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Review

Intergenerational transmission of insulin resistance and type 2 diabetes

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ABSTRACT

Studies in women with type 1 or type 2 diabetes mellitus (DM) and their children suggest that the *in utero* 'diabetic' environment in which the fetus develops can increase the risk of diabetes in the child, in a non-genetic but heritable fashion. Studies in rodents provide strong evidence for maternal transmission of diabetes, but are based primarily on a model type 1 DM and there is no standard animal model of type 2 DM in pregnancy or of gestational diabetes mellitus (GDM), although those reported uniformly show glucose intolerance in the offspring. Rodent models of diet-induced obesity have relevance to current upward trends in maternal obesity and GDM, although maternal glucose homeostasis is not always assessed and elements of the diet may have an independent influence. The mechanisms by which maternal type 2DM evokes a higher risk of the disorder in the offspring are likely to result from epigenetic modification in early life of pathways of pancreatic β cells and of liver and muscle insulin signalling pathways. Also, epigenetic processes associated with hormonal imbalance may lead to irreversible 'reordering' of hypothalamic neural networks in fetal/neonatal life, permanently alter energy balance and lead to obesity with associated insulin resistance.

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1. Introduction

The transmission of disease from mother to child is all too familiar in those countries where HIV is prevalent or in families with heritable genetic disorders. The influence of environmental perturbation in the form of teratogens or endocrine disruptors on fetal development is also well recognised, and often profound. However, the concept that the risk of disease may be transmitted in the

Abbreviations: Type 2 DM, type 2 diabetes mellitus; GDM, gestational diabetes mellitus.

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absence of any genetic susceptibility, infective particles or environmentally induced congenital defects is, to many, a 'foreign' concept. In this review the concept that susceptibility to one of the most common diseases of Western society, type 2 diabetes (type 2 DM), can be transmitted by environmental influences *in utero* from mother to child will be addressed. Should this association be proven, the increasing global prevalence of type 2 DM could be attributable, in part, to a vicious cycle of intergenerational transmission.

2. Studies in human populations

In 1975 Dorner and colleagues reported a higher incidence of diabetes in adults born to mothers with diabetes than to those with fathers who were diabetic, and were the first to propose that this might infer an epigenetic mode of inheritance (Dorner et al., 1975). Over the last 35 years, the hypothesis of transgenerational transmission of diabetes has been addressed in many observational studies in women and their children, and the majority support Dorner's original report (Poston, 2010). Maternal 'transmission' has been interrogated, and evidence accrued, through several different approaches including estimating the incidence of type 2 diabetes in offspring of diabetic mothers compared to diabetic fathers (Dorner et al., 1975; Krishnaveni et al., 2010), through comparison of siblings born before or after their mother developed diabetes (Dabelea et al., 2000), or by determining the incidence of the disorder in children born to diabetic women compared to unrelated children born to normoglycemic mothers (Silverman et al., 1995).

Whilst this review focuses on maternal/child transmission of type 2 DM, there appears to be a higher incidence of type 2 DM in offspring of both type 1 DM and type 2 DM mothers (Clausen et al., 2008; Plagemann et al., 1997; Weiss et al., 2000), i.e. the type of diabetes generally seems irrelevant. However, it should be appreciated that several negative studies are also published, in which no independent association between maternal and offspring DM of either type is evident (Cross et al., 2009; Hunter et al., 2004; Kim et al., 2004; Manderson et al., 2002; Viswanathan et al., 1996). Most notable of those implying a positive maternal influence on diabetes risk in the child are the reports of the Pima Indians from Arizona (Dabelea, 2007; Dabelea et al., 2000; Dabelea and Pettitt, 2001), a population with a very high incidence of type 2 diabetes (Dabelea et al., 2000). The greater incidence of diabetes in Pima Indian siblings exposed to diabetes *in utero* compared to those who were born before the mother developed diabetes provides some of the strongest evidence for maternal 'transmission'. The strength of sibling studies such as this is that residual confounding is minimised; any differences in type 2 DM in 'exposed' *versus* 'non-exposed' offspring occur despite shared genetic and environmental risk. In observational studies, in unrelated children of diabetic mothers, a greater degree of residual confounding is inevitable although most investigators have adjusted relationships between maternal and offspring diabetes for commonly measured potential confounders e.g. maternal BMI, the child's age and current BMI. Maternal BMI has been proposed to be a determinant of offspring diabetes risk, independent of maternal diabetes, and several studies have addressed the relative contribution of each. For example, an investigation of a small cohort of diabetic adolescents reported that exposure to maternal diabetes and exposure to maternal obesity were independently associated with offspring type 2 DM, but that these influences were additive (Dabelea et al., 2008). Similarly, adjustment for offspring BMI does not appear to nullify the relationship between maternal and offspring diabetes (Clausen et al., 2008; Sobngwi et al., 2003; Vaarasmaki et al., 2009). There has been little attempt to address the relationship between the degree of hyperglycaemia in the mother and the incidence of offspring diabetes, which would provide important additional insight and determine if there is an 'exposure dose–response' relationship. The recent Hyperglycaemia and Adverse Pregnancy Outcome study (HAPO) has investigated associations between glucose tolerance and pregnancy outcome in women *without* a proven diagnosis of gestational diabetes mellitus (GDM), and has shown evidence for adverse pregnancy outcomes in women with increasing glucose intolerance, leading to recommendations for revision of the diagnosis of GDM (a lower threshold). Although not inclusive of women with GDM as assessed by current standards, HAPO provides potential for follow up of the children over a wide range of maternal glucose tolerance with the benefit of very accurate measurement of maternal glucose status (Metzger et al., 2008).

2.1. Intervention studies

Despite the wealth of supportive evidence from observational studies for the maternal transmission of type 2DM, causality would only be proven by prospective randomised controlled trials (RCT)s in which pregnant women with type 2 DM are treated in pregnancy and childhood follow up performed. Demonstration of a lower incidence of type 2 DM in offspring of treated women in an adequately powered study would provide convincing evidence for maternal transmission of type 2 DM but no study of this design has been reported to date. In developed countries screening and treatment for type 2 DM or GDM is routinely undertaken which might imply that there is no scope for further intervention studies of this nature. However, standard treatment regimes are not always effective in prevention of macrosomia, pre-eclampsia and other complications of diabetic pregnancies, and there remains a clinical need to improve treatment of diabetic pregnant women. In view of this, two recent RCTs were undertaken in which women with GDM were randomised to routine protocols or to a more stringent treatment regime (Crowther et al., 2005; Landon et al., 2009). Both showed improved pregnancy outcome in the groups treated more intensively compared to women in the standard care arm of the trial. Follow up of glucose tolerance in the children of the women recruited to these studies, as they grow to adulthood, could provide some of the most convincing evidence for or against maternal transmission of type 2 DM.

2.2. Impaired insulin secretion or action?

Type 2 DM is associated with reduced insulin action in insulin sensitive tissues and subsequent impairment of pancreatic β cell insulin secretion. Only a few investigators have attempted to define whether one or both contribute to the development of diabetes in the offspring of diabetic women. In relation to children from type 2 DM pregnancies, results are equivocal, with some reporting a high insulin:glucose ratio in response to a oral glucose load, suggestive of reduced insulin action (Silverman et al., 1995), with others showing no abnormality in children from mothers with GDM (Pirkola et al., 2008; Plagemann et al., 1997). In adult offspring of Pima Indian women with type 2 DM, a blunted insulin response to a glucose load may suggest reduction of β cell function with age (Gautier et al., 2001). With regard to maternal factor(s) which must confer the risk of type 2 DM to the developing child, for practical reasons much of the relevant information has been gleaned from animal models (described below) but animal and human studies concur in suggesting that exaggerated trans-placental transfer of glucose leading to fetal hyperglycaemia, enhanced β cell insulin secretion and β cell hyperplasia may influence pancreatic secretory function with effects persisting into later life (Plagemann et al., 2008). Animal models have also implicated an influence of neonatal hyperinsulinaemia and hyperleptinaemia in critical periods of susceptibility in the developing hypothalamus (see later section).