Paediatric Respiratory Reviews 21 (2017) 19–26

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Mini-Symposium: Maternal Diseases effecting the newborn

Diabetes in pregnancy and lung health in offspring: developmental origins of respiratory disease

M.B. Azad [1,2,*], B.L. Moyce [1,3], L. Guillemette [1,4], C.D. Pascoe [1,5], B. Wicklow [1,2], J.M. McGavock [1,2], A.J. Halayko [1,5], V.W. Dolinsky [1,3]

[1] *Manitoba Developmental Origins of Chronic Diseases in Children Network (DEVOTION); Children's Hospital Research Institute of Manitoba, Winnipeg, Canada*
[2] *Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Canada*
[3] *Department of Pharmacology and Therapeutics, University of Manitoba, Winnipeg, Canada*
[4] *Applied Health Sciences, University of Manitoba, Winnipeg, Canada*
[5] *Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada*

EDUCATIONAL AIMS

- Review existing evidence linking diabetes in pregnancy with lung development and respiratory health in offspring.
- Describe potential mechanisms for the association between diabetes in pregnancy and respiratory health in offspring.
- Acknowledge the strengths and limitations of epidemiologic studies and rodent models addressing the association between diabetes in pregnancy and lung health in offspring.

ARTICLE INFO

Keywords:
maternal diabetes
gestational diabetes
pregnancy
developmental origins of health and disease
lung development
asthma
chronic lung disease
respiratory distress syndrome

SUMMARY

Diabetes is an increasingly common complication of pregnancy. In parallel with this trend, a rise in chronic lung disease in children has been observed in recent decades. While several adverse health outcomes associated with exposure to diabetes *in utero* have been documented in epidemiological and experimental studies, few have examined the impact of diabetes in pregnancy on offspring lung health and respiratory disease. We provide a comprehensive overview of current literature on this topic, finding suggestive evidence that exposure to diabetes *in utero* may have adverse effects on lung development. Delayed lung maturation and increased risk of respiratory distress syndrome have been consistently observed among infants born to mothers with diabetes and these findings are also observed in some rodent models of diabetes in pregnancy. Further research is needed to confirm and characterize epidemiologic observations that diabetes in pregnancy may predispose offspring to childhood wheezing illness and asthma. Parallel translational studies in human pregnancy cohorts and experimental models are needed to explore the role of fetal programming and other potential biological mechanisms in this context.

INTRODUCTION

Respiratory health is influenced by intrinsic and extrinsic environmental stressors during fetal and postnatal development, with important implications for chronic lung disease later in life [1]. Diabetes in pregnancy has long been associated with adverse maternal and neonatal outcomes and has recently emerged as an important trigger for the fetal programming of lifelong metabolic and cardiovascular health outcomes in offspring [2]. These clinical observations have been confirmed in rodent models, which have further identified specific alterations in gene expression among offspring exposed to diabetes *in utero* (reviewed in [2]). While the majority of this research has focused on short-term maternal and

* Corresponding author. Research Scientist, Children's Hospital Research Institute of Manitoba Assistant Professor, Pediatrics & Child Health, University of Manitoba 501G - 715 McDermot Ave. Winnipeg, MB Canada R3E 3P4 (204) 975-7754.
E-mail address: meghan.azad@umanitoba.ca (M.B. Azad).

http://dx.doi.org/10.1016/j.prrv.2016.08.007
1526-0542/

neonatal health outcomes, or long-term metabolic and cardiovascular consequences in offspring, there is a growing body of evidence suggesting an impact of diabetes in pregnancy on offspring lung development and respiratory health. We provide an overview of this literature and identify key knowledge gaps requiring additional research.

Maternal diabetes in pregnancy

Diabetes affects a rising proportion of pregnancies worldwide, including up to 10% in the United States [3]. Dysregulation of glycemic control during pregnancy is associated with numerous adverse maternal and neonatal outcomes, including preeclampsia, preterm birth, macrosomia and stillbirth [4]. Since the risk of harm for offspring increases with the duration and extent of hyperglycemia exposure, it is important to distinguish pre-gestational diabetes (type 1 diabetes (T1D) or type 2 diabetes (T2D) diagnosed prior to pregnancy) from gestational diabetes mellitus (GDM), defined as fasting or post-prandial hyperglycemia first detected during pregnancy [2]. T1D is characterized by hyperglycemia due to an absolute deficiency of insulin production, whereas hyperglycemia in T2D and GDM is associated with both insulin resistance (in hepatic and/or peripheral tissues) and insufficient insulin secretion to maintain euglycemia [3].

There is convincing evidence that exposure to diabetes earlier in pregnancy (i.e. exposure to pre-gestational diabetes) carries the most severe health consequences for the offspring [4], but the distinction between pre-gestational diabetes and true GDM is rarely made in respiratory health studies. Currently the standard screening protocol to detect diabetes in pregnancy is an oral glucose challenge test between 24 and 28 weeks of gestation, which would not distinguish between GDM and undiagnosed pre-gestational T2D [5]. Moreover, most health registries used in longitudinal research do not reliably distinguish between types of diabetes.

Fetal lung development

Fetal lung development occurs in five stages (Figure 1), beginning with tracheal separation from the esophagus in the embryonic stage at 3 weeks of gestation and ending with the development of mature alveoli in the alveolarization stage, which occurs following birth and extends into early childhood [6]. The intermediate stages (pseudoglandular, canalicular, and saccular) encompass the development of the branched airway structure, epithelial lined sacs that become alveoli, and various layers of the airway and pulmonary vasculature walls [7]. In addition, surfactant production begins at 24 weeks of gestation and continues until birth. Surfactant is a complex mixture of phospholipids and proteins that act to reduce surface tension in the alveoli and prevent alveolar collapse during expiration [8]. Environmental exposures throughout gestation and postnatally can therefore have significant and distinct impacts on lung development and future health. Extensive research has been undertaken to establish how maternal nutrition [9], smoking [10], and exposure to air pollution [11] influence lung development and respiratory health; however, much less is known about how diabetes in pregnancy affects fetal lung development and subsequent respiratory health in the offspring.

DIABETES IN PREGNANCY AND NEONATAL RESPIRATORY OUTCOMES

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is an important cause of neonatal morbidity, affecting 40 000 infants each year in the US [12]. RDS is characterized by a lack of functional surfactant in the neonatal lung, resulting in collapse of the terminal air spaces. Treatment involves ventilation and oxygen therapy which can

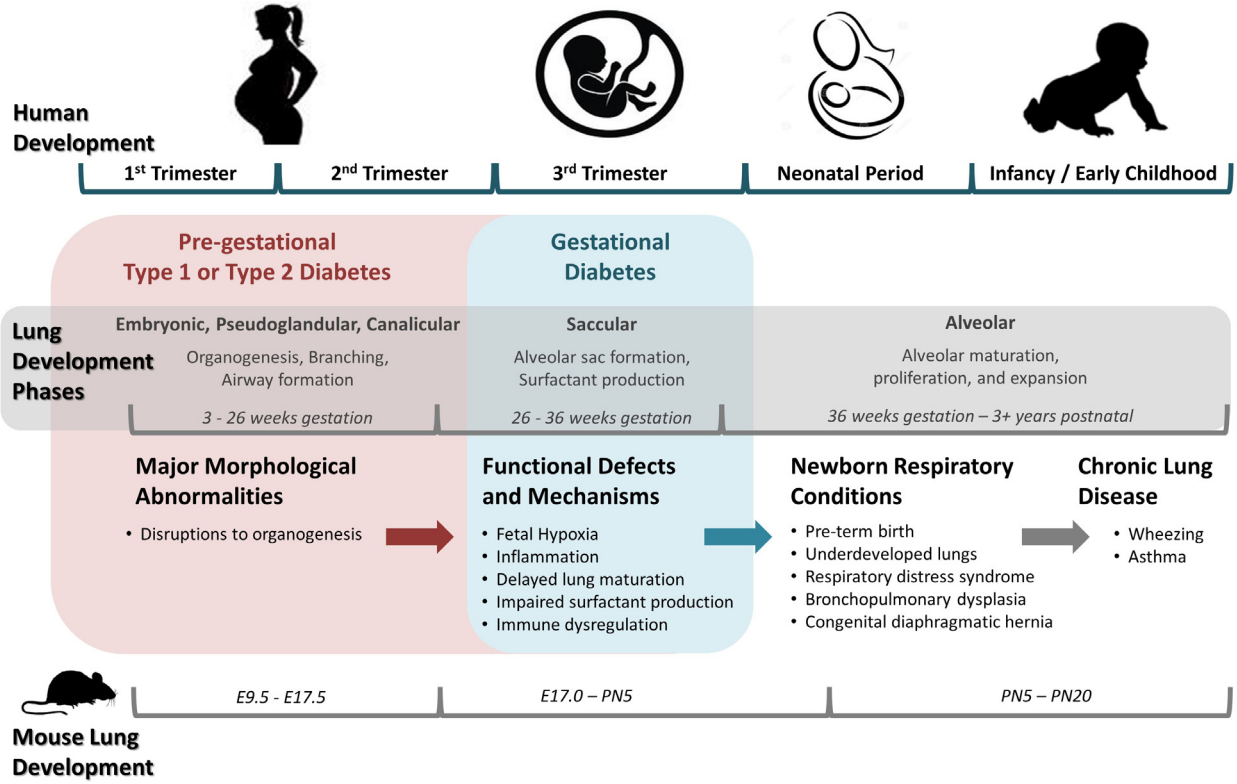

Figure 1. Diabetes in pregnancy and lung health in offspring. Timeline of human and mouse lung development overlapping with *in utero* exposure to maternal pre-gestational or gestational diabetes, and potential respiratory outcomes at birth and during early childhood. E=embryonic; PN=postnatal.