# The pancreas and the placenta: understanding gestational diabetes and why some islets fail to cope with pregnancy

**Lorna I.F. Smith** and **James E. Bowe** (King's College London, UK)

During healthy pregnancy there is a progressive decrease in sensitivity of the mother's cells to insulin signalling, known as insulin resistance, in order to divert glucose towards the growing fetus. To compensate for this, the pancreatic β-cells must adapt through various mechanisms to increase the amount of insulin produced. A failure of the β-cells to sufficiently adapt can lead to gestational diabetes and clinical consequences for both mother and baby.

The necessary β-cell adaptations are coordinated in large part by the placenta, which acts as an endocrine organ producing and releasing hormones into the maternal blood circulation. Hormones such as prolactin, placental lactogen, and kisspeptin have been identified to play important roles in initiating and maintaining the changes in the β-cells necessary for a healthy pregnancy. Further work towards understanding how the β-cells adapt to pregnancy in humans, the signals underlying these changes, and why these adaptations fail in gestational diabetes is essential in allowing us to address this increasingly prevalent form of diabetes.

## A brief introduction to gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is a distinct form of diabetes, independent of type 1 (T1DM) and type 2 (T2DM) diabetes. Developing during pregnancy, high blood glucose (hyperglycaemia) arises in the mother most commonly after week 24 of pregnancy and usually disappears upon giving birth. During 2019, hyperglycaemia was seen in 20 million (or 16%) of pregnancies worldwide, with 84% of these due to gestational diabetes. As with T2DM, levels of GDM are rising rapidly, with a 10%–100% increase seen over the last 20 years in some ethnicity groups. The fact that GDM is transient and usually resolves after birth means that it has not received the attention of T1DM or T2DM and perhaps represents the 'hidden' form of diabetes, despite the serious consequences for both mother and offspring. Clinical complications during pregnancy can include high maternal blood pressure, which can lead to preeclampsia, macrosomia (birth weight >90th centile), obstructed labour, birth injury and excessive insulin levels (hyperinsulinism) and low glucose levels (hypoglycaemia) in neonatal infants. Furthermore, whilst diabetes generally resolves after birth, 50% of mothers who experience a diabetic pregnancy will go on to develop T2DM within 5–10 years. Meanwhile, children exposed to hyperglycaemia in the womb have an increased risk of obesity, T2DM and cardiovascular disease in adulthood. GDM therefore has potential ramifications far beyond the relatively brief period of pregnancy.

Currently GDM is diagnosed through an oral glucose tolerance test at 24–28 weeks of gestation once the condition has developed (Figure 1) and is generally treated initially through lifestyle interventions. If changes to diet or exercise are not sufficient or possible then insulin administration or diabetes therapies such as metformin may be used. Given the immediate and long-term consequences for both mother and baby there is increasing interest in better understanding the causes of GDM to develop diagnostic approaches for predicting GDM risk early in pregnancy or to identify novel therapeutic targets.

## Maternal metabolism during healthy pregnancy

To investigate the causes of GDM it is first important to understand how glucose homeostasis is altered in healthy pregnancy. The mother's blood glucose not only
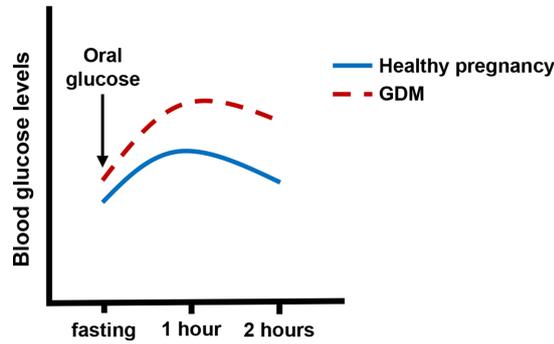
**Figure 1.** Gestational diabetes (GDM) is diagnosed in pregnant women following an oral glucose tolerance test (OGTT). Fasting blood glucose levels are measured before a glucose drink and further blood samples after 1 and 2 hours. Gestational diabetes is diagnosed if blood glucose levels are elevated above the diagnostic criteria at any point in the test.

supplies maternal tissues, but also crosses the placenta to provide essential fuel for the growing fetus. During the later stages of pregnancy increasing hormone levels, particularly progesterone, cortisol and placental growth hormone, cause increasing maternal resistance to insulin signalling in fat and muscle tissue. Sensitivity of these tissues to insulin signalling falls by between 45% and 70%. The result of this change is that after a meal the mother's blood glucose levels will remain elevated for longer as the liver, muscle and fat take longer to absorb and store the excess glucose. The prolonged elevation in maternal blood glucose allows more opportunity for the fetus to absorb glucose, effectively prioritizing glucose supply to the fetus. However, whilst some degree of insulin resistance and subsequent elevated blood glucose is beneficial in pregnancy it is important that average circulating blood glucose levels do not become too high. The mother must still be able to maintain normal blood glucose levels most of the time and prevent prolonged

hyperglycaemia. Therefore, the insulin resistance must be balanced by an increased capacity of the pancreatic β-cells to secrete insulin in response to elevated glucose.

By late pregnancy a 75% increase in serum insulin levels is required in order to maintain healthy glucose homeostasis in the mother. Animal studies have shown that the β-cells have a range of different adaptive responses that allow them to cope with this increased level of demand during pregnancy. Expression of key genes such as insulin and GLUT2, which transports glucose into the β-cells, is increased. Glucokinase, the key enzyme that allows the β-cell to detect glucose, also shows elevated activity during pregnancy. These changes result in increased sensitivity of the β-cells to glucose and increased glucose-stimulated insulin secretion. In addition to the adaptive changes in β-cell function there is a parallel increase in β-cell mass achieved through proliferation of existing β-cells and an increase in the size of individual β-cells (hypertrophy). Failure of these adaptive responses leads to an inability of the maternal β-cells to maintain normal blood glucose levels and the development of GDM (Figure 2).

Pregnancy represents a unique life event in which the pancreatic islets are put under stress and must adapt to compensate and ensure a healthy pregnancy. However, the signals and mechanisms that regulate the adaptive response of the islets are not fully understood. Our research is focused initially on identifying the signals that communicate to the β-cells driving the compensatory response.

## Communicating between placenta and β-cells

The β-cells start to adapt to pregnancy prior to the development of maternal insulin resistance, demonstrating that these changes do not simply occur in
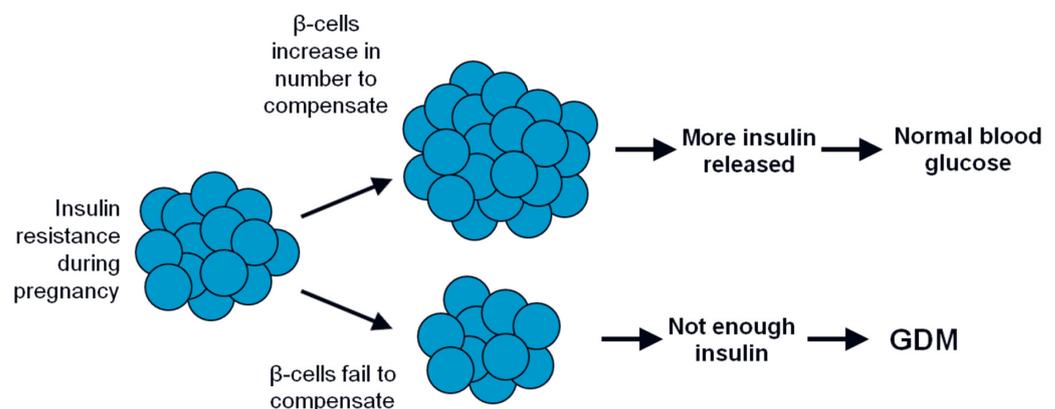
**Figure 2.** Insufficient islet adaptation and an inability to increase insulin secretory capacity to compensate for increased insulin resistance may lead to GDM

direct response to an increased demand for insulin. Thus, the question arises, how do the islets know that they are in a pregnant woman and need to adapt? The placenta has many essential functions during pregnancy, but one of its roles is to act as an endocrine organ, releasing hormones into the maternal circulation to maintain and coordinate gestation. Evidence suggests that several placental hormones are involved in communicating with the β-cells in order to produce the necessary adaptive response.

By far the most established signals that have been identified to play a role in driving the islet adaptation to pregnancy are the lactogenic hormones: pituitary-derived prolactin (PRL) and placental lactogen (PL). Both PRL and PL increase glucose-stimulated insulin secretion and induce β-cell proliferation in a manner similar to that observed in pregnancy. Perhaps the most convincing data demonstrating a role for the lactogenic hormones in pregnancy comes from genetic modification of the prolactin receptor (PRLR) in mice, through which both hormones exert their effects. Genetic knockout of PRLR exclusively in mouse β-cells has minimal effects outside of pregnancy but leads to progressively worsening glucose intolerance through gestation. These mice also exhibit reduced β-cell mass during pregnancy compared to healthy mice. Subsequent studies have found that the effects of PL on β-cell proliferation and glucose-stimulated insulin secretion appear to be in part due to stimulation of β-cell serotonin production, an autocrine/paracrine regulator of the β-cell itself and neighbouring β-cells within the islet.

Whilst the lactogenic hormones are clearly important factors, they are not the only signals involved and over recent years there has been increasing research aiming to identify novel hormones that play a role in the islet response to pregnancy. High levels of hepatocyte growth factor (HGF) are also released from the placenta, acting on β-cells through the c-Met receptor. Pancreatic c-Met knockout mice again display no phenotype outside of pregnancy but exhibit reduced β-cell proliferation and increased β-cell apoptosis during pregnancy. Similarly, adiponectin is released by the placenta at high levels and has been associated with positive effects on β-cell function during pregnancy. Commonly known as a regulator of insulin sensitivity, adiponectin has also been shown to stimulate insulin secretion in mouse islets, whilst its knockout reduces β-cell mass and serum insulin levels during pregnancy.

Our own work has focused on identifying other novel placental signals that influence the islet adaptation to pregnancy and help maintain maternal normoglycaemia. One such signal is kisspeptin, a hormone primarily known as a hypothalamic regulator of reproductive function through its receptor GPR54. Whilst circulating kisspeptin is generally very low, during pregnancy the placenta releases large quantities such that levels in the maternal blood increase several thousand-fold. In addition to the well-established effects on reproductive function, kisspeptin also acts directly on the β-cells to regulate insulin secretion and its placental release suggests a role in the islet response to pregnancy. Due to the role of hypothalamic kisspeptin in reproductive function, global GPR54 knockout mice are infertile and unsuitable for pregnancy studies. We have developed a mouse model in which GPR54 expression is specifically knocked out in the β-cells. The remaining presence of GPR54 in the hypothalamus means that these mice are fertile and able to become pregnant. Outside of pregnancy β-cell-specific knockout of GPR54 causes no obvious phenotype; however, during pregnancy the loss of islet kisspeptin signalling results in impaired glucose tolerance. The β-cells release less insulin in response to glucose and consequently the pregnant mice become hyperglycaemic.

Cell proliferation can be assessed in several ways, but one of the most common in animal models is through the use of a chemical called bromodeoxyuridine (BrdU). BrdU can be administered to animals and has no effect in itself. However, BrdU will enter cells and incorporate into any newly synthesized DNA, effectively tagging the nucleus of cells that proliferate whilst it is present in the body. By collecting the pancreas and quantifying the number of BrdU-labelled β-cells we can assess the rate of cell proliferation. It is well established that BrdU labelling significantly increases during pregnancy (Figure 3). The loss of kisspeptin signalling in the β-cell-specific GPR54 knockout mice significantly attenuates the increased proliferation normally seen in pregnancy (Figure 3). Nevertheless, levels of proliferation are not reduced to non-pregnant levels, suggesting that other signals are also involved. This is consistent with the previously established roles for signals such as the lactogenic hormones, HGF or adiponectin discussed earlier.

Our recent studies suggest that kisspeptin represents an important placental signal that plays a role in regulating the islet adaptation to pregnancy, in addition to other already established factors. Despite the identification of several signals that play potential roles in the islet adaptation to pregnancy, it is worth remembering that the placenta produces and releases a wide range of hormones to regulate fetal development and the necessary maternal changes. The placenta expresses mRNA for at least 80 different peptide hormones, the majority of which are potentially capable of signalling to the islets through at least one receptor. It is very likely that other currently unidentified hormones also play roles in communicating between placenta and islet and we are continuing to further examine these mechanisms.

Non-pregnant  Pregnant  Pregnant β-cell-specific GPR54 knockout
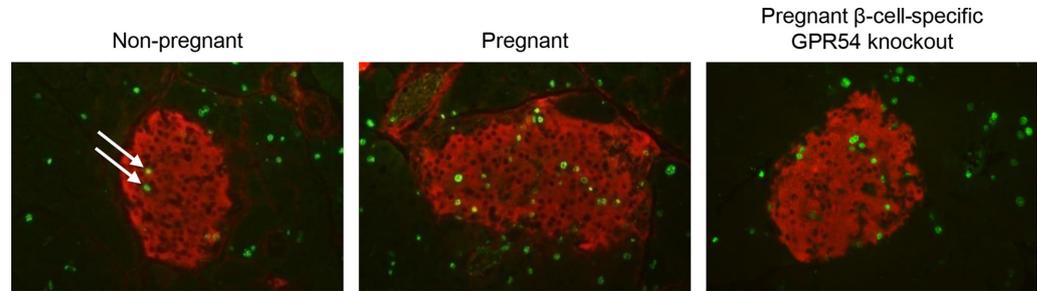
**Figure 3.** Immunofluorescence labelling of non-pregnant and pregnant pancreas sections for insulin (red) and BrdU (green). Red insulin labelling is used to identify the β-cells. Any cells with a green nucleus proliferated during the time window that BrdU was being administered to the animal (see arrow markers). Pregnancy results in a significant increase in the level of BrdU labelling in the β-cells confirming increased proliferation. Following analysis pregnant β-cell-specific GPR54 knockout mice are found to have reduced proliferation when compared to pregnant control mice.

## Human pregnancy and GDM

Whilst our understanding of how β-cells adapt to pregnancy in rodent models is growing, the major challenge in the field is understanding whether these mechanisms are also relevant in human gestation. Furthermore, why do the islets fail to sufficiently adapt in women who develop GDM?

How human β-cells adapt to pregnancy remains very poorly understood, particularly regarding β-cell mass. We can assess overall glucose homeostasis through glucose tolerance tests and indirectly assess β-cell function through measuring circulating insulin levels and through mathematical models such as HOMA-% β. However, current scanning technology is not sufficiently advanced to allow clinical measurement of β-cell mass and the only available data on this are derived from post-mortem samples taken during pregnancy. The limited human samples which have been studied confirm increased insulin release and increased β-cell mass, though these adaptations appear to occur at lower levels than seen in animal studies, with smaller increases of between 1.4- and 2.4-fold in islet mass detected. There may also be different mechanisms behind these adaptations, with expansion of human β-cell numbers thought to be more heavily reliant on the formation of new islets from progenitor cells or pancreatic duct cells (neogenesis), than from enlargement of islets by replication of existing β-cells. However, the broader principles observed in animal models, that the islets adapt to pregnancy through increased β-cell mass and increased insulin secretion, appear to be consistent with human pregnancy.

There is similarly limited data on whether the signals that drive the islet adaptation to pregnancy in rodents play a corresponding role in humans. Treatment of isolated human islets with lactogenic hormones does potentiate glucose-stimulated insulin secretion, but whether they stimulate β-cell mass in human islets is controversial and inconclusive. If the lactogenic hormones do play a key role in the islet adaptation to human pregnancy, then it follows that women with GDM may have low circulating levels of prolactin and/or placental lactogen. However, despite several studies investigating this link there appears to be no correlation between low maternal levels of prolactin and placental lactogen and an increased risk of developing GDM.

In our own studies we have shown that kisspeptin potentiates glucose-stimulated insulin secretion from isolated human islets and in clinical studies, women with GDM have significantly lower circulating kisspeptin levels compared to healthy pregnant women. Low kisspeptin levels in pregnancy also correlate with reduced insulin release in response to a glucose challenge. In this case the human data is consistent with the results from mouse models, suggesting that placental kisspeptin signalling is important for maintaining healthy glucose homeostasis.

## Conclusions

Understanding the signals involved in the human islet adaptation to pregnancy is of great clinical interest. If dysfunctional signalling between the placenta and pancreas can lead to GDM then monitoring the levels of these signals may allow us to identify mothers at high risk of developing GDM earlier. It is unlikely that any single factor will be able to predict GDM risk. However, there is on-going interest in developing a screen of multiple biomarkers that could identify susceptible women, allowing early intervention and minimizing clinical complications for mother and child.

In principle, the signals identified to increase insulin secretory capacity and β-cell mass could also have enormous therapeutic potential. If the islets of a pregnant woman are not coping with the demands of pregnancy due to kisspeptin levels being too low, e.g., then could we administer additional kisspeptin? Furthermore, if kisspeptin and similar signals increase

insulin release and β-cell mass then could they be used as diabetes therapies outside of pregnancy? In practice far more work is required to ensure that any therapeutic use would be safe and effective. Great care must be taken when administering novel treatments during pregnancy and many of these signals have other off-target side effects in other tissues.

Further work is required to understand precisely how the β-cells adapt to pregnancy in humans and the signals that regulate this response. However, despite the differences between rodent and human pregnancy, key placental peptides are likely to play a vital role in driving the islet adaptation that is required to avoid GDM. A more complete understanding of the communication between placenta and β-cell may play an important part in addressing the increasing prevalence of GDM and improving outcomes for both mothers and babies. ■

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### Further Reading

- Diabetes UK website: Gestational Diabetes resources: https://www.diabetes.org.uk/diabetes-the-basics/gestational-diabetes
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*Lorna I.F. Smith is a research associate working with Dr James Bowe at King's College London. She received her PhD in neuroendocrinology from the University of Bristol in 2016, studying steroidogenic transcriptional regulation in the adrenal cortex under the guidance of Dr Francesca Spiga and Professor Stafford Lightman. She also had the opportunity to spend 2 years working at the National Institute Health in Bethesda, USA, under the supervision of Dr Greti Aguilera as part of the NIH Graduate Partnership Programme. Email: lorna.smith@kcl.ac.uk*

*James E. Bowe is Senior Lecturer in Physiology at King's College London. He obtained his PhD in 2006, investigating the effects of stress on reproductive function within the hypothalamus. He subsequently moved into diabetes research as a post-doctoral researcher and his main research interests now lie in the adaptation of the pancreatic islets to pregnancy. He has particular interests in both the signals that regulate these adaptive functional and structural changes, including increased β-cell mass, and how a failure of these changes may lead to gestational diabetes mellitus. Email: james.bowe@kcl.ac.uk*