Impact of prematurity for pancreatic islet and beta-cell development

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Abstract

As increasing numbers of babies born preterm survive into adulthood, it is becoming clear that, in addition to the well-described risks of neurodevelopmental sequelae, there are also increased risks for non-communicable diseases, including diabetes. Epidemiological studies indicate that risks are increased even for birth at late preterm and early term gestations and for both type 1 and type 2 diabetes. Thus, factors related to preterm birth likely affect development of the fetal and neonatal beta-cell in addition to effects on peripheral insulin sensitivity. These factors could operate prior to preterm birth and be related to the underlying cause of preterm birth, to the event of being born preterm itself, to the postnatal care of the preterm neonate or to a combination of these exposures. Experimental evidence indicates that factors may be operating during all these critical periods to contribute to altered development of beta-cell mass in those born preterm. Greater understanding of how these factors impact upon development of the pancreas may lead to interventions or management approaches that mitigate the increased risk of later diabetes.

Preterm birth and the later risk of diabetes

Preterm birth (birth before 37 completed weeks’ gestation) occurs in 11.1% of births globally, with most countries showing increasing rates over the past two decades (Blencowe et al. 2012). The neonatal mortality rate from preterm birth is decreasing, counterbalanced to some extent by the increasing preterm birth rates (Blencowe et al. 2013c), most of which is due to increases in late preterm births (births at 35–36 weeks’ gestation) (Davidoff et al. 2006). Although outcomes from moderate-late preterm birth (32–36 weeks’ gestation) are excellent compared with those from very and extremely preterm birth (before 32-weeks’ gestation), because >80% of preterm babies are born at moderate-to-late preterm gestations, the majority of the global life-long health burden following preterm birth is accounted for by these babies (Blencowe et al. 2013b). The focus in the early years of neonatal intensive care was on survival; as mortality rates have decreased, the focus has been on survival free of neurodisability. As increasing numbers of people born preterm reach middle and older adulthood, there is increasing awareness of the potential for those born preterm also to be at risk of non-communicable diseases.

Population studies in Northern Ireland (Cardwell et al. 2005), England (Goldacre 2017), Western Australia (Haynes et al. 2007) and Sweden (Crump et al. 2011) have reported a 17–43% increased risk of type 1 diabetes following preterm birth. The English and Western Australian studies (Haynes et al. 2007, Goldacre 2017), and a single-centre population cohort study from Israel (Paz Levy et al. 2017), also report an increased risk of type 1 diabetes following early term birth (37- to 38-weeks’ gestation) when compared with full term births, consistent
with the concept that gestational age reflects a spectrum of maturation that crosses the traditional boundary of preterm and term at 37-weeks’ gestation (The American College of Obstetricians and Gynecologists 2013). In contrast, a population study from Norway (Stene et al. 2001) and a smaller study across Europe (Dahlquist et al. 1999) did not find an association between type 1 diabetes and gestational age. However, it is important to note that these two studies investigated childhood onset of type 1 diabetes and so would not detect an association between preterm birth and type 1 diabetes with onset beyond 15 years of age. A cross-sectional population study from Israel reported that the proportion of children with type 1 diabetes born at full term (37–42 weeks’ gestation) was significantly less than the proportion of the population without type 1 diabetes born at full term (83.8% versus 87.7%), but did not find a statistically significant increase in type 1 diabetes in those born preterm compared with those born at term (8.3% vs 7.6%) (Adar et al. 2018).

Cohort studies also suggest that there is an association between preterm birth and type 2 diabetes (Lawlor et al. 2006, Kaijser et al. 2009, Kajantie et al. 2010, Pilgaard et al. 2010). Although the sample sizes in these studies are much smaller than for the studies of type 1 diabetes, the estimated pooled relative risk from a meta-analysis suggests a 50% increased risk (95% CIs 32–72%) (Li et al. 2014). Once again, the studies are not all consistent, with a cohort study from China (Xiao et al. 2008) not reporting an association between risk of type 2 diabetes and gestational age and the Helsinki birth cohort study finding an increased risk for type 2 diabetes following preterm birth below 35-weeks’ gestation but a trend towards a decreased risk at 35- to 37-weeks’ gestation (Kajantie et al. 2010). The different findings may reflect the different subjects included in these studies, with, for example, the Scandinavian cohort studies linking birth data with diagnosis of type 2 diabetes from hospital discharge data (Kaijser et al. 2009) or with a registry of medication for diabetes (Kajantie et al. 2010), thus potentially missing mild cases of diabetes, whereas the cohort study from Beijing (Xiao et al. 2008) included 2019/2085 survivors of 12,097 births between 1921 and 1954 in one hospital in Beijing, which is likely to select for healthier individuals. For the Aberdeen birth cohort study, birth data were linked with self-reported diagnosis of diabetes.

The epidemiological findings are supported by several, but not all (Willemsen et al. 2009), experimental studies investigating insulin sensitivity in children and young adults, which report decreased insulin sensitivity in those born preterm compared with term-born controls (Hofman et al. 2004, Hovi et al. 2007, Rotteveel et al. 2008, Willemsen et al. 2008, Mathai et al. 2012). The associations between preterm birth and later insulin sensitivity are compounded by postnatal factors across the life-course, particularly environmental factors such as exercise and diet that impact upon body composition (Tinnion et al. 2014).

These associations of preterm birth with type 1 and 2 diabetes are independent of birthweight, with increasing birthweight associated with an increased risk of type 1 diabetes (Harder et al. 2009, Goldacre 2017) and both high and low birthweight associated with type 2 diabetes (Harder et al. 2007). Thus, the balance of evidence suggests that preterm birth is associated with increased incidences of both type 1 and 2 diabetes and that risk for diabetes is already present in childhood or early adulthood.

The global burden of diabetes is increasing, not only for type 2 diabetes (Chen et al. 2011), but also for type 1 diabetes, particularly in younger children (Patterson et al. 2009). Preterm births account for approximately 10% of all births and survival rates from very and extremely preterm birth are increasing. If the risk of diabetes following preterm birth is increased by 25–35% compared with those not born preterm, then prematurity potentially is contributing significantly to the global burden of diabetes.

How might preterm birth be linked with later diabetes?

Onset of type 2 diabetes is characterised by a functional pancreatic β-cell mass that is no longer able to compensate for the prevailing insulin resistance (Rhodes 2005). In contrast, in type 1 diabetes, loss of β-cell mass is a primary feature. As both types 1 and 2 diabetes are associated with preterm birth, it could be speculated that the mechanism may include a direct effect on the developing pancreas. Information on the developing human pancreas is understandably scarce, but available data indicate that most β-cell neogenesis occurs preterm with β-cell proliferation from pancreatic ductal cells occurring in both the fetus and neonate (Polak et al. 2000, Gregg et al. 2012). β-cell neogenesis after birth is thought to occur at very low rates (≤0.5%) with apoptosis also at low rates (≤1.5%) (Butler et al. 2007, Gregg et al. 2012). Thus, the baseline β-cell mass forming the population from which any later expansion, in response to metabolic demand or physiological states, such as pregnancy, is established early in life. It follows that a reduction in baseline β-cell mass is likely to impact upon a compensatory response.
to metabolic demand with limited ability for significant β-cell turnover in adulthood (Perl et al. 2010). However, there is no evidence on whether baseline β-cell mass prior to the onset of autoimmunity is a factor in the risk of developing type 1 diabetes.

In the fetal sheep (Fowden 1980, Aldoretta et al. 1998) and horse (Fowden et al. 1980, 1982, 2005), and also in altricial species such as the rat (Kervran et al. 1979, Kervran & Randon 1980), there are maturational changes in pancreatic function in late gestation with increasing insulin secretion in response to glucose and arginine stimulation. These changes are associated with increasing endogenous cortisol concentrations in the prepartum period (Fowden et al. 2005), can be modified by exogenous stimuli such as maternal undernutrition (Oliver et al. 2001), multiple conception (Rumball et al. 2008, Green et al. 2011) and exogenous glucocorticoid administration (Valenzuela et al. 2017) and extend into postnatal life. It has also been reported that there is a wave of β-cell apoptosis in late gestation in the human (Tornehave & Larsson 1997), which may represent a change from fetal β-cells to more mature β-cells in preparation for extra-uterine life. A similar wave of apoptosis has been described in the neonatal period in the rat (Scaglia et al. 1997, Hill & Duvillie 2000), reflecting different timing of pancreatic development in relation to birth in this altricial species, which may be an important factor in experiments investigating the impact of preterm birth on development of the critical β-cell mass on which later capacity to respond to metabolic demand rests.

In considering how preterm birth might impact upon the developing β-cell, it is important to bear in mind that the effects might arise from maternal, fetal or pregnancy-related factors that led to the preterm birth; the impact of preterm birth itself on the metabolism, organ development and physiology of the fetus–neonate or from the impact of any care provided to the preterm neonate following birth (Fig. 1).

### Association between factors leading to preterm birth and later glucose intolerance

Preterm birth is a syndrome with multiple preceding factors (Blencowe et al. 2013a), extending from genetic, environmental and through to iatrogenic – that is, where the medical providers make the decision to initiate

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**Factors related to preterm birth that may affect development of beta-cell mass**

![Factors related to preterm birth that may affect development of beta-cell mass](image-url)

**Figure 1**

Schematic of development of beta-cell mass. Cells staining positive for insulin (I), glucagon (G), pancreatic polypeptide (PP) and somatostatin (SS) appear early in development, before the appearance of recognisable islets (*). Around the time of birth, if labour occurs there is a prepartum surge of fetal cortisol (F), which is associated with a cluster of maturational changes. Following birth, there is a period of postnatal expansion of the beta cells, resulting in a baseline beta-cell mass that is relatively stable thereafter. Factors throughout pregnancy (and from before conception), birth and the neonatal period may impact upon establishment of this baseline beta-cell mass. Factors operating later in life, such as obesity, may contribute to impaired insulin sensitivity.
preterm delivery, usually for reasons related to maternal or fetal health. Genome-wide association studies have been relatively disappointing in identifying SNPs associated with spontaneous preterm birth, although a recent study identified four loci that were significantly associated with gestation length (Zhang et al. 2017), including Early B-cell Factor 1, which also is associated with increased blood glucose and diabetes (Singh et al. 2015). Newer approaches that integrate data on SNP interactions using spatial genomic connectivity (using chromosome conformational capture) with functional outcomes (Fadason et al. 2017) may lead to new insights into the association between gestation length and diabetes.

Maternal factors such as nutrition, multiple pregnancies and stress also are associated with preterm birth and with later risk for diabetes (Blencowe et al. 2013a). Experimental and human data suggest that the critical period for these factors is in the very early, periconceptional period. For example, poor maternal nutrition in early pregnancy is associated with preterm birth in studies in sheep (Bloomfield et al. 2003) and in humans (Rayco-Solon et al. 2005, Bloomfield 2011b) and experimental studies in sheep indicate that reduced gestation length and size in multiples also is determined in early pregnancy (Hancock et al. 2012). Similarly, maternal exposure to acute stress during pregnancy has been reported to increase preterm birth, with most studies reporting the greatest effects if the exposure is in the first trimester (Zhu et al. 2010, Class et al. 2011, Oyarzo et al. 2012, Torche & Kleinhaus 2012).

In both human and sheep studies, offspring following maternal undernutrition (Todd et al. 2009, Roseboom et al. 2011, de Rooij et al. 2014), maternal stress (Entringer et al. 2008, Brunton et al. 2013) and twin pregnancy (Grunnet et al. 2007, Monrad et al. 2009, Poulsen et al. 2009, Donovan et al. 2017) are at increased risk of impaired glucose tolerance and diabetes in adulthood. It is likely that these effects are mediated through epigenetic modifications in the fetus (Bloomfield 2011a, Cao-Lei et al. 2017).

**Potential effect of being born preterm on later glucose intolerance**

Birth at any gestation is associated with substantial physiological and endocrinological changes that enable the newborn to adapt to extra-uterine life (Riviere et al. 2017). The fetus in all species studied demonstrates an endogenous glucocorticoid surge (Fowden et al. 1998) that, together with increasing production of thyroid hormones and increased peripheral conversion of thyroxine to T3, is responsible for maturation of many enzymes and organ systems prior to birth. Maturation of both cortisol and thyroid hormone secretion are related to gestational age and are blunted in the preterm infant (Ballard et al. 1998, Travers et al. 2018). The maturational role of glucocorticoids has been harnessed as a fetal treatment in women at risk of preterm birth, resulting in reduced mortality and morbidity in preterm neonates (Liggins & Howie 1972), but the addition of thyroid-releasing hormone to this maternal treatment did not have any additional beneficial effect (Crowther et al. 2013a). Although studies in a variety of animal species have reported that antenatal glucocorticoids result in a metabolic profile in the offspring that indicates metabolic risk (Seckl & Holmes 2007), the 30-year follow-up of the original antenatal glucocorticoid trial reported only a small (~16%), although statistically significant, increase in insulin concentration 30 minutes after a 75 g oral glucose tolerance test, with decreased glucose concentration at 120 minutes, in the offspring exposed to antenatal glucocorticoids compared with those exposed to placebo (Dalziel et al. 2005). It is not yet known whether this clinically insignificant finding at age 30 years could amplify into clinically relevant insulin resistance as the subjects age. However, in the whole cohort within this trial, both a lower gestational age and being born preterm were associated with an increased insulin area under the curve in the glucose tolerance test, suggesting an independent inverse relationship between gestation length and insulin resistance age 30 years (Dalziel et al. 2007). Given that administration of antenatal glucocorticoids to women at risk of preterm birth is considered standard of care in higher income countries (Antenatal Corticosteroid Clinical Practice Guidelines Panel 2015), the potential impact of this treatment on the fetal pancreas needs to be considered as part of the context of preterm birth.

Catecholamines also are released in the peripartum period and are important in maintaining free fatty acid and glucose concentrations, but also have been implicated in developmental adaptations in fetal β cells (Boehmer et al. 2017). In addition, there are dramatic changes in arterial oxygen saturation, the requirement for thermogenesis and the cessation of a continuous supply of nutrition across the placenta. These endocrinological and physiological changes have been proposed to impact upon development of a variety of organs, with potential long-term consequences (Fowden et al. 1998). For example, preterm birth has been reported in animal studies to lead to life-long deficits in nephron endowment.
Preterm birth is a condition of altered immune function (Sharma et al. 2012) and most of the significant neonatal morbidities accompanying significantly preterm birth, such as bronchopulmonary dysplasia, necrotising enterocolitis, retinopathy of prematurity and white matter injury, are associated with a pro-inflammatory state (Dong et al. 2018). Infection is common in preterm babies, and more so in boys than in girls, and is implicated in the pathogenesis of these pro-inflammatory morbidities (O’Driscoll et al. 2017a, b, Dong et al. 2018). Furthermore, there is evidence of altered T-cell function in preterm birth with, for example, increased regulatory T cells, which may increase the risk of neonatal infection (Pagel et al. 2016).

Immune function in preterm babies may also differ by sex (O’Driscoll et al. 2017a, b). A study in Denmark identified all children over a 3-year period diagnosed with type 1 diabetes before the age of 15 years and investigated early childhood factors associated with type 1 diabetes (Svensson et al. 2005). Neonatal infection in boys, but not girls, was associated with a five-fold increased risk of developing diabetes. Thus, the association between preterm birth and type 1 diabetes may be mediated through immune mechanisms rather than a direct effect on baseline β-cell mass, consistent with the autoimmune nature of this condition.

Impact of neonatal care

The preterm neonate may be exposed to a wide variety of interventions, particularly those born at earlier gestational ages. However, given that the association between preterm birth and later risk of diabetes appears to exist across the gestational age spectrum, and even into early term gestations as discussed earlier, it seems reasonable to consider interventions that apply to all preterm babies. The most ubiquitous is nutrition and its impact upon growth (Harding et al. 2017). Preterm babies are, as a population, born smaller than their gestational age-matched counterparts who remain in utero until term (Cooke 2007) and also are very likely to suffer postnatal faltering growth (Harding et al. 2017). Breastmilk alone may not be able to sustain recommended postnatal growth rates, so additional nutritional support is often provided (Harding et al. 2017). By the time preterm babies, even those born at late preterm gestations, reach term-corrected age, they have a different body composition from term-born babies, with increased % body fat and an altered fat distribution (Uthaya et al. 2005, Gianni et al. 2009). After discharge, a period of accelerated or ‘catch-up’ growth is common in preterm infants. Postnatal ‘catch-up’ growth has been associated with increased metabolic risk in adolescence and adulthood (Rotteveel et al. 2008, Singhal et al. 2010, Belfort et al. 2013, Embleton et al. 2016). Some studies report this association even for accelerated growth in the first few weeks after birth, with preterm babies randomised to a nutrient-enriched diet having higher fasting concentrations of insulin in adolescence compared with controls (Singhal & Lucas 2004). Other studies have not found an association between growth in the early postnatal period and later metabolic risk (Embleton et al. 2016). The association between childhood growth in infants born preterm and later metabolic risk is stronger than for growth in the neonatal period. For example, in a cohort study of 945 preterm infants, a one standard deviation increase in weight between term-corrected age and 4 months was associated with a 27% increased risk of overweight and obesity at age 8 years (Belfort et al. 2013). Insulin sensitivity at age 21 years also has been reported to be lower in preterm-born subjects who demonstrated greater height and weight standard deviation scores in childhood (Rotteveel et al. 2008). However, the optimal growth trajectory and nutritional management for preterm babies for later metabolic health is not yet clear (Ong et al. 2015).

Experimental studies of preterm birth on the developing beta-cell and pancreas

In human observational studies, it is very difficult to separate out the effect of preterm birth from the antenatal factors that led to preterm birth and which may also have impacted upon organ development, particularly when in approximately 50% of cases of spontaneous preterm birth, the antecedent factors are unknown (Blencowe et al. 2013a). On the other hand, it is challenging keeping preterm animals alive, even at moderate preterm gestations (De Matteo et al. 2010), although antenatal glucocorticoids improve survival just as in the human (Nguyen et al. 2017).

In the sheep, the timing of development of the pancreas, including of islets, is similar to the human (Bryden et al. 1972, Reddy et al. 1988a, b, Reddy & Elliott 1988, Piper et al. 2004), whereas in the rodent, several aspects take place during postnatal rather than in fetal life (Cole et al. 2009, Green et al. 2010).

We recently have undertaken a series of studies in sheep aimed at separating out the effects of preterm...
Between the two studies, most notably the use of epostane as an induction agent in both preterm and term animals in the study by De Matteo compared with animals born spontaneously at term in the study by Bansal et al, raising the possibility of effects of epostane in the term-born animals that may obscure effects of preterm birth, the different glucocorticoid used and the different survival rate of preterm lambs through to adulthood (57% in the study by De Matteo vs 90% in our studies (Alsweller 2010)), which may have led to more vulnerable lambs being lost from the follow-up studies of pancreatic function. Clinically, betamethasone is the more commonly used glucocorticoid in women at risk of preterm birth, although a randomised controlled trial comparing betamethasone with dexamethasone has been completed and is expected to be reported in 2018 (Crowther et al 2013b).

**Effect of neonatal nutritional supplementation on the β-cell and pancreatic function**

We then went on to investigate the role of nutritional supplementation on pancreatic development and function in both term (Berry et al 2016, Jaquery et al 2016) and preterm lambs (Berry et al 2016). The milk supplement was designed to be analogous to a human milk fortifier used routinely in many neonatal intensive care units, providing similar percentage increases in all macronutrients but accounting for the different composition of ewe’s milk. The milk supplement was given by oral gavage four times per day for 2 weeks and did not affect milk intake from the mother, measured by deuterium oxide dilution. Despite a net increase in nutritional intake, there were minimal effects on growth (Berry et al 2016). However, there were sexually dimorphic effects on insulin secretion with effects apparent in juvenile, but not adult, females but in adult, but not juvenile males, and opposite effects in supplemented preterm and term animals. Supplemented preterm adult males had fasting insulin concentrations approximately twice those of unsupplemented preterm controls, whereas the opposite effect was found in term males (Berry et al 2016). Similarly, supplemented preterm males had a greater insulin response to an intravenous glucose tolerance test in adulthood compared with unsupplemented preterm controls, whereas supplemented term males had a lesser response than unsupplemented term controls. Supplemental preterm females demonstrated increased insulin secretion compared with control preterm females during the steady state phase of a hyperglycaemic clamp, but only at 4 months of age; by 14 months (adulthood),
there was no longer any significant difference. Once again, the converse effect was seen in supplemented term females (Berry et al. 2016).

In a separate cohort of term lambs, we demonstrated that supplementation with a ewe’s milk fortifier for 2 weeks also had sexually dimorphic effects on mRNA expression of key pancreatic genes involved in development of the β-cell 4 months later (post-weaning) in a manner consistent with the physiological findings described earlier. In males, supplementation decreased mRNA levels of the key β-cell transcription factor PDX1, the growth factor IGF2 and the beta-cell glucose transporter SLC2A2 compared with unsupplemented males, whereas in females, supplementation increased mRNA levels of INSULIN and the beta-cell glucose sensor GLUCOKINASE compared with unsupplemented females. In the case of PDX1, there were epigenetic modifications to the promoter region in supplemented animals, with decreased methylation in both sexes and altered histone methylation and acetylation in supplemented females only (Jaquiere et al. 2016), indicating that brief nutritional supplementation alters epigenetic marks in this key transcription factor that persist after cessation of supplementation and, indeed, beyond weaning, suggesting that these changes may be permanent.

Conclusions

These experiments in preterm lambs begin to unpick the different components of the environment that preterm babies are exposed to and how these may affect the developing pancreas. They demonstrate that preterm birth itself, at least in the presence of standard care with antenatal glucocorticoids, likely impacts upon the developing β-cell in a way that may reduce pancreatic capacity to secrete insulin in response to increased metabolic demand or when there is a further reduction in capacity as the animal ages. Similarly, in lambs there are effects of supplementation with a milk fortifier, analogous to human milk fortifier, which differ according to the sex of the lamb and that appear to operate, at least in part, through epigenetic mechanisms. Furthermore, these effects were independent of accelerated postnatal growth, raising the possibility that nutrition itself, irrespective of growth, may impact upon the developing beta-cell. If these findings should translate to the clinical setting, they suggest that urgent studies into whether nutrition for preterm girls and boys should be different are needed and also whether the emphasis that currently is placed on attempting to achieve intrauterine growth rates in babies born preterm is justified.

Further research clearly is needed. As survival of preterm babies improves, attention needs to focus more on the long-term outcomes, including both metabolic and neurodevelopmental outcomes. The possibility for intervention into the antecedent causes of preterm birth as a means of improving neonatal outcome is small; attention therefore needs to focus on the effects of preterm birth and management of the preterm neonate. The question of the role of antenatal glucocorticoids on the beta-cell still is not fully resolved and remains an important question as there is a move in some jurisdictions towards use of antenatal glucocorticoids prior to birth, particularly operative birth, at late preterm and early term gestations (Committee Opinion No. 713 2017). Nutrition is a fundamental component of care for all babies; yet, there is limited high-quality evidence to guide practice. The potential for nutritional practices to affect development of both the pancreas and later insulin sensitivity requires further investigation, including the possibility that nutritional requirements, macronutrient balance and long-term consequences of nutritional practices may be different in girls and boys.

Declaration of interest

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