J Physiol 600.5 (2022) pp 1089–1117

The Journal of Physiology

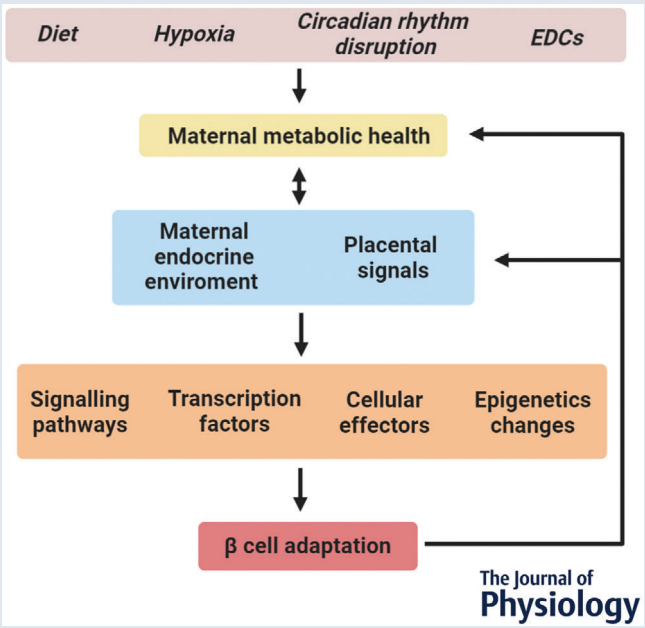
TOPICAL REVIEW

Pregnancy-induced changes in β-cell function: what are the key players?

Esteban Roberto Salazar-Petres and Amanda Nancy Sferruzzi-Perri

Centre for Trophoblast Research, Department of Physiology, Development and Neuroscience, University of Cambridge, Downing Street, Cambridge, CB2 3EG, UK

Edited by: Laura Bennet & Suzanne Miller



Abstract Maternal metabolic adaptations during pregnancy ensure appropriate nutrient supply to the developing fetus. This is facilitated by reductions in maternal peripheral insulin sensitivity, which enables glucose to be available in the maternal circulation for transfer to the fetus for growth. To balance this process and avoid excessive hyperglycaemia and glucose intolerance in the mother during pregnancy, maternal pancreatic β-cells undergo remarkable changes in their function including increasing their proliferation and glucose-stimulated insulin secretion. In this review we examine how placental and maternal hormones work cooperatively to activate several signalling pathways, transcription factors and epigenetic regulators to drive adaptations

Esteban Salazar-Petres was awarded his PhD in 2018 from Universidad Austral de Chile. Since 2019, he has been a Postdoctoral Research Fellow (funded by a Beca-Chile, ANID fellowship) in the Sferruzzi-Perri lab, at the University of Cambridge. His current research is mainly focused on understanding the regulation of maternal endocrine and metabolic adaptations to pregnancy, with an emphasis on the involvement of changes in placental function and adverse environmental conditions such as obesity, diet and stress by using animal models and human pregnancy samples.

DOI: 10.1113/JP281082

in β-cell function during pregnancy. We also explore how adverse maternal environmental conditions, including malnutrition, obesity, circadian rhythm disruption and environmental pollutants, may impact the endocrine and molecular mechanisms controlling β-cell adaptations during pregnancy. The available data from human and experimental animal studies highlight the need to better understand how maternal β-cells integrate the various environmental, metabolic and endocrine cues and thereby determine appropriate β-cell adaptation during gestation. In doing so, these studies may identify targetable pathways that could be used to prevent not only the development of pregnancy complications like gestational diabetes that impact maternal and fetal wellbeing, but also more generally the pathogenesis of other metabolic conditions like type 2 diabetes.

(Received 4 December 2020; accepted after revision 17 February 2021; first published online 11 March 2021)
Corresponding author A. N. Sferruzzi-Perri: Centre for Trophoblast Research, Department of Physiology, Development and Neuroscience, University of Cambridge, Downing Street, Cambridge, CB2 3EG UK. Email: ans48@cam.ac.uk

Abstract figure legend Abstract figure legend The metabolic health of the mother during pregnancy is modulated by environmental factors, as well as endocrine signals produced by maternal organs and placenta, which together act via various cellular and molecular pathways to regulate adaptations in β-cell function and glucose homeostasis. EDCs = endocrine disrupting chemicals.

Introduction

Multiple organ systems in the mother adapt their function during pregnancy to support the nutritional demands of the fetus for growth and development. Of particular importance are the alterations in maternal metabolism, including the acquisition of an insulin-resistant state, which increase glucose availability in the mother for transfer to the fetus. To appropriately balance the level of insulin resistance attained in the mother during pregnancy, pancreatic β-cells must functionally adapt and increase their production of insulin (Rieck & Kaestner, 2010). Metabolic adaptations begin early in pregnancy and are accompanied by changes in maternal production of hormones, including prolactin (PRL), oestrogen, progesterone and cortisol (Ryan & Enns, 1988; Grattan *et al*. 2008). The placental secretion of hormones, which commences immediately following implantation and continues throughout gestation, is essential for mediating maternal metabolic adaptations via indirectly modulating endocrine axes and directly inducing changes in metabolic tissues of the mother (Braunstein, 2011). Of note, under the influence of maternal and placental hormones, β-cell mass expands and the capacity of β-cells to produce and secrete insulin increases in gestation.

Akin to outside of pregnancy, β-cells in the mother are responsive to other physiological and environmental stimuli, such as alterations in dietary intake and stress. Therefore, maternal environmental conditions likely also play important modulatory roles in influencing β-cell adaptations during pregnancy with metabolic consequences (Rieck & Kaestner, 2010; Banerjee, 2018). Indeed, a failure to appropriately adapt β-cell function very probably occurs during pregnancy in the presence, for example, of maternal obesity or excessive gestational weight, which are both risk factors for gestational diabetes mellitus (GDM). GDM is a metabolic disorder that arises from an inability of the mother to compensate for the insulin resistance induced during pregnancy. This results in maternal hyperglycaemia and glucose intolerance with serious health outcomes for mother and offspring, including the development of type 2 diabetes mellitus (T2DM) in the decades after birth (Buchanan *et al*. 2012; Moyce & Dolinsky, 2018; Christoforou & Sferruzzi-Perri, 2020).

The aim of this review is to examine the mechanisms controlling β-cell adaptation during pregnancy and illuminate pathways that could be targeted to combat β-cell maladaptation and hence the pathogenesis of GDM. We first describe the changes in maternal glucose and insulin dynamics during gestation. We then evaluate the role of maternal and placental hormones in the regulation of β-cell adaptation and explore their underlying molecular mechanisms mediating functional changes in the β-cells during pregnancy. Finally, we explore the influence of maternal environmental conditions and their interaction with the endocrine and molecular mechanisms controlling β-cell adaptation in gestation. In doing so, we hope to highlight valuable future research areas and identify targetable pathways that could be used to prevent not only the development of pregnancy complications like gestational diabetes, but also more generally the pathogenesis of other metabolic conditions like type 2 diabetes.

Glucose homeostasis, insulin sensitivity and β-cell adaptation during pregnancy

Glucose homeostasis. Glucose levels in the mother dynamically change during pregnancy. In early gestation, fasting glucose levels drop compared to the pre-gravid state, in part due to the haemodilution effect caused by an increased maternal blood volume. Maternal fasting glucose levels remain consistently low in the second trimester and are further decreased during the third trimester, largely as a result of enhanced utilization of glucose in the circulation by the fetal–placental unit (Catalano *et al*. 1992). However, maternal fasting hypoglycaemia during gestation is compensated by enhanced hepatic gluconeogenesis, which raises glucose levels and helps to maintain nutrient flow to the fetus (Catalano *et al*. 1995). On the contrary, postprandial glucose levels progressively elevate during pregnancy, relative to the pre-gravid state (Cousins *et al*. 1980; Butte, 2000). This elevation is related to impaired peripheral tissue insulin sensitivity and hence diminished postprandial glucose utilization by the mother (Di Cianni *et al*. 2003).

Insulin sensitivity. Insulin sensitivity changes in the mother during pregnancy. In early gestation, maternal insulin sensitivity is enhanced, which facilitates the growth of maternal organs, such as the adipose, as well as the storage of nutrients like glucose as lipids or glycogen. This is driven in part by the suppression of pituitary growth hormone production by the feto-placental unit during the first weeks of pregnancy. However, later in gestation insulin sensitivity of maternal peripheral tissues, including the white adipose tissue and skeletal muscle, markedly decreases and contributes to the elevated postprandial glucose levels mentioned previously (Angueira *et al*. 2015).

Diminished insulin sensitivity is induced by increased levels of placental and maternal hormones, including placental lactogen, growth hormone variant, progesterone, cortisol and PRL, which interfere with insulin receptor signalling particularly during the third trimester of pregnancy (Newbern & Freemark, 2011; Napso *et al*. 2018). Other mediators, including leptin, adiponectin and tumour necrosis factor α (TNF-α) produced by the placenta and maternal white adipose tissue also contribute to the decreased insulin sensitivity of peripheral tissues and do so in a cooperative fashion (Lain & Catalano, 2007; Romero *et al*. 2007; Napso *et al*. 2018). For instance, whilst leptin (which acts in nutrient storage) increases during late gestation, lactogens (such as PRL) induce central leptin resistance leading to increased feeding behaviour and a maintenance of body weight during late gestation (Newbern & Freemark, 2011). Although a reduction in insulin sensitivity (as well as leptin resistance) may appear pathological from the maternal perspective, this is vital for the diversion of glucose from maternal tissues to the fetal–placental unit for growth and development. Insulin sensitivity starts to return to pre-pregnancy baseline just prior to or after term, which is thought to help meet the metabolic demands of the mother during labour and lactation and ensure metabolic health post-partum (Kirwan *et al*. 2004; Friedman *et al*. 2008).

β-Cell adaptation. Insulin levels in the mother also alter during gestation. In particular, maternal circulating insulin increases in pregnancy, which is facilitated by an enlargement of pancreatic β-cell mass and enhanced insulin secretory capacity (Lain & Catalano, 2007). There is an increase in β-cell proliferation, hypertrophy and survival, enhanced insulin synthesis and storage, and a lowering of the threshold for glucose-stimulated insulin secretion (GSIS) in pregnancy (Sorenson & Brelje, 1997). Whether adaptations in pancreatic β-cells occur in response to, or are in anticipation of, the diminished insulin sensitivity of the mother in pregnancy is a matter of debate. However, the timing, magnitude and contribution of changes in pancreatic β-cells during pregnancy and their relationship to maternal insulin sensitivity have been most extensively studied in rodents, with some scant studies performed in humans (Rieck & Kaestner, 2010). Because of this, the remaining work reviewed herein will largely be from rodents and humans.

β-Cell mass adaptation during rodent pregnancy. Studies in rodents have shown that β-cell adaptations in the mother occur prior to the onset of insulin resistance and thus they are not simply in response to increased insulin demand (Parsons, 1992; Sorenson & Brelje, 1997). In mice where pregnancy lasts around 20 days, the proliferation of pre-existing β-cells in pancreatic islets commences around day 9 of pregnancy, with a maximum rate around days 12–15, as indicated by Ki67 immunostaining or BrdU incorporation (Parsons, 1992; Xue *et al*. 2010; Szlapinski *et al*. 2019). There may also be protection from apoptosis/enhanced survival (Fujinaka *et al*. 2007; Karnik *et al*. 2007) and an increase in the size of β-cells in islets during pregnancy (Parsons *et al*. 1995; Huang *et al*. 2009) and thus enhanced viability, hyperplasia and hypertrophy contribute to the expansion of β-cell mass in gestation. However, as early as day 6 of pregnancy, proliferation of low *Glut2* expressing β-cells located in extra-islet β-cell clusters has also been observed (Beamish *et al*. 2017). Lineage tracing studies suggest that the expansion of β-cell mass in the mother may also result from the differentiation of non-insulin expressing progenitors that acquire a β-cell phenotype in pregnancy (Abouna *et al*. 2010; Toselli *et al*. 2014), although the origin of this non-β-cell source and the

contribution of trans-differentiation of mature cells into β-cells are unknown. Moreover, it is important to note that other studies have failed to detect neogenesis in the maternal pancreas during pregnancy in several mouse models (Parsons *et al.* 1995; Zhao, 2014). Whatever the mechanisms involved, these processes result an increased number of islets (Hakonen *et al.* 2014) and a 3- to 4-fold expansion of β-cell mass, with values peaking around days 14.5–16.5 of mouse gestation (Parsons *et al.* 1992; Huang *et al.* 2009; Beamish *et al.* 2017; Rieck *et al.* 2009). After delivery, the maternal β-cell mass regresses to non-pregnant levels and an increase in apoptosis of the β-cells is thought to contribute to this process (Scaglia *et al.* 1995; Kim *et al.* 2010; Nunes *et al.* 2014).

β-Cell mass adaptation during human pregnancy. Studies of β-cell adaptation in human pregnancy have come from analyses of pancreatic tissue recovered from women who died during pregnancy. Compared to rodents, many mechanisms seem conserved but there are some differences in β-cell adaptation during human pregnancy. For instance, two studies have shown that β-cell mass is increased around 1.4- to 2.4-fold in pregnant women, which is less than the reported 3- to 4-fold increase in mice (Van Assche *et al.* 1978; Butler *et al.* 2010). One of those studies also found there was no increase in size, proliferation or decrease in apoptosis of β-cells in existing islets, suggesting that islet neogenesis could contribute to β-cell mass adaptation in human pregnancy (Butler *et al.* 2010). However, studies in human samples tend to be from a single gestational period, which may not capture when proliferation rates may be elevated. Further work is thus required to understand the process and temporal regulation of β-cell adaptations, relative to changes in insulin sensitivity, in women during pregnancy.

Role of maternal and placental hormones in β-cell adaptation during pregnancy

Hormones secreted by maternal tissues and the placenta are important regulators of β-cell adaptation and, therefore, the control of glucose homeostasis during pregnancy. They function either directly by interacting with receptors on the β-cells or indirectly by modulating the nerves, vasculature or blood flow to the pancreas and/or via changes in other hormones that signal to the β-cells. The circulating abundance of hormones, such as placental lactogens, oestrogen, progesterone and kisspeptin, undergoes significant changes over the course of pregnancy, and together with the expression of local regulators, like hepatocyte growth factor (HGF) and serotonin, is instrumental to the adaptive increase in β-cell mass and insulin secretory function (Rieck & Kaestner, 2010; Banerjee, 2018). In this section we will describe the main maternal and placental endocrine and local factors facilitating β-cell adaptations during pregnancy by describing their effects on β-cells, as well as the molecular pathways governing such effects (from receptor to downstream signalling pathways, Fig. 1). To explore the importance of endocrine and local factors in β-cell adaptations during gestation, researchers have modified input signal, receptor union or abundance. Such experiments have largely been performed using genetic manipulation in rodents using the Cre–LoxP system. However, it is important to mention that there may be potential limitations due to differences in recombination events, allele susceptibility, timing and efficiency of deletion, and background of strain used when using the Cre–LoxP system (Magnuson & Osipovich, 2013). Moreover, the RIP-Cre and *Pdx1*-Cre mouse lines, which have been used to conditionally manipulate β-cell gene expression, have been reported to develop glucose intolerance and/or show signs of β-cell dysfunction even when there are no floxed transgenes to target (Lee *et al.* 2006; Pomplun *et al.* 2007; Brouwers *et al.* 2014) due to the inclusion of a bovine growth hormone (*bGH*) minigene when the lines were created (Brouwers *et al.* 2014). Thus, interpretation of findings for certain studies using the RIP-Cre and *Pdx1*-Cre mouse lines when appropriate Cre controls have not been used is warranted and highlighted below.

Endocrine factors.

Placental lactogen, prolactin and growth hormone. Placental lactogens (PL) are key members of the PRL–growth hormone (GH) family of hormones secreted by the placenta during gestation (Napso *et al.* 2018). In mouse and rat, the placenta expresses all the PRL–GH family members except for PRL and GH (namely at least 23 PRL-related proteins, including placental lactogens 1 and 2). This is in contrast to the human placenta, which only expresses the GH and PL genes (Soares *et al.* 2007). The anterior pituitary also produces PRL and GH, but production is diminished by mid-pregnancy, when placental hormone production predominates (Bridges, 2015). Placental lactogens play a central role in the β-cell adaptations during pregnancy (Banerjee, 2018; Sferruzzi-Perri *et al.* 2020). Indeed, the rise in PL concentrations during gestation is correlated with increased β-cell proliferation and function during pregnancy (Parsons *et al.*, 1992). Several studies have examined the role of PL and PRL on pancreatic islets and shown that lactogens increase β-cell insulin secretion, proliferation, survival and mass and lower the threshold for GSIS (Sorenson & Brelje, 2009).

Both PL and PRL act mainly through the prolactin receptor (PRLR), whilst GH acts through its own membrane receptor (GHR) and is able to also activate

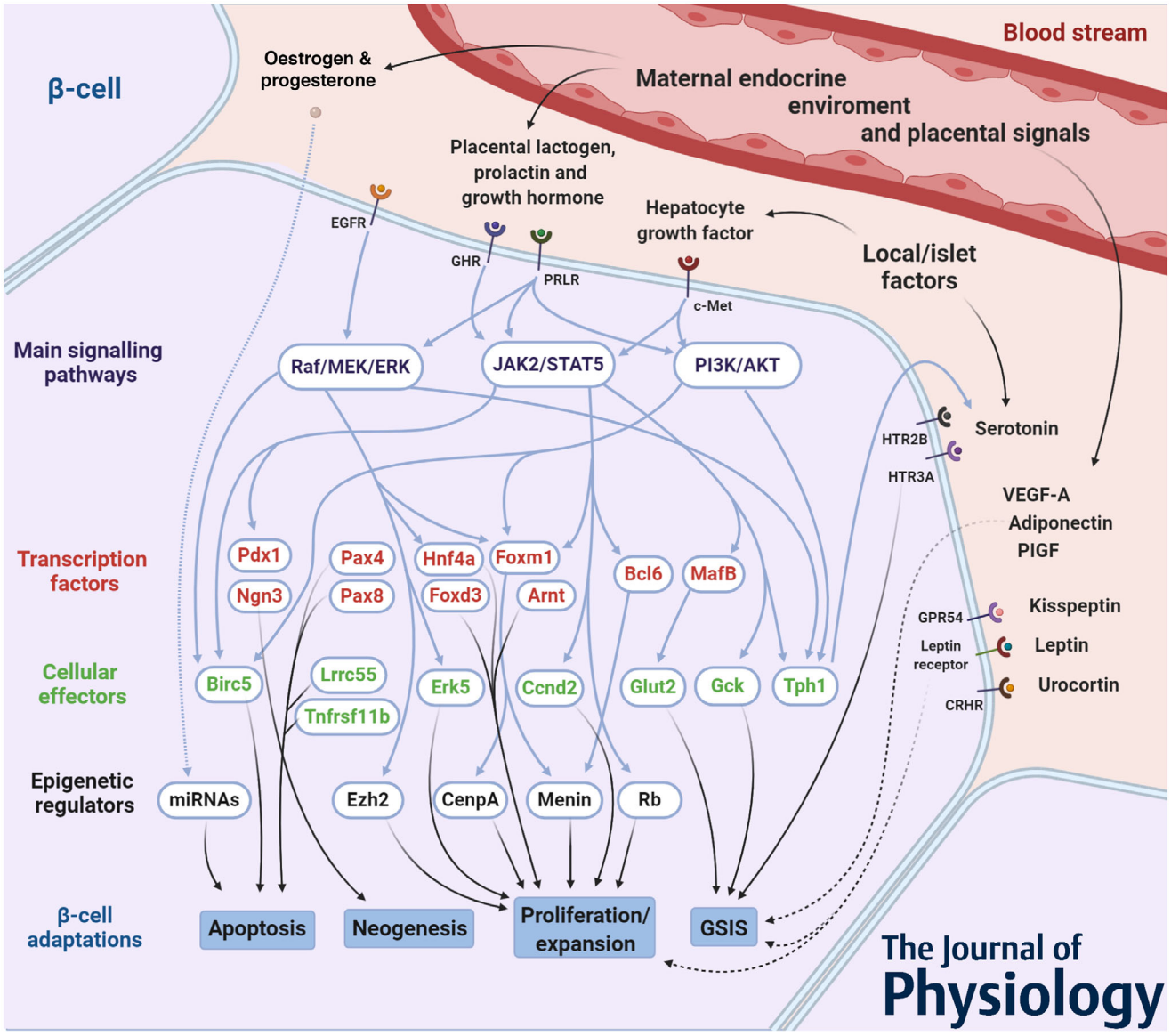


Figure 1. Summary figure showing the effect of hormones in the mother, and the intracellular pathways regulating β-cell adaptations during pregnancy
Note that serotonin acts in an autocrine and paracrine fashion to regulate β-cells. Hormones with an asterisks may be derived from the placenta. Continuous lines reflect pathways identified and dashed lines highlight those predicted. Abbreviations: Arnt, Aryl-hydrocarbon receptor nuclear translocator; Bcl6, B-cell lymphoma 6; Birc5, baculoviral inhibitor of apoptosis repeat-containing 5 or survivin; Ccnd2, cyclin D2; Cenpa, centromere protein A; c-Met, hepatocyte growth factor receptor; EGFR, epidermal growth factor receptor; Erk5, extracellular-signal-regulated kinase 5; Ezh2, enhancer of zeste homolog 2; Foxd3, forkhead box D3; Foxm1, forkhead box protein M1; Foxo1, forkhead box O1; Gck, glucokinase; GHR, growth hormone receptor; Glut2, glucose transporter 2; GPR54, Gq-protein-coupled receptor 54: corticotrophin releasing hormone; Gsk3, glycogen synthase kinase-3; Hnf4a, hepatocyte nuclear factor-4α; HTR2B, serotonin receptor subtype 2B; HTR3A, serotonin receptor subtype 3A; Lrrc55, leucine rich repeat containing 55; Mafb, V-maf musculoaponeurotic fibrosarcoma oncogene homolog B; Men1, menin 1; mTOR, mammalian target of rapamycin; Ngn3, neurogenin 3; Pax4, paired box 4; Pax8, paired box 8; Pdx1, pancreatic and duodenal homeobox 1; PRLR, prolactin receptor; Rb1, retinoblastoma; Tnfrsf11b, osteoprotegerin; Tph1, tryptophan hydroxylase 1.

PRLR. PRLR belongs to the cytokine class-1 receptor family that includes GHR (Brooks, 2012). In rodents, PRLR is expressed by β-cells and is induced during pregnancy (Møldrup *et al*. 1993; Brelje *et al*. 2002; Kim *et al*. 2010; Banerjee *et al*. 2016). In mice, an intact PRLR is required for β-cell mass changes during pregnancy, as genetic disruption of *Prlr* leads to failed β-cell mass expansion and diminished GSIS in pregnancy (Amaral *et al*. 2004; Huang *et al*. 2009; Goyvaerts *et al*. 2015; Rawn *et al*. 2015). The binding of PL to PRLR, initiates a signal transduction pathway that leads to the recruitment of Janus kinase 2 (JAK2) and the phosphorylation of signal transducer and activator of transcription 5 (STAT5), which translocates to the nucleus and regulates the expression of target genes involved in broad cellular processes, including metabolism, proliferation/expansion, death, insulin secretion and cell–cell interactions (Rieck *et al*. 2009; Kim *et al*. 2010; Layden *et al*. 2010; Schraenen *et al*. 2010*a*).

In mice, transgenic overexpression of placental lactogen in β-cells caused hypoglycaemia, hyperinsulinemia, increased β-cell proliferation and a twofold increase in β-cell mass (Vasavada *et al*. 2000). Conversely, global *Prlr* knockout mice have glucose intolerance and reductions in β-cell mass, insulin gene expression and insulin content (Freemark *et al*. 2002). *Prlr* knockout mice have reproductive abnormalities, including an inability to maintain pregnancy beyond mid-gestation, which is not ideal for investigations of pregnancy physiology (Ormandy *et al*. 1997). However, the examination of heterozygous *Prlr* null females ($Prlr^{+/-}$) during pregnancy showed that PRLR is required to maintain normal gestational glucose homeostasis, as pregnant $Prlr^{+/-}$ mice developed glucose intolerance and showed attenuated β-cell proliferation and mass expansion (Huang *et al*. 2009). These defects were related to reduced phosphorylation of JAK2, insulin receptor substrate 2 (IRS2) and protein kinase B (AKT), as well as a failure to decrease levels of menin and the cell cycle inhibitors p18 and p27 in pancreatic islets of $Prlr^{+/-}$ mice during pregnancy (Hughes & Huang, 2011). Moreover, using progesterone replacement to allow pregnancy studies in global *Prlr* knockout mice, studies have shown that expression of PRLR is required for the induction of many of the pregnancy-related mRNA changes in mouse islets (Goyvaerts *et al*. 2015). Studies using conditional deletion of *Prlr* in β-cells have further revealed that PRLR is critical for the induction of several critical pro-proliferative factors during mouse pregnancy, including tryptophan hydroxylase 1 (TPH1), forkhead box protein M1 (FOXM1) and cyclins A2, B1, B2 and D1 (Banerjee *et al*. 2016). Although these studies used the RIP-Cre mouse line to delete *Prlr* in β-cells (Banerjee *et al*. 2016), as the *bGH* minigene functions through PRLR, interpretation of those findings should not be confounded. Thus, PLs/PRLs act through several signalling pathways and transcription factors to promote β-cell mass expansion and insulin production during pregnancy.

Whilst GH is closely related to PL/PRLs and can bind to PRLR (in addition to GHR), its actions on pancreatic islets seems to be different (Somers *et al*. 1994). In addition, there are differences in the impact of GH on β-cells between species. For instance, unlike PL and PRL, GH does not significantly increase insulin secretion by adult human islets *in vitro* (Brelje *et al*. 1993). There are also marked differences in the activation of STAT5 by PRL and GH in the insulinoma cell line Ins-1 and cultured rat islets; STAT5A and B was activated in a biphasic and prolonged fashion by PRL, but this activation was not biphasic and transient in nature with GH (Brelje *et al*. 2004). In non-pregnant mice, deletion of the *Ghr* gene specifically in β-cells results in reduced GSIS but normal β-cell mass and glucose tolerance on a chow diet (Wu *et al*. 2011). It is also linked to severely blunted first-phase GSIS, reduced β-cell mass and glucose intolerance when these conditional *Ghr* mutant mice are challenged with a high-fat diet (Wu *et al*. 2011). However, the contribution of *bGH*, which is present in the RIP-Cre used in this study to conditionally delete *Ghr* gene in the mice, requires elucidation (as floxed mice were used as controls). Unlike PRLR, GHR is expressed in both α-cells and β-cells of the rodent pancreas (Brelje *et al*. 2004). Recently, in mice it has been described that pancreatic α-cells undergo important morphological and functional changes, such as reduced glucagon secretion during pregnancy, that are likely regulated by pregnancy hormones, including PLs (Quesada-Candela *et al*. 2020). Taken together, the available data suggest that GH may be a relevant endocrine factor regulating maternal β-cell insulin secretion and could have additional roles in regulating pancreas endocrine function during pregnancy.

Oestrogens and progestogens. The function of progesterone and oestrogens on β-cells during pregnancy is not totally understood (Sferruzzi-Perri *et al*. 2020). Circulating levels of progesterone and oestrogens continuously rise during gestation (Costrini & Kalkhoff, 1971; Green *et al*. 1981; Nadal *et al*. 2009). In humans, these are secreted by the ovary initially and then largely by placenta during pregnancy. However, in rodents the corpus luteum continues to contribute to the circulating pool of steroid hormones during pregnancy (Napso *et al*. 2018). Direct effects of oestrogens on β-cells include protection against oxidative stress and apoptosis and regulation of GSIS and islet lipid homeostasis (Soo *et al*. 2005; Alonso-Magdalena *et al*. 2008; Wong *et al*. 2010; Tiano *et al*. 2011; Zhou *et al*. 2018). In the case of progesterone, early studies in rats have shown that progesterone increased β-cell proliferation and did not

affect GSIS during gestation *in vivo* (Nieuwenhuizen *et al.* 1998). However, progesterone receptor-null female mice display increased β-cell proliferation, mass and insulin secretion (Picard *et al.* 2002). Moreover, progesterone and, to a lesser extent, oestrogen, reduced β-cell, proliferation, survival and insulin secretion when co-treated with prolactin *in vitro* (Sorenson *et al.* 1993; Fujinaka *et al.* 2007). These data suggest that a main function of the rise in progesterone concentration during gestation is to oppose/control the stimulatory effects of lactogens on β-cells (Sorenson *et al.* 1993). Progesterone also exerts pro-apoptotic effects in a rat β-cell line (Nunes *et al.* 2014) and mass in the peri-partum period. However, overall, further work is required to understand the role and relationship between oestrogens and progesterone in mediating β-cell adaptations throughout pregnancy.

Other endocrine signals.

Kisspeptin. Kisspeptins are a family of peptides that are the endogenous ligands for the Gq-protein-coupled receptor, GPR54. GPR54 is highly expressed in the pancreatic β-cells (Hauge-Evans *et al.* 2006). Studies in rodent, porcine and human islets have reported that exogenous kisspeptin enhances GSIS *in vitro* (Bowe *et al.* 2012, 2013) and in rats and mice *in vivo* (Bowe *et al.* 2009). In humans, kisspeptin is released from the placenta into the maternal circulation increasing circulating levels several thousand-fold (Dhillo *et al.* 2006). Placental release of kisspeptin into the maternal circulation is closely correlated with the increased insulin secretory capacity of maternal β-cells (Horikoshi *et al.* 2003; Reynolds *et al.* 2009). Furthermore, low circulating levels of kisspeptin were observed in women with GDM (Bowe *et al.* 2019). In experimental animals, maternal circulating kisspeptin is unknown, although mRNA levels in the rodent placenta increase during gestation (Herreboudt *et al.* 2015). In non-pregnant mice, kisspeptin administration increases circulating insulin levels (Bowe *et al.* 2019) whereas pharmacological blockade or genetic ablation of β-cell GPR54 in mice during pregnancy results in impaired GSIS, reduced β-cell proliferation and glucose intolerance (Bowe *et al.* 2019). Thus, placental kisspeptin acting via β-cell GPR54 is important for normal glucose homeostasis during pregnancy. However, further work is required to know whether placenta-derived kisspeptin acting via GPR54 on β-cells is the relevant signal that amplifies the insulin secretory response to compensate for the insulin resistance attained during pregnancy.

Urocortin. Urocortin peptides UCN1, UCN2 and UCN3 are part of the corticotrophin releasing hormone (CRH) peptide family usually associated with hypothalamic neuroendocrine functions. However, recently, CRH peptides were described as novel placental signals involved in the control of β-cell function (Drynda *et al.* 2018; Simpson *et al.* 2020). Of note, placental *Crh* expression and islet *Crhr1/2* are upregulated on day 12 of mouse pregnancy, when β-cell mass expansion is maximal (Drynda *et al.* 2018), and previous studies have demonstrated that CRH can modulate glucagon release (Moltz & Fawcett, 1985) and β-cell insulin synthesis and proliferation *in vitro* (Schmid *et al.* 2011). In mice, all members of the CRH family are expressed by the placenta, but only circulating levels of UCN2 are significantly increased during gestation (Simpson *et al.* 2020). Moreover, activation of CRHR2, which is responsive to UCN2, leads to amplified GSIS without concomitant alterations in β-cell mass or overt changes in glucose tolerance in pregnant mice (Simpson *et al.* 2020). Thus, urocortin/CRH peptides derived from the placenta may act via their cognate receptors on maternal β-cells to perfect β-cell adaptive responses during gestation.

Leptin and adiponectin. Hormones synthesized by maternal organs also act in an endocrine fashion to modulate β-cell adaptations during gestation. Leptin is a hormone produced by the white adipose tissue and is involved in regulating insulin production and insulin sensitivity. In humans and mice, concentrations of leptin rapidly rise throughout gestation, peaking towards term (Napso *et al.* 2018). In humans, leptin is released by the placental syncytiotrophoblast into the maternal circulation (Masuzaki *et al.* 1996). But, this is not the case for mice, as the murine placenta does not express leptin (Malik *et al.* 2005). Despite this, both the mouse and the human placenta can secrete a soluble form of the leptin receptor (Yamaguchi, 1998, Tsai, 2015), which may modulate the systemic influences of leptin on maternal β-cells. *In vitro* and *in vivo*, leptin inhibits insulin secretion from β-cells (Kulkarni, 1997). Leptin treatment also decreases fasting insulin, as well as GSIS in pregnant wild-type mice (Yamashita *et al.* 2001), whereas studies in mice have shown that a heterozygous deficiency of the leptin receptor (*db*/+) is linked to the development of glucose intolerance specifically in gestation, despite elevated rates of GSIS (Yamashita *et al.* 2001). Whether the development of glucose intolerance during gestation relates to changes in insulin sensitivity *versus* insulin production in mice with altered leptin abundance or signalling capacity needs further study. Non-pregnant mice with a β-cell-specific deletion of the leptin receptor (using the *Pdx1*-Cre line) display improved glucose tolerance and enhanced insulin secretion, β-cell hypertrophy, proliferation and mass (Morioka *et al.* 2007). These changes are associated with enhanced activation of the insulin signalling pathway in β-cells, with increased AKT–forkhead box protein O (FOXO) activity and reduced inhibitor of insulin signalling, SOCS3 (Morioka *et al.* 2007). However, pregnancy outcomes in response

to β-cell leptin receptor loss have yet to be investigated. Moreover, studies using *Pdx1*-Cre mice as a control, instead of the leptin receptor floxed mice, will help to fully discern the role of leptin in β-cell functionality and whole body glucose handling (Brouwers *et al.* 2014).

Adiponectin is an adipocyte-secreted hormone that enhances insulin sensitivity and has direct effects on β-cell function. Adiponectin receptors are highly expressed on human and mouse β-cells. In non-pregnant mice, transgenic overexpression of adiponectin protects against pancreatic β-cell loss and high fat diet-induced insulin resistance (Holland *et al.* 2011). In pregnant mice, genetic ablation of the adiponectin gene leads to glucose intolerance due to insulin deficiency and failed β-cell mass expansion, but there is no impact on GSIS (Qiao *et al.* 2017). However, β-cell-specific knockdown of the adiponectin receptor genes *AdipoR1* and *AdipoR2* does not significantly impact β-cell mass or insulin secretion (Qiao *et al.* 2021). Instead, adiponectin is proposed to promote the production of placental PL/PRLs, which in turn mediate β-cell proliferation and islet expansion during mouse pregnancy (Qiao *et al.* 2021). The adiponectin gene and protein are reported to be expressed by the human and rat placenta (Caminos *et al.* 2005; Chen *et al.* 2006). These data suggest a crosstalk between maternal fat, the placenta and β-cells involving hormones like leptin and adiponectin, which may have relevance for the pathogenesis of GDM.

Exosomes. Exosomes are extracellular vesicles (EVs) with key roles in cell to cell communication and conveying molecular signals to cells at distant locations. All cell types release exosomes, including adipose tissue, liver, pancreas, skeletal muscle and placenta during pregnancy (Jayabalan *et al.* 2017). Studies have identified that placenta-derived exosomes contain a wide variety of molecules, including 58 miRNAs encoded by a chromosome 19 cluster (Donker *et al.* 2012) and dipeptidyl peptidase IV, a biologically active molecule with the potential to regulate maternal insulin secretion (Kandzija *et al.* 2019). In addition, infusion of small EVs (sEVs) isolated from healthy pregnant women promoted GSIS, elevated insulin concentrations and skeletal muscle insulin resistance in non-pregnant mice (James-Allan *et al.* 2020). In contrast, sEVs from pregnant women with GDM failed to induce GSIS, did not increase insulin concentrations and resulted in exacerbated skeletal muscle insulin resistance and glucose intolerance in non-pregnant mice (James-Allan *et al.* 2020). However, more studies are required to understand the origin and role of circulating sEVs in regulating β-cells adaptations to pregnancy.

Local factors. In this section, involvement in the production of local factors in β-cell adaptation during pregnancy will be summarized, although, there may also be a role for nervous inputs into the pancreas in governing β-cell adaptations (Li *et al.* 2019). Further study is needed to explore whether this may have significance in the context of maternal β-cell function and glucose control during pregnancy.

Hepatocyte growth factor. Hepatocyte growth factor (HGF) levels are markedly increased during pregnancy. Both the placenta and amnion produce and secrete HGF, with the former likely contributing to maternal circulating concentrations (Horibe *et al.* 1995). However, during pregnancy HGF is also highly expressed within islet endothelial cells and HGF is thought to play an important local role in driving β-cell adaptations in the mother during gestation. In particular, islet endothelial cell proliferation and HGF expression are increased from early gestation, peaking on days 10–15 of pregnancy, prior to the enlargement of β-cell mass in rats *in vivo* (Johansson *et al.* 2006). Moreover, increased expression of both HGF and its receptor, c-Met (also called tyrosine-protein kinase Met or hepatocyte growth factor receptor), within islets is correlated with the peak of β-cells proliferation (Demirci *et al.* 2012). *In vitro*, vascular endothelial growth factor-A (VEGF-A) derived from pancreatic islet endothelial cells stimulates β-cell proliferation through secretion of HGF (Johansson *et al.* 2006). Taken together, the available data suggest a paracrine crosstalk between the islet vasculature and β-cells, which may be relevant during gestation and warrant examination.

Mice lacking c-Met in the pancreas (using *Pdx1*-Cre) have reduced β-cell proliferation, decreased GSIS and increased apoptosis during gestation, which manifests as reduced β-cell mass, glucose intolerance, reduced plasma insulin and hyperglycaemia (Demirci *et al.* 2012). Defects in β-cell adaptations in these null mice were related to a failure in PRLR signalling and reduced STAT5 nuclear localization. These data suggest that PRLR signalling in the β-cell requires intact c-Met activity. In addition, pancreas deficient c-Met mice fail to decrease levels of the cell cycle inhibitor p27, as well as upregulate GLUT2 in their islets during pregnancy (Demirci *et al.* 2012). However, further work is required to verify these studies as wild-type mice instead of *Pdx1*-Cre were used as controls when studying the effect of pancreatic c-Met deficiency on pregnancy physiology (Demirci *et al.* 2012; Brouwers *et al.* 2014). In addition, HGF from gestational tissues, like the placenta, may also be important for β-cell adaptations and requires study.

Serotonin. Serotonin is an indoleamine molecule derived from the amino acid tryptophan which contributes to β-cell adaptations to pregnancy (Kim *et al.* 2010; Pasek & Gannon, 2013). Serotonin principally acts locally, in either an autocrine or a paracrine fashion (Berger *et al.* 2009; Amireault *et al.* 2013). Evidence from mouse models has shown that serotonin expression

in islets increases during pregnancy and drives β-cell mass expansion (Kim *et al.* 2010). Serotonin signalling also plays an important role in enhancing GSIS in the mother during pregnancy (Ohara-Imaizumi *et al.* 2013), thereby maintaining glucose homeostasis and sensitivity. Moreover, interfering with serotonin signalling by dietary tryptophan restriction or inhibiting TPH1, the rate-limiting enzyme responsible for the synthesis of serotonin, leads to impaired β-cell proliferation and insulin secretion during pregnancy (Kim *et al.* 2010; Schraenen *et al.* 2010*b*). Consistent with this, serotonin treatment of mouse islets *in vitro* induces β-cell proliferation (Kim *et al.* 2010).

The gene encoding TPH1 is one of the most highly upregulated genes in islets during gestation, and both PRL and PL signalling through PRLR in the β-cells activate *Tph1* expression (Rieck *et al.* 2009; Kim *et al.* 2010; Schraenen *et al.* 2010*b*; Pepin *et al.* 2019). In particular, upon binding to PRLR, STAT5 is phosphorylated by JAK2 and migrates to the nucleus (Horvath, 2000) where it recognizes an interferon γ-activated motif in the *Tph1* gene promoter to induce expression in β-cells (Iida *et al.* 2015). However, induction of *Tph1* expression by PRL and PLs is thought to be more complex, as this process also requires the activation of extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K) signalling in β-cells (Iida *et al.* 2015). β-Cells contain all the machinery needed for serotonin synthesis, storage and secretion (Ohta *et al.* 2011). Thus, β-cells are thought to synthesize and co-secrete serotonin with insulin during pregnancy (Kim *et al.* 2010; Schraenen *et al.* 2010*b*; Goyvaerts *et al.* 2016).

Secreted serotonin acts in an autocrine fashion by binding to serotonin receptors on β-cells and regulates GSIS during pregnancy. Of note, 5-hydroxytryptamine (serotonin) receptor 3A (HTR3A) is an ionotropic receptor that functions as a serotonin-gated cationic ion channel on β-cells (Ohara-Imaizumi *et al.* 2013). When bound by serotonin, HTR3A allows the leak of extracellular Na^+ ions into the β-cell, mildly depolarizing the membrane and lowering the threshold for GSIS (Ohara-Imaizumi *et al.* 2013). In support of this, blocking HTR3A signalling reduces β-cell insulin secretion and impairs glucose tolerance in pregnant mice (Ohara-Imaizumi *et al.* 2013). Mice lacking another serotonin receptor, HTR2B, as well as mice treated with HTR2B antagonists also show defective β-cell proliferation, mass expansion and impaired glucose tolerance during pregnancy (Kim *et al.* 2010). There are also data which suggest that switching serotonin receptor subtype from HTR2B to HTR1D just prior to term may be an inhibitory signal that promotes postpartum regression of β-cell mass in mice (Kim *et al.* 2010). Taken collectively, these studies highlight the important role of serotonin signalling in the local regulation of β-cells and suggest that interfering with serotonin signalling through pharmacological agents and diets depleted in tryptophan may disrupt maternal β-cell expansion and increase the risk of developing GDM.

Vascular endothelial growth factor and placental growth factor. VEGF-A is a master regulator of endothelial–β-cell crosstalk during β-cell development and regeneration. As previously mentioned, VEGF-A originating from pancreatic endothelium stimulates HGF production with positive impacts on β-cell proliferation *in vitro* (Johansson *et al.* 2006). However, conditional reduction of VEGF-A signalling in β-cells reduces islet vessel maintenance and induces transient glucose intolerance without altering β-cell mass expansion in pregnant mice *in vivo* (Staels *et al.* 2017). Placental growth factor (PlGF) is a member of the VEGF family that is highly secreted by the placenta during gestation. PlGF is also expressed by β-cells, and local islet production is increased during pregnancy (Yang *et al.* 2020). Studies in mice have shown that knock-down of PlGF in β-cells results in compromised β-cell proliferation, reduced β-cell mass expansion and impaired glucose tolerance during pregnancy (Yang *et al.* 2020). Moreover, in part these effects in the β-cell PlGF knockdown mice are mediated by reduced recruitment of macrophages to pancreatic islets during pregnancy, as macrophages highly express the receptor VEGFR1, which binds PlGF (Yang *et al.* 2020). In a mouse model showing gestational hypertension and significantly reduced serum PlGF levels, β-cell proliferation and mass expansion were impaired during pregnancy (Li *et al.* 2015). Further work in this model showed that defects in β-cell adaptations were rescued by exogenous PlGF treatment to the mother during pregnancy (Li *et al.* 2015). Collectively, these data highlight the importance of growth factors in the endocrine, paracrine and autocrine regulation of β-cell adaptations during pregnancy. Moreover, defects in such regulation during pregnancy could play a major role in the development of GDM.

Molecular mechanisms involved in β-cell adaptation during pregnancy

Intracellular effectors (signal transduction pathways). In this section, the main pathways and other key molecular mechanisms that have been reported to be implicated in β-cell adaptation during pregnancy will be summarized.

JAK2/STAT5 signalling. The JAK2/STAT5 cascade is the canonical signalling pathway downstream of PRLR, which largely contributes to PRL and PL impacts on β-cells *in vitro* and during pregnancy *in vivo* (Amaral *et al.* 2004; Brelje *et al.* 2004; Hughes & Huang, 2011; Iida *et al.* 2015). As mentioned previously, PLs bind to PRLR

and recruit JAK2, which then phosphorylates STAT5 and STAT5 activation leads to the expression of key genes involved in β-cell growth and proliferation. However, these effects are amplified as lactogenic signalling leads to the auto-upregulation of PRLR expression via STAT5 (Galsgaard *et al*. 1999). This increase in PRLR is needed to maintain the prolonged activation of STAT5 by PLs in β-cells (Brelje *et al*. 2004). In addition to PLs, GH and PRL both acutely stimulate STAT5A and 5B isoform activity, but only PRL is responsible for STAT5B activation in rat islets and INS-1 cells. Whether this isoform preference is also observed *in vivo* and has relevance during gestation has not been established (Brelje *et al*. 2004). Interestingly, mice with β-cell-specific STAT5A/B deficiency (using RIP-Cre) do not show defects in islet development or function when they are young, but develop glucose intolerance as they get older and demonstrate slightly more glucose intolerance than normal during pregnancy (Lee *et al*. 2007). STAT5 regulates the expression of several genes that may be significant for β-cell adaptations during gestation. For instance, in mice during pregnancy, STAT5 activation in β-cells promotes the expression of cyclin–cyclin-dependent kinase (CDK) genes and upregulates phosphorylation of retinoblastome protein (Rb), which are both important for promoting cell cycle progression (Zhao *et al*. 2019). The STAT5 pathway may also be responsive to other local and endocrine factors important for β-cell adaptations. In particular, HGF is believed to execute its actions on β-cells through the STAT5 pathway, as pancreatic loss of c-Met signalling and failed maternal β-cell adaptation during gestation are accompanied by reduced nuclear localization of STAT5 (Demirci *et al*. 2012). Thus, through STAT5, PLs, PRLs, GH, HGF and possibly other factors command relevant cellular pathways involved in maternal β-cell adaptation during gestation. However, due to the intricacy and interplay between cellular pathways, failures in STAT5 activation may be compensated by other signalling transduction pathways in the β-cells. Moreover, additional work is required to further delineate the contribution of STAT5/B in β-cell adaptations and glucose handling as floxed mice rather than RIP-Cre mice were used as controls when studying the effect of β-cell-specific Stat5/B deficiency (Lee *et al*. 2006; Lee *et al*. 2007).

PI3K–AKT signalling. The PI3K–AKT cascade is also activated by PRLR signalling and plays a dominant role in the regulation of β-cell function in both non-pregnant (Jiang *et al*. 2018) and pregnant states (Banerjee *et al*. 2016). PI3K–AKT regulates β-cell proliferation through modulation of multiple proteins, including forkhead box protein O1 (FOXO1), glycogen synthase kinase-3 (GSK3) and mechanistic target of rapamycin (mTOR) (Jiang *et al*. 2018). Several studies in rodents have shown that pregnancy and lactogenic signalling activate IRS1, IRS2, PI3K, AKT, p70S6K and mTOR in β-cells (Amaral *et al*. 2004; Zahr *et al*. 2008; Hughes & Huang, 2011). Pregnant rats treated with antisense oligonucleotides to reduce PRLR have reduced AKT phosphorylation and p70S6K protein levels in pancreatic islets (Amaral *et al*. 2004). Treatment of mice with rapamycin, an inhibitor of mTOR signalling, impairs β-cell proliferation and expansion during pregnancy, but does not alter blood glucose levels or glucose tolerance (Zahr *et al*. 2008). In addition, PI3K activation seems to play a central role in in the HGF-induced mitogenic effect on β-cells (Gahr *et al*. 2002; Vasavada *et al*. 2007). Furthermore, activation of PI3K–AKT signalling is involved in the protective effect of HGF against pharmacologically induced cell death in pancreatic β-cells (García-Ocaña *et al*. 2003). However, the exact role of the PI3K–AKT signalling cascade in β-cell adaptations in response to local and endocrine factors has not been specifically addressed in the context of pregnancy. Interestingly, c-Met receptor loss in β-cells (using *Pdx1*-Cre) from pregnant mice reduced GSIS and expression of islet *Glut2*, *Pdx1* and insulin mRNAs, but this was not observed in the pregnant mice with β-cell PRLR deficiency (mediated by RIP-Cre) (Demirci *et al*. 2012; Pepin *et al*. 2019). These data suggest that HGF and PLs/PRLs may mediate β-cell adaptations during pregnancy via divergent mechanisms downstream of PI3K–AKT. They may also highlight the difference between PRL/PL and GH in signalling via PRLR, as the *bGH* minigene is present in both the Cre transgenic lines used when studying c-Met and PRLR loss in β-cells, but appropriate Cre controls are needed to provide any firm conclusions (Lee *et al*. 2006; Demirci *et al*. 2012; Brouwers *et al*. 2014; Pepin *et al*. 2019).

Raf–MEK–ERK signalling. The Raf–mitogen-activated protein kinase kinase (MEK)–ERK signalling pathway is also activated downstream of PRLR in rodent β-cells. Activation of this pathway modulates cell growth, proliferation and differentiation via interaction with menin, a tumour suppressor protein (Chamberlain *et al*. 2014). In addition to PRLR, epidermal growth factor receptor (EGFR) also acts through the MEK–ERK signalling cascade. Expression of a dominant-negative EGFR in pregnant mice blocks placental lactogen-induced β-cell expansion and expression of survivin (Birc5), a key cell-cycle protein and anti-apoptotic factor (Hakonen *et al*. 2014). However, serotonin synthesizing enzymes and other key genes involved in β-cell adaptation were still upregulated in these mutant pregnant mice treated with placental lactogen (Hakonen *et al*. 2014). ERK5 activation is increased in islets coincidentally with β-cell expansion during mouse pregnancy (Chen *et al*. 2018). Pharmacological suppression of ERK5 activation during pregnancy reduced β-cell proliferation and cyclin D

levels, increased blood glucose levels and impaired GSIS (Chen *et al*. 2018). Finally, ERK1/2 activation is required for platelet derived growth factor receptor (PDGFR) to promote β-cell expansion during development (Chen *et al*. 2011). Interestingly, enhancer of zeste homologue 2 (EZH2) expression was suppressed in pregnant mice with selective deletion of PRLR in β-cells (Pepin *et al*. 2019). Together, these data support the notion of a close interaction between PRLR and ERK signalling and the involvement of ERK signalling in mediating β-cell adaptations during pregnancy, more broadly.

Serotonin signalling. In pregnant mice, serotonin synthesis is increased in at least 50% of β-cells within pancreatic islets (Goyvaerts et al. 2015). Transcriptomic analyses of islets in response to pregnancy have identified very strong upregulation of two paralogous genes encoding TPH enzymes, *Tph1* and *Tph2*, which catalyse the formation of 5-hydroxytryptophan (Rieck *et al*. 2009; Kim *et al*. 2010, Pepin *et al*. 2019). The induction of these genes in β-cells is strongly dependent on the PRLR and JAK2/STAT5 signalling pathway during pregnancy (Schraenen *et al*. 2010b; Iida *et al*. 2015). Serotonin acts in an autocrine/paracrine fashion on β-cells expressing serotonin receptors to drive functional adaptations during pregnancy. For instance, serotonin can act locally on other β-cells through HTR2B and HTR3 receptors or may regulate blood flow to the islet, since serotonin has potent vasoconstricting effects. In addition, β-cell serotonin enters the blood circulation and mediates systemic effects (Goyvaerts et al. 2016). Mice which are deficient in *Htr2b* display impaired glucose tolerance and decreased β-cell proliferation rates in pregnancy (Kim *et al*. 2010). However, there are discrepancies about the relevance of HTR2B in mediating pregnancy-related changes in β-cells, as other studies have found only minor or weak expression of *Htr2b* in islets (Layden *et al*. 2010; Schraenen *et al*. 2010b). Interestingly, mice deficient in *Htr3a* do not show any alterations in the pregnancy-induced expansion of β-cell mass, but have insufficient GSIS and display glucose intolerance in gestation (Ohara-Imaizumi *et al*. 2013). Data suggest that serotonin acts through HTR3 to depolarize β-cells and lower the threshold for GSIS during pregnancy (Ohara-Imaizumi *et al*. 2013). Thus, serotonin is released from β-cells in response to lactogenic signalling and acts in an autocrine fashion to increase proliferation and insulin secretion via HTR2B an HTR3, respectively.

CISH and SOCS signalling. Cytokine-inducible SH2-containing protein (CISH) is a member of the suppressor of cytokine signalling (SOCS) family that negatively regulates PRLR signalling by blocking STAT5 activation and is strongly induced during gestation (Rieck *et al*. 2009; Kim *et al*. 2010; Layden *et al*. 2010; Pepin *et al*. 2019). Of note, the *Cish* and *Socs2* (a SOCS family member) genes are highly expressed by pancreatic islets during pregnancy and are thought to play a critical role in limiting or controlling both the rate of proliferation and survival of β-cells (Rieck *et al*. 2009). However, ablation of *Cish* did not augment β-cell STAT5 activation, proliferation or expansion in mice during pregnancy (Jiao *et al*. 2013). In part, the lack of an effect of *Cish* loss on β-cells likely stemmed from compensatory upregulation of *Socs2* in islets of mutant mice during pregnancy (Jiao *et al*. 2013).

Glucokinase. In β-cells, glucokinase is a recognized glucose sensor important for maintaining whole body and cellular glucose homeostasis (Matschinsky & Wilson, 2019). In response to pregnancy and lactogenic signalling, levels and activity of glucokinase increase in β-cells, resulting in a lower threshold for GSIS (Weinhaus *et al*. 1996). This is mediated via PRLRs on β-cells and through activation of the JAK2/STAT5 signalling pathway, which increases transcription of genes encoding glucokinase and insulin (Weinhaus *et al*. 2007). GLUT2 on β-cells is also induced via this process, which results in enhanced glucose utilization and oxidation that is important for enhanced glucose-stimulated insulin synthesis during pregnancy (Weinhaus *et al*. 2007).

Neogenic signalling. As previously mentioned, the formation of β-cells from non-β-cell progenitors (neogenesis) is one of the processes thought to be involved in β-cell expansion during murine pregnancy (Bonner-Weir *et al*. 2004; Abouna *et al*. 2010; Toselli *et al*. 2014). In part, this is thought to be related to the transcription factor, neurogenin-3 (NGN3), which is expressed by progenitor cells and becomes down-regulated, secondary to the upregulation of its inhibitors, *Pdx1*, *Sox9* and *Hes1*, in islets during pregnancy (Toselli *et al*. 2014). This process if thought to facilitate the differentiation of progenitor cells into hormone producing β-cells that can enter the cell cycle and proliferate in the mother. Indeed, the expression of many NGN3 target genes, including *Tle3*, *NeuroD*, *Nkx2*.2, *IA1* and *Rfx6*, are also modified in maternal islets during pregnancy (Toselli *et al*. 2014).

Apoptosis signalling. A reduction in PRLR expression does not affect β-cell apoptosis in pregnant mice, likely due to the low apoptosis rates naturally observed (Huang *et al*. 2009). However, pregnant mice lacking c-Met and rat insulinoma cells treated with PRLR siRNAs show increased β-cell apoptosis rates (Demirci *et al*. 2012; Arumugam *et al*. 2014). Moreover, transcriptomic analysis indicates that at least 60 genes involved in apoptosis processes, including *Ngfr*, *Tnfrsf11b* (Osteoprotegerin), *Acvr1c*, *Nupr1* and *Survivin*, may be important in β-cell adaptations during pregnancy (Rieck *et al*. 2009). Interestingly, Survivin acts as an inhibitor of both the

intrinsic and extrinsic apoptosis pathways by blocking the activity of several caspase proteins (Tamm *et al.* 1998) and Survivin expression is increased 5-fold in islets during pregnancy (Rieck *et al.* 2009), in part via EGFR signalling (Hakonen *et al.* 2014). Survivin is also induced by PRL signalling downstream of AKT, STAT5 and ERK and participates in PRL-mediated β-cell proliferation during pregnancy (Xu *et al.* 2015). Recently, overexpression of the transcription factor, paired box 8 (PAX8) was shown to reduce apoptosis rate in both murine and human pancreatic islets (Martin-Montalvo *et al.* 2019). In addition in mice, expression of PAX4 stimulated the proliferation of a β-cell subpopulation that expands during pregnancy and provides protection against endoplasmic reticulum stress-induced apoptosis (Lorenzo *et al.* 2015). Moreover, *Lrrc55*, a gene highly induced in islets during pregnancy, protects β-cells from glucolipotoxicity-induced apoptosis, through upregulation of pro-survival signals and attenuated calcium depletion (Makkar *et al.* 2019). Studies in rats have shown the presence of condensed chromatin, apoptotic bodies and programmed cell death in β-cells after delivery, which were related to TRPM2 and TGFβ1 expression (Scaglia *et al.* 1995). Thus, regulation of apoptotic pathways may be important in various aspects of β-cell adaptations in the mother both during and after pregnancy.

Transcription factors. Downstream of signalling pathways, transcription factors execute pregnancy-related changes in β-cell function by controlling the expression of genes critical for proliferation, survival and GSIS. This section will describe the main transcription factors relevant for β-cell adaptation during pregnancy.

FOXD3. In mice, pancreas-specific deletion of the transcription factor forkhead box D3 (FOXD3) (mediated by *Pdx1*-Cre) resulted in impaired glucose tolerance and decreased β-cell mass, proliferation and size in pregnancy (Plank *et al.* 2011). Defects in β-cell adaptations were related to the mis-expression of several genes known to regulate proliferation, including *Foxm1*, *Skp2*, *Ezh2*, *Akt2* and *Cdkn1a* (Plank *et al.* 2011). Mice carrying floxed *Foxd3* alleles were used as controls instead of *Pxd1*-Cre mice (Plank *et al.* 2011). Hence, further studies are needed to be sure of the involvement of FOXD3 in mediating decreased β-cell mass, proliferation and size in pregnancy (Brouwers *et al.* 2014) Indeed, this is relevant as *Foxd3* gene expression is normally downregulated in islets at mid-late pregnancy (Plank *et al.* 2011) and while PL reduces islet *Foxd3* expression *in vitro*, β-cell-specific PRLR deficiency does not impact *Foxd3* expression in mid–late gestation *in vivo* (Banerjee *et al.* 2016). Thus, FOXD3 may be required to promote β-cell proliferation before PLs and PRLs rise in the maternal circulation and PRLR signalling appears to be required for *Foxd3* down-regulation during pregnancy.

MafB. *MafB* is expressed in immature β-cells during prenatal development and is then re-expressed in approximately 25% of β-cells in the mother during mouse pregnancy (Pechhold *et al.* 2009). This transient gestational expression of *MafB* requires lactogenic signalling and deletion of *MafB* in β-cells reduces both β-cell proliferation and mass during pregnancy, although the RIP-Cre mice were not used as controls for the *in vivo* observations so further study in this context is needed (Banerjee *et al.* 2016). MafB is the principal factor activating insulin expression during β-cell development (Artner *et al.* 2007). Furthermore, MafB is required for inducing MafA transcription in precursor β-cells and is a primary regulator of *Pdx1*, *Nkx6.1* and *Glut2* expression in mature β-cells (Artner *et al.* 2007). Thus, additional studies are warranted to explore whether MafB operates downstream of PLs/PRLs to help drive maternal β-cell adaptations in pregnancy.

FOXM1. The cell-cycle-associated transcription factor FOXM1 is normally upregulated in maternal islets during late mouse gestation and decreases after parturition (Zhang *et al.* 2010). *Foxm1* deletion in mice results in a failure to increase β-cell proliferation during pregnancy and this defect is coupled to an increase in islet Menin and nuclear p27 staining (Zhang *et al.* 2010). Islets treated with PL show increased *Foxm1* expression *in vitro*, suggesting that FOXM1 may be a downstream mediator of PRLR signalling in β-cells (Zhang *et al.* 2010; Pepin *et al.* 2019). Insulin signalling in β-cells is required for FOXM1 activity, as signalling via (a) ERK facilitates FOXM1 localization to the nucleus, and (b) PI3K enhances FOXM1 mediated upregulation of *CenpA* and *Plk1* expression, which promotes cell proliferation and viability (Shirakawa *et al.* 2017). In mice, *CenpA* deficiency in β-cells leads to impaired proliferation in response to pregnancy (Shirakawa *et al.* 2017). Specific inhibitors of STAT5, AKT and ERK pathways significantly decreased the protein levels of FOXM1 and Survivin in PRL-stimulated INS-1 cells (Xu *et al.* 2015). Thus, FOXM1 and Survivin are common downstream effectors of these pathways mediating β-cells adaptations during pregnancy with PRL (Xu *et al.* 2015).

HNF-4α. The orphan nuclear receptor hepatocyte nuclear factor-4α (HNF-4α) is required in β-cells for their proliferative response during pregnancy. Mice with β-cell HNF-4α deficiency fail to expand their β-cell mass during pregnancy (Gupta *et al.* 2007). Gene expression analysis of islets from these pregnant mice has shown that this failure is linked to the altered expression of numerous genes and pathways involved in metabolism, signal transduction and β-cell proliferation

(Gupta *et al*. 2007). In addition, activation of Ras–ERK signalling during pregnancy was significantly reduced in HNF-4α-deficient islets, apparently in part by the downregulation of suppression of tumorigenicity 5 (ST5; Gupta *et al*. 2007). However, conditionally over-expressing ST5 in β-cells is not sufficient to enhance their proliferation during pregnancy (Ou *et al*. 2018). In part, the lack of an effect in ST5 transgenic animals may be due to increased islet activation of Rassf1a, a factor that inhibits cell cycle progression (Ou *et al*. 2018). Thus, there are complex interactions that determine the effect of HNF-4α in β-cell mass enhancement during gestation.

Menin. Menin, the protein product of *MEN1 gene*, is mutated in multiple endocrine neoplasia type 1, a disease characterized by tumours in endocrine glands, including pancreatic islets (Thakker, 2014). In mice, islet levels of Menin decrease in pregnancy and then increase to pre-gestational levels 1 week after birth. In addition, the transgenic induction of Menin expression in β-cells prevents islet expansion, induces hyperglycaemia and impairs glucose tolerance during mouse pregnancy (Karnik *et al*. 2007). In mice, PRL infusion reduces islet Menin expression in association with a decrease in the expression of the CDK inhibitors p27 and p18, which prevent β-cell proliferation. Attenuation of Menin expression in islets by PRL during mouse pregnancy involves an intact PRLR, AKT signalling and STAT5 mediated expression of Bcl6, a transcriptional repressor of the *Menin1* gene (Karnik *et al*. 2007; Hughes & Huang, 2011). Thus, the downregulation of Menin via lactogenic signalling is important for the β-cells to functionally adapt during pregnancy.

Aryl-hydrocarbon receptor nuclear translocator. Aryl-hydrocarbon receptor nuclear translocator (ARNT) is a transcription factor that is decreased in islets from individuals with type 2 diabetes and is upregulated two-fold in maternal islets during pregnancy in mice (Lau *et al*. 2013). In mice, β-cell-specific deletion of ARNT (mediated by RIP-Cre) impairs glucose tolerance, insulin secretion and β-cell proliferation during pregnancy in alliance with decreases in the expression of *Irs2*, *G6pi* and cyclin D2 in islets (Lau *et al*. 2013). Although RIP-Cre mice were not used as controls for this study, the investigators reported that there are no deviations in glucose tolerance when compared to either wild-type or *Arnt* floxed mice, but there was no mention of studying this with respect to pregnancy (Lau *et al*. 2013). In the non-pregnant state, mutant mice also exhibit defects in GSIS and glucose intolerance and this is related to reduced HNF-4α and insulin and AKT signalling components in pancreatic islets (Gunton *et al*. 2005). However, further work is required to fully understand the significance, and upstream regulators and signalling pathways governing ARNT action in β-cells in the mother during pregnancy.

Epigenetic mechanisms. There are data that suggest that epigenetic processes, namely non-coding RNAs, chromatin remodelling/histone modifications and DNA methylation, are involved in mediating β-cell adaptations during pregnancy. MicroRNAs (miRNAs) have important roles in modulating β-cell gene expression with impacts on β-cell differentiation, proliferation, function and survival (Filios & Shalev, 2015). Transcriptomic analysis of islets from rats identified that β-cell expansion during pregnancy was associated with changes in the expression of five miRNAs (Jacovetti *et al*. 2012). Of note, miR-218, miR-338-3p and miR-874 were downregulated, whereas miR-144 and miR-451 were upregulated and both sets of changes were strongly correlated with the peak of β-cell proliferation around gestational day 15 (Jacovetti *et al*. 2012). Reducing miR-338-3p in either rat or human islets *in vitro* did not alter insulin secretion but lead to enhanced *Survivin*, *Foxm1*, *Ccnd*, *Igf1r*, *Irs2*, *Bcl2* and *Bcl2l1* expression, which are important for β-cell proliferation and survival during pregnancy *in vivo* (Jacovetti *et al*. 2012). Oestrogens potentially regulate the expression of miRNAs in β-cells during gestation, as exposure of both rat and human β-cells to oestradiol potently reduced the expression of miR-338-3p *in vitro* (Jacovetti *et al*. 2012). The expression of miR-338-3p and miR-451 (but not the other miRs altered by pregnancy) is also coupled to the improved resistance of β-cells to pro-apoptotic stimuli and compensatory β-cell mass expansion in response to developmental and environmental cues, including nutritional challenges in rodents (Jacovetti *et al*. 2012). In women with poor glycaemic control or GDM during pregnancy, circulating miR-330-3p levels are elevated and correlated to low insulin concentrations and pregnancy outcome (Sebastiani *et al*. 2017; Pfeiffer *et al*. 2020). Moreover, in humans, several studies have identified miRNAs that are associated with abnormal weight gain and the development of GDM during pregnancy (Vasu *et al*. 2019). Thus, many miRNAs may participate in β-cell adaptations with important implications for glucose control in the mother during pregnancy. Further work is still required to explore the upstream and downstream mediators of miRNA actions in β-cells.

Molecular profiling of islets from pregnant mice with β-cell PRLR deletion has revealed aberrant expression of several epigenetic modifiers that regulate chromatin remodelling (Ezh2 and Suz12) and DNA methylation (Gadd45g and Dnmt3b) (Pepin *et al*. 2019). Moreover, other work has shown that PRL downregulates pancreatic islet expression of Menin, which functions as part of a histone methyltransferase complex to promote tri-methylation of histone 3 lysine 4 and expression of cell cycle inhibitors p27 and p18 (Karnik *et al*. 2007). These findings suggest that downstream of PRLR, many genetic and epigenetic regulators coordinate β-cell adaptations during pregnancy (Pepin *et al*. 2019). Platelet derived

growth factor receptor (PDGFR) also upregulates the chromatin remodelling protein EZH2, a protein required for β-cell expansion during development (Chen *et al.* 2011) that was suppressed in pregnant mice with β-cell PRLR loss (Pepin *et al.* 2019). This suggests there may be overlap in the epigenetic pathways contributing to β-cell adaptations during gestation. Finally, insulin expression is regulated by DNA methylation and increased methylation of CpG sites in the insulin promoter is associated with elevated occupancy of methyl CpG binding protein 2 (MeCP2) and reduced binding of the transcription factors ATF2 and CREB in islets (Kuroda *et al.* 2009). However, work is required to examine the contribution of DNA methylation in the regulation of insulin production and in β-cell adaptations during pregnancy.

Maternal conditions that affect glucose metabolism and β-cell adaptation during pregnancy

Conditions that impact maternal physiology have the capacity to disrupt β-cell adaptation and thus the development of GDM during pregnancy. In this section, the impact of different environmental conditions that alter maternal body weight, adiposity and insulin–glucose homeostasis will be described in the context of β-cell function during pregnancy (Table 1). In addition, the effects of maternal conditions on the placenta will be mentioned because of the role of placenta in transferring nutrients to the fetus and in the endocrine regulation of maternal insulin sensitivity and β-cell adaptations.

Maternal diet or nutritional status.

Obesity and incidence of GDM in pregnant women. Abnormal nutrient status, indicated by maternal obesity, over-nutrition and altered gestational weight gain, as well as certain genetic predispositions, can lead to failed β-cell adaptation, hyperglycaemia and GDM during pregnancy. However, the mechanisms underlying failed or aberrant β-cell adaptation particularly under conditions of abnormal maternal nutritional status are not clear (Moyce & Dolinsky, 2018). For instance, there are some studies that suggest that while obese women have increased insulin resistance, they may have either an increased or a decreased insulin response compared to normal weight women during pregnancy (Catalano, 2010; Fan *et al.* 2020). Examinations of islets from women during pregnancy also vary widely with respect to maternal body mass index (BMI) and gestational age and do not include samples from mothers with GDM (Van Assche *et al.* 1978; Butler *et al.* 2010). However, studies relating dietary intake (reported through food frequency questionnaires) to the development of glucose abnormalities during pregnancy, like GDM have provided some insights. For instance, increased fat and

Table 1. Summary of the impact of different environmental conditions on maternal β-cell adaptations relative to maternal metabolic state and placental endocrine function

	β-Cell mass and/or proliferation	β-Cell apoptosis	β-Cell molecular mechanisms	Glucose levels	Insulin levels	Glucose tolerance	Insulin sensitivity	Body weight	Fat mass
High fat diet	↑	↑	↓ (*Pax6*, *Pdx1*, *Mafa* and *Glut2*)	↑	↑	→	→	↑	↑
High sugar diet	–	–	–	↑	↑	—	→	—	–
High sugar and fat diet	↑	–	–	↑	↑	→	↑ (liver)↓ (adipose and muscle)	↑	↑
Low protein diet	→	–	↓ (β-catenin and connexins)	—	—	—	–	— (6% diet)↑ (18% diet)	–
Hypoxia	–	–	–	— (10% O_2)↓ (13% O_2)	— (10% O_2)— (13% O_2)	↑ (10% O_2)	↑	↓ (10% and 15% O_2)	→
Circadian disruption	–	–	–	Daily changes	Daily changes	— (rat)↓ (sheep)	–	→	→
Endocrine disrupting chemicals	↓ (post-partum)	↑(post-partum)	↑ (p16 p53, (post-partum)	↑	↑	→	→	↑	↑

↑: high/increased; ↓: low/decreased; —: unchanged; –: not reported

low carbohydrate intakes during the second trimester of pregnancy were associated with an increased risk of impaired glucose tolerance and GDM in women (Saldana *et al.* 2004). In another prospective study, pre-pregnancy BMI and elevated intake of $n-3$ fatty acids in the first trimester were associated with the development of GDM (Radesky *et al.* 2008). However, studies in pregnant rodents subjected to dietary manipulations have provided further information of the changes in maternal glucose homeostasis and the contributions of regulatory pathways governing β-cell adaptations during pregnancy. These findings are summarized below.

High sugar diet. Rats fed a high fructose and/or sucrose diet (HSD) from the start of pregnancy show normal glucose tolerance but increased plasma insulin concentration, likely as a result of compensatory β-cell mass expansion (Jen *et al.* 1991; Alzamendi *et al.* 2012). A maternal HSD during pregnancy was also associated with disrupted placental development (Jen *et al.* 1991; Alzamendi *et al.* 2012) suggesting that the placental production of endocrine signals important for adapting β-cell function may be altered and contribute to the maternal hyperinsulinaemia observed. While the impacts of maternal HSD intake from prior to pregnancy on β-cell adaptations have not been studied, β-cells can become overwhelmed by prolonged exposure to high glucose leading to glucotoxicity, oxidative stress, apoptosis and insulin insufficiency (Bensellam *et al.* 2012). Thus, a maternal HSD, both acute or chronic, may lead to β-cell dysfunction and increased susceptibility of the mother to develop GDM.

High fat diet. The impact of a high fat diet (HFD) on β-cell adaptations and glucose homeostasis during pregnancy depends on the duration of feeding, the percentage of dietary fat and the gestational day studied. In rodents, exposure to a HFD from prior to and/or during pregnancy increases maternal body weight/adiposity (Jones *et al.* 2009; Liang *et al.* 2010; Carter & Tenlep, 2015) and impairs glucose tolerance during gestation (Carter & Tenlep, 2015; Wu *et al.* 2015; Huang *et al.* 2017, 2019; Chung *et al.* 2019). In addition, concentrations of glucose, insulin and leptin are increased in HFD fed dams during pregnancy (Holness *et al.* 2007; Liang *et al.* 2010; Li *et al.* 2013; Aye *et al.* 2015; Huang *et al.* 2017). Maternal lipid profile is also altered in HFD-fed dams of most studies (Jones *et al.* 2009; Heerwagen *et al.* 2013; Carter & Tenlep, 2015; Chung *et al.* 2019) together with an increase in the levels of inflammatory markers in the blood (Li *et al.* 2013). Mice fed a HFD for >3 months prior to pregnancy show greater β-cell mass but higher rates of apoptosis and pro-inflammatory markers in their β-cells (Li *et al.* 2013). Mice fed a HFD just during pregnancy also show greater β-cell mass (Huang *et al.* 2019). In rats fed a HFD during gestation, GSIS is enhanced *in vivo*, but insulin secretion response to glucose in islet perifusions is impaired (Holness *et al.* 2007). These latter findings are thought to reflect a partial compensation of β-cells for peripheral insulin resistance that is limited by an intrinsic defect in insulin secretion in the pregnant mother in response to the HFD. In support of this, female rats fed a HFD from around the time of mating show decreased expression of β-cell functional genes, namely *Pax6*, *Pdx1*, *MafA* and *Glut2*, in their pancreas (Wu *et al.* 2015). In part, interference of maternal β-cells with HFD feeding was rescued by a pharmacological induction of peroxisome proliferator-activated receptor α activation (Holness *et al.* 2007). Transcriptomic analysis of islets from HFD fed mice compared to β-cell-specific *Prlr* knockout mice suggests that dietary and lactogenic signalling operate via different mechanisms to modulate maternal β-cell functions during pregnancy (Pepin *et al.* 2019). Indeed indirect influences from other endocrine signals disrupted by exposure to a HFD could also impact β-cell adaptations during gestation (Moyce & Dolinsky, 2018). However, there could also be some common mechanisms involved, as miR-338-3p has been described as a mediator of compensatory β-cell mass expansion with both pregnancy and HFD-induced obesity in rodents (Jacovetti *et al.* 2012).

Studies in rodents have also demonstrated that the placenta is susceptible to HFD, whereby a HFD is associated with elevated oxidative stress and endothelial cellular damage (Liang *et al.* 2010). Placental size and lipid content are also increased (Heerwagen *et al.* 2013), insulin and mTORC1 signalling is greater (Aye *et al.* 2015) and transport of glucose and amino acids is elevated *in vivo* in mice fed a HFD (Jones *et al.* 2009; Aye *et al.* 2015). As a consequence of the abnormal maternal metabolic profile and increased placental nutrient transport in HFD fed dams, the fetus is exposed to hyperglycaemia and displays increased fetal weight (Jones *et al.* 2009; Aye *et al.* 2015). However, whether abnormalities in placental hormone production contribute to the altered maternal metabolic profile with a HFD during gestation or not is unknown. These studies show that consumption of a HFD by the mother impacts β-cell adaptations, glucose homeostasis and the placenta with consequences for maternal metabolic health and offspring development.

High fat and sugar, obesogenic and cafeteria diet. Intake of a diet high in both sugar and fat (HSHF) during pregnancy also impacts maternal β-cell adaptations, but the specific effect depends on the diet composition and dietary protocol used. Nevertheless, pregnant mice fed a HSHF diet show increased adiposity in association with an altered lipid profile, increased levels of leptin and defects in tissue insulin sensitivity (Holemans *et al.* 2004; Sferruzzi-Perri *et al.* 2013; Rosario, *et al.* 2015; Fernandez-Twinn *et al.* 2017; Musial *et al.* 2017, 2019;

Martins Terra *et al*. 2019). In addition, a HSHF diet during gestation induces hyperinsulinaemia, hyperglycaemia and glucose intolerance in the mother (Sferruzzi-Perri *et al*. 2013; Fernandez-Twinn *et al*. 2017; Musial *et al*. 2017; Martins Terra *et al*. 2019). Rats fed a HSHF diet also present with increased maternal adiposity and impaired glucose tolerance in gestation (Holemans *et al*. 2004; Vanzela *et al*. 2010). Moreover, consumption of a HSHF diet for 1 week prior to pregnancy is sufficient to cause glucose intolerance, impair β-cell proliferation and reduce fasting insulin in mid-pregnancy (Pennington *et al*. 2017). Thus, a HSHF diet, even if consumed acutely or just prior to pregnancy, is able to alter glucose homeostasis and β-cell adaptations, increasing the risk of the mother to develop GDM. Obesity is associated with increased production of pro-inflammatory cytokines like interleukin (IL)-1β, IL-6 and TNF-α from the placenta and/or maternal adipose during pregnancy (Pantham *et al*. 2015; Moyce & Dolinsky, 2018). Recent work has shown that such pro-inflammatory cytokines induce β-cell dedifferentiation and diminish insulin secretion capacity *in vitro* (Nordmann *et al*. 2017). Thus, further work is warranted to explore how a pregnancy-induced inflammatory profile which is aggregated by obesity may modify β-cell adaptation and the development of GDM.

In most cases studied, placental function was disturbed by a HSHF diet and there were alterations in placental glucose metabolism, nutrient transport and/or growth (Sferruzzi-Perri *et al*. 2013; Rosario *et al*. 2015; Musial *et al*. 2017). Of note, placentas from HSHF diet fed dams also show reduced expression of PRL- and PL-related genes, which may have consequences for β-cell proliferation and secretion of insulin in response to the hyperglycaemia induced by the dietary manipulation (Huang *et al*. 2009; Banerjee *et al*. 2016; Musial *et al*. 2017; Sferruzzi-Perri *et al*. 2020). Further work is required to examine the interaction of changes in maternal β-cell adaptations, glucose handling and the placenta in pregnancies when the mother is consuming a HSHF diet.

Low protein diet. Studies have evaluated the importance of dietary protein intake during pregnancy on maternal metabolism. This has involved using diets that contain anywhere between 6% casein and 23% casein as control. In rodents, intake of low protein diets containing 6–9% casein during pregnancy does not change the weight of the pregnant dam (Rutland *et al*. 2007; Salvatierra *et al*. 2015). However, a more minor reduction of dietary protein content (18% casein) in pregnant mice is associated with an increase in maternal hysterectomized body weight in late gestation, although whether this reflects an expansion of select tissues, lean and/or fat mass is unknown (Coan *et al*. 2011). In addition, a 6% low protein diet fed to rats during pregnancy does not impact maternal glucose tolerance but is linked to reduced pancreatic islet abundance of proteins important for intercellular communication and coupled release of insulin by β-cells, including connexin 36 and β-catenin (Milanski *et al*. 2005; Marçal-Pessoa *et al*. 2015). The same diet during pregnancy also reduced maternal islet area in association with reduced PI3K signalling, but no change in insulin content was observed (Salvatierra *et al*. 2015). Interestingly, pregnant female mice exposed to chronic protein restriction show reduced body weight, glucose intolerance, impaired β-cell GSIS and attenuation of the phospholipase C–protein kinase C signalling pathway that is involved in the insulin secretory process (Ignácio-Souza *et al*. 2013; Szlapinski *et al*. 2019).

In part, alterations in β-cell adaptations and glucose handling during pregnancy with maternal dietary protein restriction are thought to be mediated via changes in local serotonin production (Baeyens *et al*. 2016). This is because tryptophan is an essential amino acid found in dietary proteins that is required for the synthesis of serotonin (Kim *et al*. 2010; Nongonierma & Fitzgerald, 2015). Indeed, a reduction in dietary tryptophan intake is linked to reduced β-cell mass expansion and impaired glucose tolerance in mice during pregnancy (Kim *et al*. 2010). Changes in maternal β-cell adaptations and glucose homeostasis could also stem from alterations in the placenta in response to a low protein diet. Decreased protein intake during pregnancy alters the development and nutrient transport capacity of the placenta (Rutland *et al*. 2007; Coan *et al*. 2011). Maternal dietary protein deprivation is linked to altered formation of placental endocrine cells and expression of the PRL-related genes in the mouse placenta (Gonzalez *et al*. 2016). Future work should examine the impact of poor maternal dietary protein intake on the relationships between changes in maternal β-cells, local islet signalling and the placenta.

Although there are some differences in β-cell adaptations between rodent and human pregnancies, the available data using rodent models have been instrumental in showing the importance of maternal diet and nutritional status, including body adiposity, in the capacity of the mother to undergo β-cell adaptations and appropriately control blood glucose concentrations during pregnancy.

Hypoxia. Hypoxia generated by living at high altitude (>2500 m) is a frequent cause of maternal physiological maladaptation during pregnancy (Moore *et al*. 2004), but prevalence of GDM is not increased in high altitude populations (Euser *et al*. 2018). Compared to women at sea level, pregnant women at high altitude present with decreased fasting plasma glucose concentrations and higher insulin sensitivity, although calculated β-cell function is similar and fasting insulin concentration is lower (Krampl *et al*. 2001*a*,*b*). Studies in rodents

have evaluated the effect of different levels of inhalation hypoxia on maternal metabolic support of fetal growth. Pregnant mice maintained under 15% hypoxia from the start of pregnancy show reduced maternal weight gain and adipocyte area during gestation (Määttä *et al.* 2018). They also show greater glucose tolerance, fail to acquire insulin resistance and have elevated serum glucagon levels in late pregnancy (Määttä *et al.* 2018). Pregnant mice maintained under 10% hypoxia, but not 13% hypoxia, in the last third of gestation also have reduced maternal body weight although they have normal circulating insulin and glucose concentrations (Higgins *et al.* 2016). Exposure to 13% hypoxia from mid gestation, however, reduced maternal glucose concentration without a change in circulating insulin abundance (Higgins *et al.* 2016). Together the available data indicate that, under hypoxic conditions, maternal glucose homeostasis adapts differentially depending on the timing, duration and severity of the oxygen reduction. Indeed, there are severity- and timing-dependent effects of hypoxia on the transport function as well as the size and metabolism of the endocrine region in the placenta in mice (Higgins *et al.* 2016; Sferruzzi-Perri *et al.* 2019). However, it is not known if exposure to hypoxia during gestation alters the production of hormones that impact maternal metabolic adaptations, namely β-cell adaptations during pregnancy.

Although the maternal pancreas is a probable target of hypoxia-induced changes in glucose handling, there are no studies exploring if, and how, hypoxia may directly impact β-cell adaptations during pregnancy. ARNT, which helps to mediate the cellular effects of hypoxia, is implicated in the regulation of β-cell function and is significantly decreased in humans with T2DM (Gunton *et al.* 2005). As previously mentioned, ARNT expression is increased in β-cells during pregnancy and may be required for the normal augmentation of insulin secretion and β-cell proliferation although further examination is needed (Lau *et al.* 2013). Therefore, pancreatic islets could be particularly sensitive to changes in oxygen levels/hypoxia during pregnancy.

Circadian disruption during pregnancy.

Simulated shift work. Circadian disruption, also known as chronodisruption, refers to a breakdown between the phasing of internal biological systems relative to external environmental changes. It can be induced by exposure to shift work, which leads to a disturbance or desynchronization of the organization of physiological functions that normally have a rhythm over a 24 h period (Erren & Reiter, 2009). Epidemiological studies suggest that shift work is associated with an increased risk of chronic diseases, including diabetes and obesity (Gan *et al.* 2015; Proper *et al.* 2016). For instance, 4 days of simulated night shift work is sufficient to reduce insulin sensitivity and glucose tolerance in healthy non-shift workers (Bescos *et al.* 2018). Research in humans has revealed associations between chronodisruption and problems with fertility and pregnancy, particularly miscarriage (Fernandez *et al.* 2016). However, no studies have assessed a direct relationship between shift work before and/or during pregnancy and changes in glucose homeostasis associated with β-cell dysfunction in the mother. Studies in rats have revealed that exposure to chronic phase shifts during pregnancy, simulating a shift work schedule, is associated with altered maternal daily rhythms of several key endocrine signals, including melatonin, insulin, glucose, leptin and corticosterone (Varcoe *et al.* 2013; Mendez *et al.* 2016). However, maternal weight is only transiently decreased in early gestation and there are no significant differences in glucose and insulin tolerance in these exposed pregnant rats (Varcoe *et al.* 2013; Mendez *et al.* 2016). Exposure to chronic phase shifts during pregnancy reduced weight of the rat placenta, but the impact on the production of placental hormones with systemic metabolic effects in the mother is not known (Mendez *et al.* 2016). Studies in pregnant sheep with circadian disruption due to a simulated shift work protocol show reduced pregnancy weight gain, disrupted daily profiles of melatonin, glucose and insulin, impaired glucose tolerance and increased GSIS (Gatford *et al.* 2019). Thus, there appear to be species-specific differences in the effect of chronodisruption on maternal β-cell adaptations and glucose homeostasis in pregnancy.

A common feature of shift workers is the exposure to artificial light at night leading to the suppression of plasma melatonin concentration. Melatonin has a fundamental role in regulating the timing of several physiological functions, including glucose homeostasis, insulin secretion and energy metabolism (Owino *et al.* 2019). In addition, melatonin stimulates glucagon release from pancreatic α-cells (Gottlieb *et al.* 2005; Donga *et al.* 2010). It is perhaps not surprising then that genetic variants of melatonin receptors have been associated with a number of metabolic disorders, such as T2DM, GDM and obesity (Bouatia-Naji *et al.* 2009; Lyssenko *et al.* 2009). For instance, the melatonin receptor 1B variant rs10830963 is associated with GDM in a European Cohort (Rosta *et al.* 2017). This same variant is also correlated with the development of GDM and the absolute level of insulin secretion and β-cell compensation in a cohort of Mexican Americans (Ren *et al.* 2014). These data highlight that circadian rhythm disruption is able to negatively impact maternal β-cell adaptations and glucose homeostasis during pregnancy likely through the melatonin signalling pathway.

Sleep duration and quality. Studies have shown that short sleep duration and frequent snoring are positively

correlated with impaired glucose tolerance and high circulating glucose concentrations in women during pregnancy, particularly when the woman is obese (Facco *et al*. 2010; Qiu *et al*. 2010). Indeed, each hour of reduced sleep time is associated with a 4% increase in glycaemia during gestation and pregnant women with increased sleep-disordered breathing, frequent snoring and sleep duration of 7 h per night have increased risk of developing GDM (Reutrakul *et al*. 2011). Other studies have found a U-shaped association of sleep duration and GDM, with less or more than 7–9 h of sleep being associated with an increased risk of GDM (Rawal *et al*. 2017; Wang *et al*. 2017).

Endocrine disrupting chemicals. Endocrine disrupting chemicals (EDCs) are structurally similar to many hormones and are capable of mimicking and interfering with the synthesis, secretion, transport, activity and/or elimination of natural hormones. Because of this, exposure to EDCs may cause a wide range of adverse health effects, including T2DM and obesity. Moreover, exposure to EDCs during pregnancy may disrupt maternal β-cell adaptations, glucose homeostasis and increase the risk of GDM (Ehrlich *et al*. 2016). However, whether impacts of EDCs on maternal metabolic status are brought about via changes in placental hormone output warrants investigation (Strakovsky & Schantz, 2018; Filardi *et al*. 2020).

Bisphenol A. Bisphenol-A (BPA) is a synthetic oestrogen used as the base compound in the manufacture of polycarbonate plastic and as an additive in others. BPA can leach from polycarbonate containers and heat, acidic or basic conditions can accelerate the release of BPA, with resultant impacts on the levels of human exposure. Epidemiological studies have investigated the association between BPA and clinically diagnosed GDM risk, but no strong associations have been found (Robledo *et al*. 2013; Shapiro *et al*. 2015), although other studies have shown BPA exposure during the second trimester of pregnancy is positively associated with blood glucose concentration in sub-fertile women (Chiu *et al*. 2017). In addition, urinary concentrations of BPA are associated with higher glucose levels among overweight/obese women (Bellavia *et al*. 2018). Conversely, in a cohort of Chinese pregnant women, high urinary BPA concentrations were associated with reduced risk of GDM, an effect that was maintained even after adjustment for pre-pregnancy BMI and other covariates (Wang *et al*. 2017).

Research in rodents strongly supports BPA as a disruptor of maternal glucose homeostasis, and apparently this effect is mediated by the activation of oestrogen receptor β (Alonso-Magdalena *et al*. 2015*a*). During pregnancy, oestrogens are relevant signals involved in β-cell mass expansion with their function partly mediated through repression of miR-338-3p (Jacovetti *et al*. 2012). Interestingly, *in vitro* studies have shown that the expression of miR-338 is altered in BPA-exposed islets (Wei *et al*. 2017). Moreover, exposure of β-cells to BPA for 48 h *in vitro* increases insulin secretion capacity (Makaji *et al*. 2011), likely via its impacts on both oestrogen receptor-α and oestrogen receptor-β (Nadal, 2019). More prolonged BPA exposure, however, reduces β-cell viability *in vitro* (Weldingh *et al*. 2017). Pregnant mice treated with BPA during gestation develop a GDM-like metabolic profile with impaired glucose tolerance, hyperinsulinaemia and increased triglyceride and leptin concentrations (Alonso-Magdalena *et al*. 2010). The metabolic effects of BPA exposure on the mother were found to persist until 4–6 months post-partum, with increased body weight, insulin, leptin and triglyceride concentrations, as well as glucose intolerance and decreased insulin sensitivity observed (Alonso-Magdalena *et al*. 2010, 2015*b*). A final assessment of mice 7 months after exposure to BPA during pregnancy revealed that dams had decreased pancreatic β-cell mass and reduced insulin secretion both *in vivo* and *in vitro* (Alonso-Magdalena *et al*. 2015*b*). Interestingly, expression of cyclin D2 and cyclin-dependent kinase-4 were diminished and apoptosis and expression of the cell cycle inhibitors p16 and p53 were increased in the β-cells of exposed post-partum dams (Alonso-Magdalena *et al*. 2015a). Altogether, these data suggest that BPA exposure during pregnancy impacts maternal β-cell adaptations with important consequences for the development of GDM, as well as the subsequent progression to T2DM in later life.

Phthalates. Phthalates are EDCs widely used in the manufacture of plastic. Similar to BPA, phthalates have been found to exert specific oestrogenic activity with important biological consequences (Harris *et al*. 1997). However, phthalate metabolites are less potent than BPA in inducing reduced viability and increased insulin release from the pancreatic β-cells *in vitro* (Weldingh *et al*. 2017). In pregnant rats injected with streptozocin to induce GDM, di-*n*-butyl phthalate further exaggerated maternal hyperglycaemia and impaired glucose handling *in vivo* (Chen *et al*. 2020). In addition, di-*n*-butyl phthalate impaired STAT1 signalling and led to inhibition of FoxM1 and reduced viability of β-cells *in vitro* (Chen *et al*. 2020). In a Mexican GDM cohort of women, a significant association was found between specific phthalate metabolites in urine and the circulating abundance of miRNAs implicated in metabolic disease, namely miR-9-5p, miR-29a-3p and miR-330-3p (Martínez-Ibarra *et al*. 2019). In addition, there were specific associations between distinct urinary

phthalate metabolite concentrations and maternal body mass during pregnancy (James-Todd *et al.* 2016). Of note, mono-ethyl phthalate was associated with impaired glucose tolerance and excessive gestational weight gain in the second trimester, whereas a high di-2-ethylhexyl phthalate was associated with a lower risk of impaired glucose tolerance (James-Todd *et al.* 2016). In addition, phthalate metabolites are also found to be linked to glucose intolerance during pregnancy, with possible stronger associations in certain racial/ethnic subgroups (Shaffer *et al.* 2019). Whether the impacts of phthalates on glucose handling during pregnancy relate to alterations in maternal β-cell adaptations requires further study.

Summary

Maternal β-cell adaptations are critical for appropriate handling of glucose during pregnancy. This process is governed by a variety of environmental, hormonal, cellular and molecular factors (Fig. 2). For instance, maternal β-cell adaptations are mediated via hormones secreted by the placenta and organs like the adipose tissue, which promote β-cell proliferation, growth, neogenesis, enhanced insulin secretion and protection from apoptosis. Such hormones operate through several signalling cascades, transcription factors and epigenetic regulators that modify receptor abundance, cell cycle-related genes and the threshold for glucose-stimulated insulin secretion. The environment of the mother is also a key factor in determining β-cell adaptations during pregnancy, as dietary variations, exposure to hypoxia, circadian disruption and endocrine disrupting chemicals are able to interfere with β-cell proliferation, survival, insulin secretion and/or associated molecular pathways. In part, environmentally induced changes in β-cells seem to link to alterations in placental endocrine function and maternal body weight, adipose mass and insulin sensitivity. However, the precise mechanisms through which β-cells integrate the various environmental, metabolic and endocrine cues and thereby determine appropriate β-cell adaptation during gestation requires further research. Combining β-cell-specific knock-out models, placental hormone-specific models, environmental manipulations and high throughput molecular analysis of isolated β-cells will provide powerful tools for understanding pathways and relevant factors controlling β-cell adaptations and the pathways leading to the development of GDM. These studies may also have broader implications in paving the way to understanding the mechanistic underpinnings of metabolic dysfunctions including T2DM.

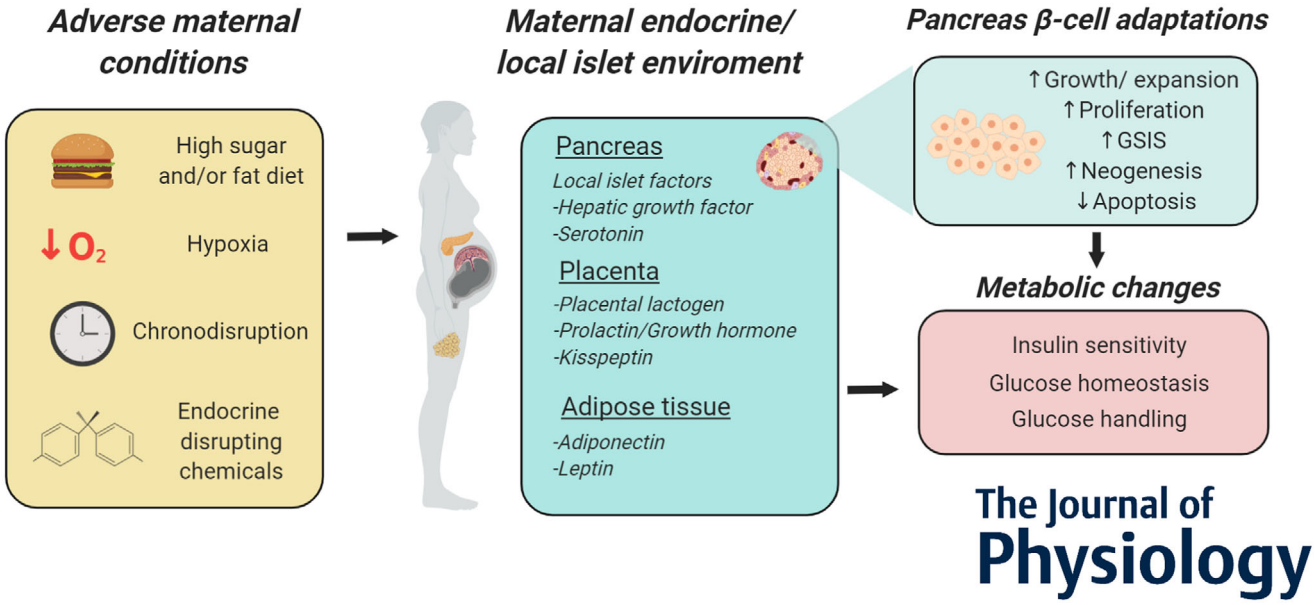


Figure 2. Summary description
An abnormal diet, hypoxia, circadian disruption or endocrine disrupting chemicals directly modify the endocrine maternal environment impacting normal β-cell adaptation. In addition, endocrine and metabolic signals coming from the cross-talk between placenta and maternal tissues tightly regulate β-cell function promoting proliferation, growth/expansion, neogenesis, GSIS, and apoptosis. Disruption of the coordinated process described will alter insulin sensitivity, glucose homeostasis and handling in the pregnant mother.

References

Abouna S, Old RW, Pelengaris S, Epstein D, Ifandi V, Sweeney I & Khan M (2010). Non-β-cell progenitors of β-cells in pregnant mice. *Organogenesis* **6**, 125–133.

Alonso-Magdalena P, García-Arévalo M, Quesada I & Nadal Á (2015*a*). Bisphenol-A treatment during pregnancy in mice: a new window of susceptibility for the development of diabetes in mothers later in life. *Endocrinology* **156**, 1659–1670.

Alonso-Magdalena P, Quesada I & Nadal Á (2015*b*). Prenatal exposure to BPA and offspring outcomes: The diabesogenic behavior of BPA. *Dose Response* **13**, 1559325815590395.

Alonso-Magdalena P, Ropero AB, Carrera MP, Cederroth CR, Baquié M, Gauthier BR, Nef S, Stefani E & Nadal A (2008). Pancreatic insulin content regulation by the estrogen receptor ERα. *PLoS One* **3**, e2069

Alonso-Magdalena P, Vieira E, Soriano S, Menes L, Burks D, Quesada I & Nadal A (2010). Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. *Environ Health Perspect* **118**, 1243–1250.

Alzamendi A, Del Zotto H, Castrogiovanni D, Romero J, Giovambattista A & Spinedi E (2012). Oral metformin treatment prevents enhanced insulin demand and placental dysfunction in the pregnant rat fed a fructose-rich diet. *ISRN Endocrinol* **2012**, 757913.

Amaral MEC, Cunha DA, Anhê GF, Ueno M, Carneiro EM, Velloso LA, Bordin S & Boschero AC (2004). Participation of prolactin receptors and phosphatidylinositol 3-kinase and MAP kinase pathways in the increase in pancreatic islet mass and sensitivity to glucose during pregnancy. *J Endocrinol* **183**, 469–476.

Amireault P, Sibon D & Coîté F (2013). Life without peripheral serotonin: insights from tryptophan hydroxylase 1 knockout mice reveal the existence of paracrine/autocrine serotonergic networks. *ACS Chem Neurosci* **4**, 64–71.

Angueira AR, Ludvik AE, Reddy TE, Wicksteed B, Lowe WL & Layden BT (2015). New insights into gestational glucose metabolism: lessons learned from 21st century approaches. *Diabetes* **64**, 327–334.

Artner I, Blanchi B, Raum JC, Guo M, Kaneko T, Cordes S, Sieweke M & Stein R (2007). MafB is required for islet β cell maturation. *Proc Natl Acad Sci U S A* **104**, 3853–3858.

Arumugam R, Fleenor D & Freemark M (2014). Knockdown of prolactin receptors in a pancreatic beta cell line: effects on DNA synthesis, apoptosis, and gene expression. *Endocrine* **46**, 568–576.

Aye ILMH, Rosario FJ, Powell TL & Jansson T (2015). Adiponectin supplementation in pregnant mice prevents the adverse effects of maternal obesity on placental function and fetal growth. *Proc Natl Acad Sci U S A* **112**, 12858–12863.

Baeyens L, Hindi S, Sorenson RL & German MS (2016). β-Cell adaptation in pregnancy. *Diabetes Obe Metab* **18**, 63–70.

Banerjee RR (2018). Piecing together the puzzle of pancreatic islet adaptation in pregnancy. *Ann N Y Acad Sci* **1411**, 120–139.

Banerjee RR, Cyphert HA, Walker EM, Chakravarthy H, Peiris H, Gu X, Liu Y, Conrad E, Goodrich L, Stein RW & Kim SK (2016). Gestational diabetes mellitus from inactivation of prolactin receptor and MafB in islet β-cells. *Diabetes* **65**, 2331–2341.

Beamish CA, Zhang L, Szlapinski SK, Strutt BJ & Hill DJ (2017). An increase in immature β-cells lacking Glut2 precedes the expansion of β-cell mass in the pregnant mouse. *PLoS One* **12**, e0182256.

Bellavia A, Cantonwine DE, Meeker JD, Hauser R, Seely EW, McElrath TF & James-Todd T (2018). Pregnancy urinary bisphenol-A concentrations and glucose levels across BMI categories. *Environ Int* **113**, 35–41.

Bensellam M, Laybutt DR & Jonas JC (2012). The molecular mechanisms of pancreatic β-cell glucotoxicity: recent findings and future research directions. *Mol Cell Endocrinol* **364**, 1–27.

Berger M, Gray JA & Roth BL (2009). The expanded biology of serotonin. *Annu Rev Med* **60**, 355–366.

Bescos R, Boden MJ, Jackson ML, Trewin AJ, Marin EC, Levinger I, Garnham A, Hiam DS, Falcao-Tebas F, Conte F, Owens JA, Kennaway DJ & McConell GK (2018). Four days of simulated shift work reduces insulin sensitivity in humans. *Acta Physiologica* **223**, e13039,

Bonner-Weir S, Toschi E, Inada A, Reitz P, Fonseca SY, Aye T & Sharma A (2004). The pancreatic ductal epithelium serves as a potential pool of progenitor cells. *Pediatr Diabetes* **5**, 16–22.

Bouatia-Naji N, Bonnefond A, Cavalcanti-Proença C, Sparsø T, Holmkvist J, Marchand M, Delplanque J, Lobbens S, Rocheleau G, Durand E, De Graeve F, Chèvre J-C, Borch-Johnsen K, Hartikainen A-L, Ruokonen A, Tichet J, Marre M, Weill J, Heude B, Tauber M, Lemaire K, Schuit F, Elliott P, Jørgensen T, Charpentier G, Hadjadj S, Cauchi S, Vaxillaire M, Sladek R, Visvikis-Siest S, Balkau B, Lévy-Marchal C, Pattou F, Meyre D, Blakemore AIF, Jarvelin M-R, Walley AJ, Hansen T, Dina C, Pedersen O & Froguel P (2009). A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. *Nat Genet* **41**, 89–94.

Bowe JE, Chander A, Liu B, Persaud SJ & Jones PM (2013). The permissive effects of glucose on receptor-operated potentiation of insulin secretion from mouse islets: a role for ERK1/2 activation and cytoskeletal remodelling. *Diabetologia* **56**, 783–791.

Bowe JE, Foot VL, Amiel SA, Huang GC, Lamb M, Lakey J, Jones PM & Persaud SJ (2012). GPR54 peptide agonists stimulate insulin secretion from murine, porcine and human islets. *Islets* **4**, 20–23.

Bowe JE, Hill TG, Hunt KF, Smith LIF, Simpson SJS, Amiel SA & Jones PM (2019). A role for placental kisspeptin in β cell adaptation to pregnancy. *JCI Insight* **4**, e124540.

Bowe JE, King AJ, Kinsey-Jones JS, Foot VL, Li XF, O'Byrne KT, Persaud SJ & Jones PM (2009). Kisspeptin stimulation of insulin secretion: Mechanisms of action in mouse islets and rats. *Diabetologia* **52**, 855–862.

Braunstein, GD (2011). Endocrine changes in pregnancy. Melmed, S, Polonsky, KS, Larsen, PR & Kronenberg, HM, *Williams Textbook of Endocrinology*. 21, Philadelphia: Elsevier/Saunders, 819–832.

Brelje TC, Scharp DW, Lacy PE, Talamantes F, Robertson M, Friesen, HG & Sorenson, RL (1993). Effect of homologous placental lactogens, prolactins, and growth hormones on islet B-cell division and insulin secretion in rat, mouse, and human islets: implication for placental lactogen regulation of islet function pregnancy. *Endocrinology* **132**, 879–887.

Brelje TC, Stout LE, Bhagroo NV & Sorenson RL (2004). Distinctive roles for prolactin and growth hormone in the activation of signal transducer and activator of transcription 5 in pancreatic islets of Langerhans. *Endocrinology* **145**, 4162–4175.

Brelje TC, Svensson AM, Stout LE, Bhagroo NV & Sorenson RL (2002). An immunohistochemical approach to monitor the prolactin-induced activation of the JAK2/STAT5 pathway in pancreatic islets of Langerhans. *J Histochem Cytochem* **50**, 365–383.

Bridges RS (2015). Neuroendocrine regulation of maternal behavior. *Front Neuroendocrinol* **36**, 178–196.

Brooks CL (2012). Molecular mechanisms of prolactin and its receptor. *Endocr Rev* **33**, 504–525.

Brouwers B, de Faudeur G, Osipovich AB, Goyvaerts L, Lemaire K, Boesmans L, Cauwelier EJ, Granvik M, Pruniau VP, Van Lommel L, Van Schoors J, Stancill JS, Smolders I, Goffin V, Binart N, in't Veld P & Declercq JMA (2014). Impaired islet function in commonly used transgenic mouse lines due to human growth hormone minigene expression. *Cell Metab* **20**, 979–990.

Buchanan TA, Xiang AH & Page KA (2012). Gestational diabetes mellitus: risks and management during and after pregnancy. *Nat Rev Endocrinol* **8**, 639–649.

Butler AE, Cao-Minh L, Galasso R, Rizza RA, Corradin A, Cobelli C & Butler PC (2010). Adaptive changes in pancreatic beta cell fractional area and beta cell turnover in human pregnancy. *Diabetologia* **53**, 2167–2176.

Butte NF (2000). Carbohydrate and lipid metabolism in pregnancy: Normal compared with gestational diabetes mellitus. *Am J Clin Nutr* **71**, 1256S-1261S.

Caminos JE, Nogueiras R, Gallego R, Bravo S, Tovar S, García-Caballero T, Casanueva FF & Diéguez C (2005). Expression and regulation of adiponectin and receptor in human and rat placenta. *J Clin Endocrinol Metab* **90**, 4276–4286.

Carter LG & Tenlep SYN (2015). Exercise improves glucose disposal and insulin signaling in pregnant mice fed a high fat diet. *J Diabetes Metab* **6**, 634.

Catalano PM (2010). The impact of gestational diabetes and maternal obesity on the mother and her offspring. *J Dev Orig Health Dis* **1**, 208–215.

Catalano PM, Drago NM & Amini SB (1995). Maternal carbohydrate metabolism and its relationship fetal growth and body composition. *Am J Obstet Gynecol* **172**, 1464–1470.

Catalano PM, Tyzbir ED, Wolfe RR, Roman NM, Amini BS & Sims EAH (1992). Longitudinal changes in basal hepatic glucose production and suppression during insulin infusion in normal pregnant women. *Am J Obstet Gynecol* **167**, 913–919.

Chamberlain CE, Scheel DW, McGlynn K, Kim H, Miyatsuka T, Wang J, Nguyen V, Zhao S, Mavropoulos A, Abraham AG, O'Neill E, Ku GM, Cobb MH, Martin GR & German MS (2014). Menin determines K-RAS proliferative outputs in endocrine cells. *J Clin Invest* **124**, 4093–4101.

Chen C, Wu S, Lin X, Wu D, Fischbach S & Xiao X (2018). ERK5 plays an essential role in gestational beta-cell proliferation. *Cell Prolif* **51**, e12410.

Chen H, Gu X, Liu Y, Wang J, Wirt SE, Bottino R, Schorle H, Sage J & Kim SK (2011). PDGF signalling controls age-dependent proliferation in pancreatic β-cells. *Nature* **478**, 349–355.

Chen J, Tan B, Karteris E, Zervou S, Digby J, Hillhouse EW, Vatish M & Randeva HS (2006). Secretion of adiponectin by human placenta: Differential modulation of adiponectin and its receptors by cytokines. *Diabetologia* **49**, 1292–1302.

Chen M, Zhao S, Guo WH, Zhu YP, Pan L, Xie ZW, Sun W-L & Jiang JT (2020). Maternal exposure to Di-n-butyl phthalate (DBP) aggravate gestational diabetes mellitus via FoxM1 suppression by pSTAT1 signalling. *Ecotoxicol Environ Saf* **205**, 111154.

Chiu YH, Mínguez-Alarcón L, Ford JB, Keller M, Seely EW, Messerlian C, Petrozza J, Williams PL, Ye X, Calafat AM, Hauser R & James-Todd T (2017). Trimester-specific urinary bisphenol a concentrations and blood glucose levels among pregnant women from a fertility clinic. *J Clin Endocrinol Metab* **102**, 1350–1357.

Christoforou ER & Sferruzzi-Perri AN (2020). Molecular mechanisms governing offspring metabolic programming in rodent models of in utero stress. *Cell Mol Life Sci* **77**, 4861–4898.

Chung E, Grue KA, Kaur G, Mallory B, Serrano CR, Ullevig SL, Kottapalli KR, Lee SC, Dufour JM, Shen C-L & Umeda M (2019). Maternal exercise before and during pregnancy alleviates metabolic dysfunction associated with high-fat diet in pregnant mice, without significant changes in gut microbiota. *Nutr Res* **69**, 42–57.

Coan PM, Vaughan OR, McCarthy J, Mactier C, Burton GJ, Constância M & Fowden AL (2011). Dietary composition programmes placental phenotype in mice. *J Physiol* **589**, 3659–3670.

Costrini NV & Kalkhoff RK (1971). Relative effects of pregnancy, estradiol, and progesterone on plasma insulin and pancreatic islet insulin secretion. *J Clin Invest* **50**, 992–999.

Cousins L, Rigg L, Hollingsworth D, Brink G, Aurand J & Yen SSC (1980). The 24-hour excursion and diurnal rhythm of glucose, insulin, and C-peptide in normal pregnancy. *Am J Obstet Gynecol* **136**, 483–488.

Demirci C, Ernst S, Alvarez-Perez JC, Rosa T, Valle S, Shridhar V, Casinelli GP, Alonso LC, Vasavada RC & García-Ocana A (2012). Loss of HGF/c-Met signaling in pancreatic β-cells leads to incomplete maternal β-cell adaptation and gestational diabetes mellitus. *Diabetes* **61**, 1143–1152.

Dhillo WS, Savage P, Murphy KG, Chaudhri OB, Patterson M, Nijher GM, Foggo VM, Dancey GS, Mitchell H, Seckl MJ, Ghatei MA & Bloom SR (2006). Plasma kisspeptin is raised in patients with gestational trophoblastic neoplasia and falls during treatment. *Am J Physiol Endocrinol Metab* **291**, E878–E884.

Di Cianni G, Miccoli R, Volpe L, Lencioni C & Del Prato S (2003). Intermediate metabolism in normal pregnancy and in gestational diabetes. *Diabetes Metab Res Rev* **19**, 259–270.

Donga E, Van Dijk M, Van Dijk JG, Biermasz NR, Lammers GJ, Van Kralingen KW, Corssmit EPM & Romijn JA (2010). A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects. *J Clin Endocrinol Metab* **95**, 2963–2968.

Donker RB, Mouillet JF, Chu T, Hubel CA, Stolz DB, Morelli AE & Sadovsky Y (2012). The expression profile of C19MC microRNAs in primary human trophoblast cells and exosomes. *Mol Hum Reprod* **18**, 417–424.

Drynda R, Persaud SJ, Bowe JE & Jones PM (2018). The placental secretome: identifying potential cross-talk between placenta and islet β-cells. *Cell Physiol Biochem* **45**, 1165–1171.

Ehrlich S, Lambers D, Baccarelli A, Khoury J, Macaluso M & Ho SM (2016). Endocrine disruptors: a potential risk factor for gestational diabetes mellitus. *Am J Perinatol* **33**, 1313–1318.

Erren TC & Reiter RJ (2009). Defining chronodisruption. *J Pineal Res* **46**, 245–247.

Euser AG, Hammes A, Ahrendsen JT, Neshek B, Weitzenkamp DA, Gutierrez J, Koivunen P, Julian CG & Moore LG (2018). Gestational diabetes prevalence at moderate and high altitude. *High Alt Med Biol* **19**, 367–372.

Facco FL, Grobman WA, Kramer J, Ho KH & Zee PC (2010). Self-reported short sleep duration and frequent snoring in pregnancy: impact on glucose metabolism. *Am J Obstet Gynecol* **203**, 142.e1–e5.

Fan Y, Wang L, Liu H, Zhang S, Tian H, Shen Y, Tuomilehto J, Yu Z, Yang X, Hu G & Liu M (2020). β-Cell function or insulin resistance was associated with the risk of type 2 diabetes among women with or without obesity and a history of gestational diabetes. *BMJ Open Diabetes Res Care* **8**, e001060.

Fernandez RC, Marino JL, Varcoe TJ, Davis S, Moran LJ, Rumbold AR, Brown HM, Whitrow MJ, Davies MJ & Moore VM (2016). Fixed or rotating night shift work undertaken by women: implications for fertility and miscarriage. *Semin Reprod Med* **34**, 74–82.

Fernandez-Twinn DS, Gascoin G, Musial B, Carr S, Duque-Guimaraes D, Blackmore HL, Alfaradhi MZ, Loche E, Sferruzzi-Perri AN, Fowden AL & Ozanne SE (2017). Exercise rescues obese mothers' insulin sensitivity, placental hypoxia and male offspring insulin sensitivity. *Sci Rep* **7**, 44650.

Filardi T, Panimolle F, Lenzi A & Morano S (2020). Bisphenol A and phthalates in diet: an emerging link with pregnancy complications. *Nutrients* **12**, 525.

Filios SR & Shalev A (2015). β-Cell microRNAs: small but powerful. *Diabetes* **64**, 3631–3644.

Freemark M, Avril I, Fleenor DON, Driscoll P, Petro ANN, Opara E, Kendall W, Oden J, Bridges S, Binart N, Breant B & Kelly PA (2002). Targeted deletion of the PRL receptor: effects on islet development, insulin production, and glucose tolerance. *Endocrinology* **143**, 1378–1385.

Friedman JE, Kirwan JP, Jing M, Presley L & Catalano PM (2008). Increased skeletal muscle tumor necrosis factor-α and impaired insulin signaling persist in obese women with gestational diabetes mellitus 1 year postpartum. *Diabetes* **57**, 606–613.

Fujinaka Y, Takane K, Yamashita H & Vasavada RC (2007). Lactogens promote beta cell survival through JAK2/STAT5 activation and Bcl-XL upregulation. *J Biol Chem* **282**, 30707–30717.

Gahr S, Merger M, Bollheimer LC, Hammerschmied CG, Schölmerich J & Hügl SR (2002). Hepatocyte growth factor stimulates proliferation of pancreatic β-cells particularly in the presence of subphysiological glucose concentrations. *J Mol Endocrinol* **28**, 99–110.

Galsgaard ED, Nielsen JH & Møldrup A (1999). Regulation of prolactin receptor (PRLR) gene expression in insulin-producing cells. Prolactin and growth hormone activate one of the rat PRLR gene promoters via STAT5a and STAT5b. *J Biol Chem* **274**, 18686–18692.

Gan Y, Yang C, Tong X, Sun H, Cong Y, Yin X, Li L, Cao S, Dong X, Gong Y, Shi O, Deng J, Bi H & Lu Z (2015). Shift work and diabetes mellitus: a meta-analysis of observational studies. *Occup Environ Med* **72**, 72–78.

García-Ocaña A, Takane KK, Reddy VT, Lopez-Talavera JC, Vasavada RC & Stewart AF (2003). Adenovirus-mediated hepatocyte growth factor expression in mouse islets improves pancreatic islet transplant performance and reduces beta cell death. *J Biol Chem* **278**, 343–351.

Gatford KL, Kennaway DJ, Liu H, Kleemann DO, Kuchel TR & Varcoe TJ (2019). Simulated shift work disrupts maternal circadian rhythms and metabolism, and increases gestation length in sheep. *J Physiol* **597**, 1889–1904.

Gonzalez PN, Gasperowicz M, Barbeito-Andrés J, Klenin N, Cross JC & Hallgrímsson B (2016). Chronic protein restriction in mice impacts placental function and maternal body weight before fetal growth. *PLoS One* **11**, 8–11.

Gottlieb DJ, Punjabi NM, Newman AB, Resnick HE, Redline S, Baldwin CM & Nieto FJ (2005). Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med* **165**, 863–867.

Goyvaerts L, Lemaire K, Arijs I, Auffret J, Granvik M, Van Lommel L, Binart N, in't Veld P, Schuit F & Schraenen A (2015). Prolactin receptors and placental lactogen drive male mouse pancreatic islets to pregnancy-related mRNA changes. *PLoS One* **10**, e0121868.

Goyvaerts L, Schraenen A & Schuit F (2016). Serotonin competence of mouse beta cells during pregnancy. *Diabetologia* **59**, 1356–1363.

Grattan DR, Steyn FJ, Kokay IC, Anderson GM & Bunn SJ (2008). Pregnancy-induced adaptation in the neuroendocrine control of prolactin secretion. *J Neuroendocrinol* **20**, 497–507.

Green IC, El Seifi S, Perrin D & Howell SL (1981). Cell replication in the islets of langerhans of adult rats: effects of pregnancy, ovariectomy and treatment with steroid hormones. *J Endocrinol* **88**, 219–224.

Gunton JE, Kulkarni RN, Yim SH, Okada T, Hawthorne WJ, Tseng YH, Roberson RS, Ricordi C, O'Connell PJ, Gonzalez FJ & Kahn CR (2005). Loss of ARNT/HIF1β mediates altered gene expression and pancreatic-islet dysfunction in human type 2 diabetes. *Cell* **122**, 337–349.

Gupta RK, Gao N, Gorski RK, White P, Hardy OT, Rafiq K, Brestelli JE, Chen G, Stoeckert CJ & Kaestner KH (2007). Expansion of adult β-cell mass in response to increased metabolic demand is dependent on HNF-4α. *Genes Dev* **21**, 756–769.

Hakonen E, Ustinov J, Palgi J, Miettinen PJ & Otonkoski T (2014). EGFR signaling promotes β-cell proliferation and survivin expression during pregnancy. *PLoS One* **9**, e93651.

Harris CA, Henttu P, Parker MG & Sumpter JP (1997). The estrogenic activity of phthalate esters in vitro. *Environ Health Perspect* **105**, 802–811.

Hauge-Evans AC, Richardson CC, Milne HM, Christie MR, Persaud SJ & Jones PM (2006). A role for kisspeptin in islet function. *Diabetologia* **49**, 2131–2135.

Heerwagen MJR, Stewart MS, de la Houssaye BA, Janssen RC & Friedman JE (2013). Transgenic increase in N-3/N-6 fatty acid ratio reduces maternal obesity-associated inflammation and limits adverse developmental programming in mice. *PLoS One* **8**, e67791

Herreboudt AM, Kyle VRL, Lawrence J, Doran J & Colledge WH (2015). Kiss1 mutant placentas show normal structure and function in the mouse. *Placenta* **36**, 52–58.

Higgins JS, Vaughan OR, Fernandez de Liger E, Fowden AL & Sferruzzi-Perri AN (2016). Placental phenotype and resource allocation to fetal growth are modified by the timing and degree of hypoxia during mouse pregnancy. *J Physiol* **594**, 1341–1356.

Holemans K, Caluwaerts S, Poston L & Van Assche FA (2004). Diet-induced obesity in the rat: a model for gestational diabetes mellitus. *Am J Obstet Gynecol* **190**, 858.

Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, Davis KE, Bikman BT, Halberg N, Rutkowski JM, Wade MR, Tenorio VM, Kuo M-S, Brozinick JT, Zhang BB, Birnbaum MJ, Summers SA & Scherer PE (2011). Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. *Nat Med* **17**, 55–63.

Holness MJ, Smith ND, Greenwood GK & Sugden MC (2007). PPARα activation reverses adverse effects induced by high-saturated-fat feeding on pancreatic β-cell function in late pregnancy. *Am J Physiol Endocrinol Metab* **292**, E1087–E1094.

Horibe N, Okamoto T, Itakura A, Nakanishi T, Suzuki T, Kazeto S & Tomoda Y (1995). Levels of hepatocyte growth factor in maternal serum and amniotic fluid. *Am J Obstet Gynecol* **173**, 937–942.

Horikoshi Y, Matsumoto H, Takatsu Y, Ohtaki T, Kitada C, Usuki S & Fujino M (2003). Dramatic elevation of plasma metastin concentrations in human pregnancy: Metastin as a novel placenta-derived hormone in humans. *J Clin Endocrinol Metab* **88**, 914–919.

Horvath CM (2000). STAT proteins and transcriptional responses to extracellular signals. *Trends Biochem Sci* **25**, 496–502.

Huang B, Huang C, Zhao H, Zhu W, Wang B, Wang H, Chen J, Xiao T, Niu J & Zhang J (2019). Impact of GPR1 signaling on maternal high-fat feeding and placenta metabolism in mice. *Am J Physiol Endocrinol Metab* **316**, E987–E997.

Huang C, Snider F & Cross JC (2009). Prolactin receptor is required for normal glucose homeostasis and modulation of β-cell mass during pregnancy. *Endocrinology* **150**, 1618–1626.

Huang Y, Ye T, Liu C, Fang F, Chen Y & Dong Y (2017). Maternal high-fat diet during pregnancy and lactation affects hepatic lipid metabolism in early life of offspring rat. *J Biosci* **42**, 311–319.

Hughes E & Huang C (2011). Participation of Akt, menin, and p21 in pregnancy-induced β-cell proliferation. *Endocrinology* **152**, 847–855.

Ignácio-Souza LM, Reis SR, Arantes VC, Botosso BL, Veloso RV, Ferreir F, Boschero AC, Carneiro EM, de Barros Reis MA & Latorraca MQ (2013). Protein restriction in early life is associated with changes in insulin sensitivity and pancreatic β-cell function during pregnancy. *Br J Nutr* **109**, 236–247.

Iida H, Ogihara T, Min MK, Hara A, Gi Kim Y, Fujimaki K, Tamaki M, Fujitani Y, Kim H & Watada H (2015). Expression mechanism of tryptophan hydroxylase 1 in mouse islets during pregnancy. *J Mol Endocrinol* **55**, 41–53.

Jacovetti C, Abderrahmani A, Parnaud G, Jonas JC, Peyot ML, Cornu M, Laybutt R, Meugnier E, Rome S, Thorens B, Prentki M, Bosco D & Regazzi R (2012). MicroRNAs contribute to compensatory β cell expansion during pregnancy and obesity. *J Clin Invest* **122**, 3541–3551.

James-Allan LB, Rosario FJ, Barner K, Lai A, Guanzon D, McIntyre HD, Lappas M, Powell TL, Salomon C & Jansson T (2020). Regulation of glucose homeostasis by small extracellular vesicles in normal pregnancy and in gestational diabetes. *FASEB J* **34**, 5724–5739.

James-Todd TM, Meeker JD, Huang T, Hauser R, Ferguson KK, Rich-Edwards JW, McElrath TF & Seely EW (2016). Pregnancy urinary phthalate metabolite concentrations and gestational diabetes risk factors. *Environ Int* **96**, 118–126.

Jayabalan N, Nair S, Nuzhat Z, Rice GE, Zuñiga FA, Sobrevia L, Leiva A, Sanhueza C, Gutiérrez JA, Lappas M, Freeman DJ & Salomon C (2017). Cross talk between adipose tissue and placenta in obese and gestational diabetes mellitus pregnancies via exosomes. *Front Endocrinol* **8**, 239.

Jen KLC, Rochon C, Zhong S & Whitcomb L (1991). Fructose and sucrose feeding during pregnancy and lactation in rats changes maternal and pup fuel metabolism. *J Nutr* **121**, 1999–2005.

Jiang WJ, Peng YC & Yang KM (2018). Cellular signaling pathways regulating β-cell proliferation as a promising therapeutic target in the treatment of diabetes (Review). *Exp Ther Med* **16**, 3275–3285.

Jiao Y, Rieck S, Le Lay J & Kaestner KH (2013). CISH has no non-redundant functions in glucose homeostasis or beta cell proliferation during pregnancy in mice. *Diabetologia* **56**, 2435–2445.

Johansson M, Mattsson G, Andersson A, Jansson L & Carlsson PO (2006). Islet endothelial cells and pancreatic β-cell proliferation: Studies in vitro and during pregnancy in adult rats. *Endocrinology* **147**, 2315–2324.

Jones HN, Woollett LA, Barbour N, Prasad PD, Powell TL & Jansson T (2009). High-fat diet before and during pregnancy causes marked up-regulation of placental nutrient transport and fetal overgrowth in C57/BL6 mice. *FASEB J* **23**, 271–278.

Kandzija N, Zhang W, Motta-Mejia C, Mhlomi V, McGowan-Downey J, James T, Cerdeira AS, Tannetta D, Sargent I, Redman CW, Bastie CC & Vatish M (2019). Placental extracellular vesicles express active dipeptidyl peptidase IV; levels are increased in gestational diabetes mellitus. *J Extracell Vesicles* **8**, 1617000.

Karnik SK, Chen H, McLean GW, Heit JJ, Gu X, Zhang AY, Fontaine M, Yen MH & Kim SK (2007). Menin controls growth of pancreatic β-cells in pregnant mice and promotes gestational diabetes mellitus. *Science* **318**, 806–809.

Kim H, Toyofuku Y, Lynn FC, Chak E, Uchida T, Mizukami H, Fujitani Y, Kawamori R, Miyatsuka T, Kosaka Y, Yang K, Honig G, van der Hart M, Kishimoto N, Wang J, Yagihashi S, Tecott LH, Watada H & German MS (2010). Serotonin regulates pancreatic beta cell mass during pregnancy. *Nat Med* **16**, 804–808.

Kirwan JP, Varastehpour A, Jing M, Presley L, Shao J, Friedman JE & Catalano PM (2004). Reversal of insulin resistance postpartum is linked to enhanced skeletal muscle insulin signaling. *J Clin Endocrinol Metab* **89**, 4678–4684.

Krampl E, Kametas NA, Cacho Zegarra AM, Roden M & Nicolaides KH (2001*a*). Maternal plasma glucose at high altitude. *Br J Obstet Gynaecol* **108**, 254–257.

Krampl E, Kametas NA, Nowotny P, Roden M & Nicolaides KH (2001*b*). Glucose metabolism in pregnancy at high altitude. *Diabetes Care* **24**, 817–822.

Kulkarni, RN, Wang, ZL, Wang, RM, Hurley, JD, Smith, DM, Ghatei, MA, Withers, DJ, Gardiner, JV, Bailey, CJ & Bloom, SR (1997). Leptin rapidly suppresses insulin release from insulinoma cells, rat and human islets and, in vivo, in mice. *J Clin Investig*, **100**, 2729–2736.

Kuroda A, Rauch TA, Todorov I, Ku HT, Al-Abdullah IH, Kandeel F, Mullen Y, Pfeifer GP & Ferreri K (2009). Insulin gene expression is regulated by DNA methylation. *PLoS One* **4**, e6953.

Lain KY & Catalano PM (2007). Metabolic changes in pregnancy. *Clin Obstet Gynecol* **50**, 938–948.

Lau SM, Cha KM, Karunatillake A, Stokes RA, Cheng K, McLean M, Cheung NW, Gonzalez FJ & Gunton JE (2013). Beta-cell ARNT is required for normal glucose tolerance in murine pregnancy. *PLoS One* **8**, e77419.

Layden BT, Durai V, Newman MV, Marinelarena AM, Ahn CW, Feng G, Lin S, Zhang X, Kaufman DB, Jafari N, Sørensen GL & Lowe WL (2010). Regulation of pancreatic islet gene expression in mouse islets by pregnancy. *J Endocrinol* **207**, 265–279.

Lee JY, Gavrilova O, Davani B, Na R, Robinson GW & Hennighausen L (2007). The transcription factors Stat5a/b are not required for islet development but modulate pancreatic β-cell physiology upon aging. *Biochim Biophys Acta* **1773**, 1455–1461.

Lee JY, Ristow M, Lin X, White MF, Magnuson MA & Hennighausen L (2006). RIP-Cre revisited, evidence for impairments of pancreatic β-cell function. *J Biol Chem* **281**, 2649–2653.

Li HP, Chen X & Li MQ (2013). Butyrate alleviates metabolic impairments and protects pancreatic β cell function in pregnant mice with obesity. *Int J Clin Exp Pathol* **6**, 1574–1584.

Li J, Ying H, Cai G, Guo Q & Chen L (2015). Impaired proliferation of pancreatic beta cells, by reduced placental growth factor in pre-eclampsia, as a cause for gestational diabetes mellitus. *Cell Prolif* **48**, 166–174.

Li W, Yu G, Liu Y & Sha L (2019). Intrapancreatic ganglia and neural regulation of pancreatic endocrine secretion. *Front Neurosci* **13**, 21.

Liang C, DeCourcy K & Prater MR (2010). High-saturated-fat diet induces gestational diabetes and placental vasculopathy in C57BL/6 mice. *Metabolism* **59**, 943–950.

Lorenzo PI, Fuente-Martín E, Brun T, Cobo-Vuilleumier N, Jimenez-Moreno CM, Herrera Gomez G, Noriega ILL, Mellado-Gil JM, Martin-Montalvo A, Soria B & Gauthier BR (2015). PAX4 defines an expandable β-cell subpopulation in the adult pancreatic islet. *Sci Rep* **5**, 15672.

Lyssenko V, Nagorny CLF, Erdos MR, Wierup N, Jonsson A, Spégel P, Bugliani M, Saxena R, Fex M, Pulizzi N, Isomaa B, Tuomi T, Nilsson P, Kuusisto J, Tuomilehto J, Boehnke M, Altshuler D, Sundler F, Eriksson JG, Jackson AU, Laakso M, Marchetti P, Watanabe RM, Mulder H & Groop L (2009). Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. *Nat Genet* **41**, 82–88.

Määttä J, Sissala N, Dimova EY, Serpi R, Moore LG & Koivunen P (2018). Hypoxia causes reductions in birth weight by altering maternal glucose and lipid metabolism. *Sci Rep* **8**, 13583.

Magnuson MA & Osipovich AB (2013). Pancreas-specific Cre driver lines and considerations for their prudent use. *Cell Metab* **18**, 9–20.

Makaji E, Raha S, Wade MG & Holloway AC (2011). Effect of environmental contaminants on beta cell function. *Int J Toxicol* **30**, 410–418.

Makkar G, Shrivastava V, Hlavay B, Pretorius M, Kyle BD, Braun AP, Lynn FC & Huang C (2019). Lrrc55 is a novel pro-survival factor in pancreatic islets. *Endocrinol Metab* **317**, E7.

Malik NM, Carter ND, Wilson CA, Scaramuzzi RJ, Stock MJ & Murray JF (2005). Leptin expression in the fetus and placenta during mouse pregnancy. *Placenta* **26**, 47–52.

Marçal-Pessoa AF, Bassi-Branco CL, Dos Salvatierra CSB, Stoppiglia LF, Ignacio-Souza LM, De Reis SRL, Veloso RV, de Barros Reis MA, Carneiro EM, Boschero AC, Arantes VC & Latorraca MQ (2015). A low-protein diet during pregnancy prevents modifications in intercellular communication proteins in rat islets. *Biol Res* **48**, 3.

Martínez-Ibarra A, Martínez-Razo LD, Vázquez-Martínez ER, Martínez-Cruz N, Flores-Ramírez R, García-Gómez E, López-López M, Ortega-González C, Camacho-Arroyo I & Cerbón M (2019). Unhealthy levels of phthalates and bisphenol a in mexican pregnant women with gestational diabetes and its association to altered expression of miRNAs involved with metabolic disease. *Int J Mol Sci* **20**, 3343.

Martin-Montalvo A, López-Noriega L, Jiménez-Moreno C, Herranz A, Lorenzo PI, Cobo-Vuilleumier N, Tamayo A, González-Guerrero C, Hofsteede J, Lebreton F, Bosco D, Toscano MG, Herranz L, Anselmo J, Moreno JC & Gauthier BR (2019). Transient PAX8 expression in islets during pregnancy correlates with B-cell survival, revealing a novel candidate gene in gestational diabetes mellitus. *Diabetes* **68**, 109–118.

Martins Terra M, Schaeffer Fontoura T, Oliveira Nogueira A, Ferraz Lopes J, De Freitas Mathias PC, Andreazzi AE, de Oliveira Guerra M & Maria Peters V (2020). Multigenerational effects of chronic maternal exposure to a high sugar/fat diet and physical training. *J Dev Orig Health Dis* **11**, 159-167.

Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, Nishimura H, Yoshimasa Y, Tanaka I, Mori T & Nakao K (1996). Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. *Nat Med* **3**, 1029–1033.

Matschinsky FM & Wilson DF (2019). The central role of glucokinase in glucose homeostasis: A perspective 50 years after demonstrating the presence of the enzyme in islets of Langerhans. *Front Physiol* **10**, 148.

Mendez N, Halabi D, Spichiger C, Salazar ER, Vergara K, Alonso-Vasquez P, Carmona P, Sarmiento JM, Richter HG, Seron-Ferre M & Torres-Farfan C (2016). Gestational chronodisruption impairs circadian physiology in rat male offspring, increasing the risk of chronic disease. *Endocrinology* **157**, 4654–4668.

Milanski M, Arantes VC, Ferreira F, de Reis MAB, Carneiro EM, Boschero AC, Collares-Buzato CB & Latorraca MQ (2005). Low-protein diets reduce PKAα expression in islets from pregnant rats. *J Nutr* **135**, 1873–1878.

Møldrup A, Petersen ED & Nielsen JH (1993). Effects of sex and pregnancy hormones on growth hormone and prolactin receptor gene expression in insulin-producing cells. *Endocrinology* **133**, 1165–1172.

Moltz JH & Fawcett CP (1985). Corticotropin-releasing factor: Its action on the islets of langerhans. *Endocr Res* **11**, 87–93.

Moore LG, Shriver M, Bemis L, Hickler B, Wilson M, Brutsaert T & Vargas EP, (2004). Maternal adaptation to high-altitude pregnancy: an experiment of nature – A review. *Placenta* **25**, S60–S71.

Morioka T, Asilmaz E, Hu J, Dishinger JF, Kurpad AJ, Elias CF, Li H, Elmquist JK, Kennedy RT & Kulkarni RN (2007). Disruption of leptin receptor expression in the pancreas directly affects β cell growth and function in mice. *J Clin Invest* **117**, 2860–2868.

Moyce BL & Dolinsky VW (2018). Maternal β-cell adaptations in pregnancy and placental signalling: Implications for gestational diabetes. *Int J Mol Sci* **19**, 3467.

Musial B, Fernandez-Twinn DS, Duque-Guimaraes D, Carr SK, Fowden AL, Ozanne SE & Sferruzzi-Perri AN (2019). Exercise alters the molecular pathways of insulin signaling and lipid handling in maternal tissues of obese pregnant mice. *Physiol Rep* **7**, e14202.

Musial B, Vaughan OR, Fernandez-Twinn DS, Voshol P, Ozanne SE, Fowden AL & Sferruzzi-Perri AN (2017). A Western-style obesogenic diet alters maternal metabolic physiology with consequences for fetal nutrient acquisition in mice. *J Physiol* **595**, 4875–4892.

Nadal Á (2019). Actions of endocrine disrupting chemicals on pancreatic beta cells and risk of diabetes mellitus. *Endocrine Abstracts* **63**, S7.2.

Nadal A, Alonso-Magdalena P, Soriano S, Quesada I & Ropero AB (2009). The pancreatic β-cell as a target of estrogens and xenoestrogens: Implications for blood glucose homeostasis and diabetes. *Mol Cell Endocrinol* **304**, 63–68.

Napso T, Yong HEJ, Lopez-Tello J & Sferruzzi-Perri AN (2018). The role of placental hormones in mediating maternal adaptations to support pregnancy and lactation. *Front Physiol* **9**, 1091.

Newbern D & Freemark M (2011). Placental hormones and the control of maternal metabolism and fetal growth. *Curr Opin Endocrinol Diabetes Obes* **18**, 409–416.

Nieuwenhuizen AG, Schuiling GA, Hilbrands LG, Bisschop EM & Koiter TR (1998). Proliferation of pancreatic islet-cells in cyclic and pregnant rats after treatment with progesterone. *Horm Metab Res* **30**, 649–655.

Nongonierma AB & Fitzgerald RJ (2015). Milk proteins as a source of tryptophan-containing bioactive peptides. *Food Function* **6**, 2115–2127.

Nordmann TM, Dror E, Schulze F, Traub S, Berishvili E, Barbieux C, Böni-Schnetzler M & Donath MY (2017). The role of inflammation in β-cell dedifferentiation. *Sci Rep* **7**, 6285.

Nunes VA, Portioli-Sanches EP, Rosim MP, Araujo MS, Praxedes-Garcia P, Valle MMR, Roma LP, Hahn C, Gurgul-Convey E, Lenzen S & Azevedo-Martins AK (2014). Progesterone induces apoptosis of insulin-secreting cells: Insights into the molecular mechanism. *J Endocrinol* **221**, 273–284.

Ohara-Imaizumi M, Kim H, Yoshida M, Fujiwara T, Aoyagi K, Toyofuku Y, Nakamichi Y, Nishiwaki C, Okamura T, Uchida T, Fujitani Y, Akagawa K, Kakei M, Watada H, German MS & Nagamatsu S (2013). Serotonin regulates glucose-stimulated insulin secretion from pancreatic β cells during pregnancy. *Proc Natl Acad Sci U S A* **110**, 19420–19425.

Ohta Y, Kosaka Y, Kishimoto N, Wang J, Smith SB, Honig G, Kim H, Gasa RM, Neubauer N, Liou A, Tecott LH, Deneris ES & German MS (2011). Convergence of the insulin and serotonin programs in the pancreatic β-cell. *Diabetes* **60**, 3208–3216.

Ormandy CJ, Camus A, Barra J, Damotte D, Lucas B, Buteau H, Edery M, Brousse N, Babinet C, Binart N & Kelly PA (1997). Null mutation of the prolactin receptor gene produces multiple reproductive defects in the mouse. *Genes Dev* **11**, 167–178.

Ou K, Zhang J, Jiao Y, Wang ZV, Scherer P & Kaestner KH (2018). Overexpression of ST5, an activator of Ras, has no effect on β-cell proliferation in adult mice. *Mol Metab* **11**, 212–217.

Owino S, Buonfiglio DDC, Tchio C & Tosini G (2019). Melatonin signaling a key regulator of glucose homeostasis and energy metabolism. *Front Endocrinol* **10**, 488.

Pantham P, Aye ILMH & Powell TL (2015). Inflammation in maternal obesity and gestational diabetes mellitus. *Placenta* **36**, 709–715.

Parsons JA, Bartke A & Sorenson RL (1995). Number and size of islets of Langerhans in pregnant, human growth hormone-expressing transgenic, and pituitary dwarf mice: effect of lactogenic hormones. *Endocrinology* **136**, 2013–2021.

Parsons, JA, Brelje, TC & Sorenson, RL (1992). Adaptation of islets of Langerhans to pregnancy: increased islet cell proliferation and insulin secretion correlates with the onset of placental lactogen secretion. *Endocrinology*, **130**, 1459–1466.

Pasek RC & Gannon M (2013). Advancements and challenges in generating accurate animal models of gestational diabetes mellitus. *Am J Physiol Endocrinol Metab* **305**, E1327–E1338.

Pechhold S, Stouffer M, Walker G, Martel R, Seligmann B, Hang Y, Stein R, Harlan DM & Pechhold K (2009). Transcriptional analysis of intracytoplasmically stained, FACS-purified cells by high-throughput, quantitative nuclease protection. *Nat Biotechnol* **27**, 1038–1042.

Pennington KA, van der Walt N, Pollock KE, Talton OO & Schulz LC (2017). Effects of acute exposure to a high-fat, high-sucrose diet on gestational glucose tolerance and subsequent maternal health in mice. *Biol Reprod* **96**, 435–445.

Pepin ME, Bickerton HH, Bethea M, Hunter CS, Wende AR & Banerjee RR (2019). Prolactin receptor signaling regulates a pregnancy-specific transcriptional program in mouse islets. *Endocrinology* **160**, 1150–1163.

Pfeiffer S, Sánchez-Lechuga B, Donovan P, Halang L, Prehn JHM, Campos-Caro A, Byrne MM & López-Tinoco C (2020). Circulating miR-330-3p in late pregnancy is associated with pregnancy outcomes among lean women with GDM. *Sci Rep* **10**, 908.

Picard F, Wanatabe M, Schoonjans K, Lydon J, O'Malley BW & Auwerx J (2002). Progesterone receptor knockout mice have an improved glucose homeostasis secondary to β-cell proliferation. *Proc Natl Acad Sci U S A* **99**, 15644–15648.

Plank JL, Frist AY, LeGrone AW, Magnuson MA & Labosky PA (2011). Loss of Foxd3 results in decreased β-cell proliferation and glucose intolerance during pregnancy. *Endocrinology* **152**, 4589–4600.

Pomplun D, Florian S, Schulz T, Pfeiffer AFH & Ristow M (2007). Alterations of pancreatic beta-cell mass and islet number due to Ins2-controlled expression of Cre recombinase: RIP-Cre revisited; part 2. *Horm Metab Res* **39**, 336–340.

Proper KI, Van De Langenberg D, Rodenburg W, Vermeulen RCH, Van Der Beek AJ, Van Steeg H & Van Kerkhof LWM (2016). The relationship between shift work and metabolic risk factors: a systematic review of longitudinal studies. *Am J Prev Med* **50**, e147–e157.

Qiao L, Saget S, Lu C, Hay WW, Karsenty G & Shao J (2021). Adiponectin promotes maternal β-cell expansion through placental lactogen expression. *Diabetes* **70**, 132–142.

Qiao L, Wattez JS, Lee S, Nguyen A, Schaack J, Hay WW & Shao J (2017). Adiponectin deficiency impairs maternal metabolic adaptation to pregnancy in mice. *Diabetes* **66**, 1126–1135.

Qiu C, Enquobahrie D, Frederick IO, Abetew D & Williams MA (2010). Glucose intolerance and gestational diabetes risk in relation to sleep duration and snoring during pregnancy: a pilot study. *BMC Womens Health* **10**, 17.

Quesada-Candela, C, Tudurí E, E, Marroquí, L, Alonso-Magdalena, P, Quesada, I & Nadal, Á (2020). Morphological and functional adaptations of pancreatic alpha-cells during late pregnancy in the mouse. *Metabolism*, **102**, 153963.

Radesky, JS, Oken, E, Rifas-Shiman, SL, Kleinman, KP, Rich-Edwards, JW & Gillman, MW (2008). Diet during early pregnancy and development of gestational diabetes. *Paediatr Perinat Epidemiol*, **22**, 47–59.

Rawal S, Hinkle SN, Zhu Y, Albert PS & Zhang C (2017). A longitudinal study of sleep duration in pregnancy and subsequent risk of gestational diabetes: findings from a prospective, multiracial cohort. *Am J Obstet Gynecol* **216**, 399.e1–e8.

Rawn SM, Huang C, Hughes M, Shaykhutdinov R, Vogel HJ & Cross JC (2015). 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* **93**, 75.

Ren J, Xiang AH, Trigo E, Takayanagi M, Beale E, Lawrence JM, Hartiala J, Richey JM, Allayee H, Buchanan TA & Watanabe RM (2014). Genetic variation in *MTNR1B* is associated with gestational diabetes mellitus and contributes only to the absolute level of beta cell compensation in Mexican Americans. *Diabetologia* **57**, 1391–1399.

Reutrakul S, Zaidi N, Wroblewski K, Kay HH, Ismail M, Ehrmann DA & Van Cauter E (2011). Sleep disturbances and their relationship to glucose tolerance in pregnancy. *Diabetes Care* **34**, 2454–2457.

Reynolds RM, Logie JJ, Roseweir AK, McKnight AJ & Millar RP (2009). A role for kisspeptins in pregnancy: Facts and speculations. *Reproduction* **138**, 1–7.

Rieck S & Kaestner KH (2010). Expansion of β-cell mass in response to pregnancy. *Trends Endocrinol Metab* **21**, 151–158.

Rieck S, White P, Schug J, Fox AJ, Smirnova O, Gao N, Gupta RK, Wang ZV, Scherer PE, Keller MP, Attie AD & Kaestner KH (2009). The transcriptional response of the islet to pregnancy in mice. *Mol Endocrinol* **23**, 1702–1712.

Robledo C, Peck JD, Stoner JA, Carabin H, Cowan L, Koch HM & Goodman JR (2013). Is bisphenol-A exposure during pregnancy associated with blood glucose levels or diagnosis of gestational diabetes? *J Toxicol Environ Health A* **76**, 865–873.

Romero R, Gotsch F, Pineles B & Kusanovic JP (2007). Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. *Nutr Rev* **65**, S194–S202.

Rosario FJ, Kanai Y, Powell TL & Jansson T (2015). Increased placental nutrient transport in a novel mouse model of maternal obesity with fetal overgrowth. *Obesity* **23**, 1663–1670.

Rosta K, Al-Aissa Z, Hadarits O, Harreiter J, Nádasdi Á, Kelemen F, Bancher-Todesca D, Komlósi Z, Németh L, Rigó J, Sziller I, Somogyi A, Kautzky-Willer A & Firneisz G (2017). Association study with 77 SNPs confirms the robust role for the rs10830963/G of MTNR1B variant and identifies two novel associations in gestational diabetes mellitus development. *PLoS One* **12**, e0169781.

Rutland CS, Latunde-Dada AO, Thorpe A, Plant R, Langley-Evans S & Leach L (2007). Effect of gestational nutrition on vascular integrity in the murine placenta. *Placenta* **28**, 734–742.

Ryan EA & Enns L (1988). Role of gestational hormones in the induction of IR. *J Clin Endocrinol Metab* **67**, 341–347.

Saldana, TM, Siega-Riz, AM & Adair, LS (2004). Effect of macronutrient intake on the development of glucose intolerance during pregnancy. *Am J Clin Nutr* **79**, 479–486.

Salvatierra CSB, Reis SRL, Pessoa AFM, De Souza LMI, Stoppiglia LF, Veloso RV, Reis MAB, Carneiro EM, Boschero AC, Colodel EM, Arantes VC & Latorraca MQ (2015). Short-term low-protein diet during pregnancy alters islet area and protein content of phosphatidylinositol 3-kinase pathway in rats. *An Acad Bras Cienc* **87**, 1007–1018.

Scaglia L, Smith FE & Bonner-Weir S (1995). Apoptosis contributes to the involution of beta cell mass in the post pax-turn rat pancreas. *Endocrinology* **136**, 5461–5468.

Schmid J, Ludwig B, Schally AV, Steffen A, Ziegler CG, Block NL, Koutmani Y, Brendel MD, Karalis KP, Simeonovic CJ, Licinio J, Ehrhart-Bornstein M & Bornstein SR (2011). Modulation of pancreatic islets-stress axis by hypothalamic releasing hormones and 11β-hydroxysteroid dehydrogenase. *Proc Natl Acad Sci U S A* **108**, 13722–13727.

Schraenen A, De Faudeur G, Thorrez L, Lemaire K, Van Wichelen G, Granvik M, Van Lommel L, in't Veld P & Schuit F (2010*a*). MRNA expression analysis of cell cycle genes in islets of pregnant mice. *Diabetologia* **53**, 2579–2588.

Schraenen A, Lemaire K, De Faudeur G, Hendrickx N, Granvik M, Van Lommel L, Mallet J, Vodjdani G, Gilon P, Binart N, in't Veld P & Schuit F (2010*b*). Placental lactogens induce serotonin biosynthesis in a subset of mouse beta cells during pregnancy. *Diabetologia* **53**, 2589–2599.

Sebastiani G, Guarino E, Grieco GE, Formichi C, Poggi CD, Ceccarelli E & Dotta F (2017). Circulating microRNA (miRNA) expression profiling in plasma of patients with gestational diabetes mellitus reveals upregulation of miRNA miR-330-3p. *Front Endocrinol* **8**, 345.

Sferruzzi-Perri AN, Higgins JS, Vaughan OR, Murray AJ & Fowden AL (2019). Placental mitochondria adapt developmentally and in response to hypoxia to support fetal growth. *Proc Natl Acad Sci U S A* **116**, 1621–1626.

Sferruzzi-Perri AN, Lopez-Tello J, Napso T & Yong HEJ (2020). Exploring the causes and consequences of maternal metabolic maladaptations during pregnancy: Lessons from animal models. *Placenta* **98**, 43–51.

Sferruzzi-Perri AN, Vaughan OR, Haro M, Cooper WN, Musial B, Charalambous M, Pestana D, Ayyar S, Ferguson-Smith AC, Burton GJ, Constancia M & Fowden AL (2013). An obesogenic diet during mouse pregnancy modifies maternal nutrient partitioning and the fetal growth trajectory. *FASEB J* **27**, 3928–3937.

Shaffer RM, Ferguson KK, Sheppard L, James-Todd T, Butts S, Chandrasekaran S, Swan SH, Barrett ES, Nguyen R, Bush N, McElrath TF & Sathyanarayana S (2019). Maternal urinary phthalate metabolites in relation to gestational diabetes and glucose intolerance during pregnancy. *Environ Int* **123**, 588–596.

Shapiro GD, Dodds L, Arbuckle TE, Ashley-Martin J, Fraser W, Fisher M, Taback S, Keely E, Bouchard MF, Monnier P, Dallaire R, Morisset A & Ettinger AS (2015). Exposure to phthalates, bisphenol A and metals in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: The MIREC study. *Environ Int* **83**, 63–71.

Shirakawa J, Fernandez M, Takatani T, El Ouaamari A, Jungtrakoon P, Okawa ER, Zhang W, Yi P, Doria A & Kulkarni RN (2017). Insulin signaling regulates the FoxM1/PLK1/CENP-A pathway to promote adaptive pancreatic β cell proliferation. *Cell Metab* **25**, 868–882.e5.

Simpson SJS, Smith LIF, Jones PM & Bowe JE (2020). UCN2: a new candidate influencing pancreatic β-cell adaptations in pregnancy. *J Endocrinol* **245**, 247–257.

Soares MJ, Konno T & Alam SMK (2007). The prolactin family: effectors of pregnancy-dependent adaptations. *Trends Endocrinol Metab* **18**, 114–121.

Somers W, Ultsch M, De Vos AM & Kossiakoff AA (1994). The X-ray structure of a growth hormone-prolactin receptor complex. *Nature* **372**, 478–481.

Soo BC, Jin SJ & Park S (2005). Estrogen and exercise may enhance β-cell function and mass via insulin receptor substrate 2 induction in ovariectomized diabetic rats. *Endocrinology* **146**, 4786–4794.

Sorenson RL & Brelje TC (1997). Adaptation of islets of Langerhans to pregnancy: beta-cell growth, enhanced insulin secretion and the role of lactogenic hormones. *Horm Metab Res* **29**, 301–307.

Sorenson RL & Brelje TC (2009). Prolactin receptors are critical to the adaptation of islets to pregnancy. *Endocrinology* **150**, 1566–1569.

Sorenson RL, Brelje TC & Roth C (1993). Effects of steroid and lactogenic hormones on islets of langerhans: A new hypothesis for the role of pregnancy steroids in the adaptation of islets to pregnancy. *Endocrinology* **133**, 2227–2234.

Staels W, Heremans Y, Leuckx G, Van Gassen N, Salinno C, De Groef S, Cools M, Keshet E, Dor Y, Heimberg H & De Leu N (2017). Conditional islet hypovascularisation does not preclude beta cell expansion during pregnancy in mice. *Diabetologia* **60**, 1051–1056.

Strakovsky RS & Schantz SL (2018). Using experimental models to assess effects of bisphenol A (BPA) and phthalates on the placenta: challenges and perspectives. *Toxicol Sci* **53**, 1689–1699.

Szlapinski SK, King RT, Retta G, Yeo E, Strutt BJ & Hill DJ (2019). A mouse model of gestational glucose intolerance through exposure to a low protein diet during fetal and neonatal development. *J Physiol* **597**, 4237–4250.

Tamm I, Wang Y, Sausville E, Scudiero DA, Vigna N, Oltersdorf T & Reed JC (1998). IAP-family protein Survivin inhibits caspase activity and apoptosis induced by Fas (CD95), bax, caspases, and anticancer drugs. *Cancer Res* **58**, 5315–5320.

Thakker RV (2014). Multiple endocrine neoplasia type 1 (MEN1) and type 4 (MEN4). *Mol Cell Endocrinol* **386**, 2–15.

Tiano JP, Delghingaro-Augusto V, Le May C, Liu S, Kaw MK, Khuder SS, Latour MG, Bhatt SA, Korach KS, Najjar SM, Prentki M & Mauvais-Jarvis F (2011). Estrogen receptor activation reduces lipid synthesis in pancreatic islets and prevents β cell failure in rodent models of type 2 diabetes. *J Clin Invest* **121**, 3331–3342.

Toselli C, Hyslop CM, Hughes M, Natale DR, Santamaria P & Huang CTL (2014). Contribution of a non-β-cell source to β-cell mass during pregnancy. *PLoS One* **9**, e100398.

Tsai, PJ, Davis, J & Bryant-Greenwood, G (2015). Systemic and placental leptin and its receptors in pregnancies associated with obesity. *Reprod Sci* **22**, 189–197.

Van Assche FA, Aerts L & De Prins F (1978). A morphological study of the endocrine pancreas. *Br J Obstet Gynaecol* **85**, 818–820.

Vanzela EC, Ribeiro RA, De Oliveira CAM, Rodrigues FB, Bonfleur ML, Carneiro EM, Souza KLA & Boschero AC (2010). Pregnancy restores insulin secretion from pancreatic islets in cafeteria diet-induced obese rats. *Am J Physiol Endocrinol Metab* **298**, 320–328.

Varcoe TJ, Boden MJ, Voultsios A, Salkeld MD, Rattanatray L & Kennaway DJ (2013). Characterisation of the maternal response to chronic phase shifts during gestation in the rat: implications for fetal metabolic programming. *PLoS One* **8**, e53800.

Vasavada RC, Garcia-Ocaña A, Zawalich WS, Sorenson RL, Dann P, Syed M, Ogren L, Talamantes F & Stewart AF (2000). Targeted expression of placental lactogen in the beta cells of transgenic mice results in beta cell proliferation, islet mass augmentation, and hypoglycemia. *J Biol Chem* **275**, 15399–15406.

Vasavada RC, Wang L, Fujinaka Y, Takane KK, Rosa TC, Mellado-Gil JM, Friedman PA & Garcia-Ocaña A (2007). Protein kinase C-ζ activation markedly enhances beta-cell proliferation: an essential role in growth factor mediated beta-cell mitogenesis. *Diabetes* **56**, 2732–2743.

Vasu S, Kumano K, Darden CM, Rahman I, Lawrence MC & Naziruddin B (2019). MicroRNA signatures as future biomarkers for diagnosis of diabetes states. *Cells* **8**, 1533.

Wang H, Leng J, Li W, Wang L, Zhang C, Li W, Liu H, Zhang S, Chan J, Hu G, Yu Z & Yang X (2017). Sleep duration and quality, and risk of gestational diabetes mellitus in pregnant Chinese women. *Diabet Med* **34**, 44–50.

Wang X, Wang X, Chen Q, Luo ZC, Zhao S, Wang W, Zhang H-J, Zhang J & Ouyang F (2017). Urinary bisphenol a concentration and gestational diabetes mellitus in Chinese women. *Epidemiology* **28**, S41–S47.

Wei J, Ding D, Wang T, Liu Q & Lin Y (2017). MiR-338 controls BPA-triggered pancreatic islet insulin secretory dysfunction from compensation to decompensation by targeting Pdx-1. *FASEB J* **31**, 5184–5195.

Weinhaus AJ, Stout LE, Bhagroo NV, Brelje TC & Sorenson RL (2007). Regulation of glucokinase in pancreatic islets by prolactin: A mechanism for increasing glucose-stimulated insulin secretion during pregnancy. *J Endocrinol* **193**, 367–381.

Weinhaus AJ, Stout LE & Sorenson RL (1996). Glucokinase, hexokinase, glucose transporter 2, and glucose metabolism in islets during pregnancy and prolactin-treated islets in vitro: mechanisms for long term up-regulation of islets. *Endocrinology* **137**, 1640–1649.

Weldingh NM, Jørgensen-Kaur L, Becher R, Holme JA, Bodin J, Nygaard UC & Bølling AK (2017). Bisphenol A is more potent than phthalate metabolites in reducing pancreatic β-cell function. *Biomed Res Int* **2017**, 4614379.

Wong WPS, Tiano JP, Liu S, Hewitt SC, Le May C, Dalle S, Katzenellenbogen JA, Katzenellenbogen BS, Korach KS & Mauvais-Jarvis F (2010). Extranuclear estrogen receptor-α stimulates NeuroD1 binding to the insulin promoter and favors insulin synthesis. *Proc Natl Acad Sci U S A* **107**, 13057–13062.

Wu H, Liu Y, Wang H & Xu X (2015). High-fat diet induced insulin resistance in pregnant rats through pancreatic Pax6 signaling pathway. *Int J Clin Exp Pathol* **8**, 5196–5202.

Wu Y, Liu C, Sun H, Vijayakumar A, Giglou PR, Qiao R, Oppenheimer J, Yakar S & LeRoith D (2011). Growth hormone receptor regulates β cell hyperplasia and glucose-stimulated insulin secretion in obese mice. *J Clin Investig* **121**, 2422–2426.

Xu Y, Wang X, Gao L, Zhu J, Zhang H, Shi H, Woo M & Wu X (2015). Prolactin-stimulated survivin induction is required for beta cell mass expansion during pregnancy in mice. *Diabetologia* **58**, 2064–2073.

Xue Y, Liu C, Xu Y, Yuan Q, Xu K, Mao X, Chen G, Wu X, Brendel MD & Liu C (2010). Study on pancreatic islet adaptation and gene expression during pregnancy in rats. *Endocrine* **37**, 83–97.

Yamaguchi, M, Murakami, T, Yasui, Y, Otani, S, Kawai, M, Kishi, K, Kurachi, H, Shima, A, Aono, T & Murata, Y(1998). Mouse placental cells secrete soluble leptin receptor (sOB-R): cAMP inhibits sOB-R production. *Biochem Biophys Res Commun* **252**, 363–367.

Yamashita H, Shao J, Ishizuka T, Klepcyk PJ, Muhlenkamp P, Qiao L, Hoggard N & Friedman JE (2001). Leptin administration prevents spontaneous gestational diabetes in heterozygous $Lepr^{db/+}$ mice: Effects on placental leptin and fetal growth. *Endocrinology* **142**, 2888–2897.

Yang W, Jiang Y, Wang Y, Zhang T, Liu Q, Wang C, Swisher G, Wu N, Chao C, Prasadan K, Gittes GK & Xiao X (2020). Placental growth factor in beta cells plays an essential role in gestational beta-cell growth. *BMJ Open Diabetes Res Care* **8**, e000921.

Zahr E, Molano RD, Pileggi A, Ichii H, San Jose S, Bocca N, An W, Gonzalez-Quintana J, Fraker C, Ricordi C & Inverardi L (2008). Rapamycin impairs β-cell proliferation in vivo. *Transplant Proc* **40**, 436–437.

Zhang H, Zhang J, Pope CF, Crawford LA, Vasavada RC, Jagasia SM & Gannon M (2010). Gestational diabetes mellitus resulting from impaired β-cell compensation in the absence of FoxM1, a novel downstream effector of placental lactogen. *Diabetes* **59**, 143–152.

Zhao X (2014). Increase of beta cell mass by beta cell replication, but not neogenesis, in the maternal pancreas in mice. *Endocr J* **61**, 623–628.

Zhao X, Xu Y, Wu Y, Zhang H, Shi H, Zhu H, Woo M & Wu X (2019). Involvement of the STAT5-cyclin D/CDK4-pRb pathway in β-cell proliferation stimulated by prolactin during pregnancy. *Am J Physiol Endocrinol Metab* **316**, E135–E144.

Zhou Z, Ribas V, Rajbhandari P, Drew BG, Moore TM, Fluitt AH, Reddish BR, Whitney KA, Georgia S, Vergnes L, Reue K, Liesa M, Shirihai O, van der Bliek AM, Chi N-W, Mahata SK, Tiano JP, Hewitt SC, Tontonoz P, Korach KS, Mauvais-Jarvis F, Hevener AL (2018). Estrogen receptor protects pancreatic β-cells from apoptosis by preserving mitochondrial function and suppressing endoplasmic reticulum stress. *J Biol Chem* **293**, 4735–4751.

Additional information

Competing interests

The authors declare there are no competing or conflicts of interests to disclose.

Author contributions

E.S.P. and A.N.S.-P. planned the content of the manuscript together. E.S.P. wrote the first draft and A.N.S.-P. then edited the manuscript. Both authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

E.S.P. is funded by a Beca-Chile, ANID Postdoctoral Scholarship: 74190055. A.N.S.-P. is funded by a MRC New Investigator Grant (MR/R022690/1; RG93186) and a Lister Institute of Preventative Medicine Research Prize (RG93692).

Acknowledgements

We thank Dr Samantha Lean for proof reading the manuscript prior to submission and Dr Jorge Lopez-Tello for feedback on the figures.

Keywords

β-cells, insulin resistance, gestational diabetes, maternal adaptations, metabolism, pancreas, pregnancy