T, Miyakoshi K, et al. DNA methylation analysis of cord blood samples in neonates born to gestational diabetes mothers diagnosed before 24 gestational weeks. *BMJ Open Diabetes Res Care* 2022; **10:** e002539.

192 Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 2009; **373:** 1773–79.

193 Benhalima K, Lens K, Bosteels J, Chantal M. The risk for glucose intolerance after gestational diabetes mellitus since the introduction of the IADPSG criteria: a systematic review and meta-analysis. *J Clin Med* 2019; **8:** 1431.

194 Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. *BMJ* 2020; **369:** m1361.

195 Ratner RE, Christophi CA, Metzger BE, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008; **93:** 4774–79.

196 Pathirana MM, Lassi ZS, Ali A, Arstall MA, Roberts CT, Andraweera PH. Association between metabolic syndrome and gestational diabetes mellitus in women and their children: a systematic review and meta-analysis. *Endocrine* 2021; **71:** 310–20.

197 Retnakaran R, Shah BR. Role of type 2 diabetes in determining retinal, renal, and cardiovascular outcomes in women with previous gestational diabetes mellitus. *Diabetes Care* 2017; **40:** 101–08.

198 Retnakaran R, Shah BR. Glucose screening in pregnancy and future risk of cardiovascular disease in women: a retrospective, population-based cohort study. *Lancet Diabetes Endocrinol* 2019; **7:** 378–84.

199 Gunderson EP, Sun B, Catov JM, et al. Gestational diabetes history and glucose tolerance after pregnancy associated with coronary artery calcium in women during midlife: the CARDIA study. *Circulation* 2021; **143:** 974–87.

200 Cosma V, Imbernon J, Zagdoun L, et al. A prospective cohort study of postpartum glucose metabolic disorders in early versus standard diagnosed gestational diabetes mellitus. *Sci Rep* 2021; **11:** 10430.
201 Lekva T, Godang K, Michelsen AE, et al. Prediction of gestational diabetes mellitus and pre-diabetes 5 years postpartum using 75 g oral glucose tolerance test at 14–16 weeks' gestation. *Sci Rep* 2018; **8:** 13392.
202 Nicholson WK, Asao K, Brancati F, Coresh J, Pankow JS, Powe NR. Parity and risk of type 2 diabetes: the Atherosclerosis Risk in Communities Study. *Diabetes Care* 2006; **29:** 2349–54.
203 Tian Y, Shen L, Wu J, et al. Parity and the risk of diabetes mellitus among Chinese women: a cross-sectional evidence from the Tongji-Dongfeng cohort study. *PLoS One* 2014; **9:** e104810.
204 Berggren EK, Presley L, Amini SB, Hauguel-de Mouzon S, Catalano PM. Are the metabolic changes of pregnancy reversible in the first year postpartum? *Diabetologia* 2015; **58:** 1561–68.
205 Peters RK, Kjos SL, Xiang A, Buchanan TA. Long-term diabetogenic effect of single pregnancy in women with previous gestational diabetes mellitus. *Lancet* 1996; **347:** 227–30.
206 Aryan L, Medzikovic L, Umar S, Eghbali M. Pregnancy-associated cardiac dysfunction and the regulatory role of microRNAs. *Biol Sex Differ* 2020; **11:** 14.
207 Nair S, Ormazabal V, Carrion F, Handberg A, McIntyre HD, Salomon C. Extracellular vesicle-mediated targeting strategies for long-term health benefits in gestational diabetes. *Clin Sci* 2023; **137:** 1311–32.