Outcomes of offspring born to mothers with gestational diabetes

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Abstract

With the global explosion of Diabetes and obesity at epidemic proportions, keeping Asia at its epicenter, 1 in 7 live births get complicated with hyperglycaemia; either pre-existing Diabetes or Gestational Diabetes. In utero, exposure to an adverse metabolic environment with nutrient excess or deficiencies and toxic metabolites with teratogenic potential, leads to short and long term consequences to the offspring. Multisystemic congenital malformations, macrosomia associated obstetric complications and perinatal metabolic derangements complicate the early neonatal stage. Epigenetic changes taking place during foetal development initiate foetal metabolic programming and create adverse metabolic memory leading to childhood obesity, metabolic syndrome and Diabetes. Hyperglycaemia and poor metabolic parameters throughout pregnancy correlate with adverse offspring outcomes. Novel management strategies targeting near normoglycaemia have achieved marked improvements in rates of perinatal mortality and other adverse outcomes. Therapies for management of Diabetes in pregnancy should be carefully selected upon the safety profile for the offspring.

Keywords: Diabetes, Gestational DM, Pregnancy, Offspring, obesity.

Introduction

Hyperglycaemia is one of the most prevalent metabolic disorders occurring during pregnancy.

This can be a result of either previously existing diabetes in a pregnant woman, or due to the development of insulin resistance later in the pregnancy resulting in glucose intolerance with onset or first recognition during pregnancy, known as gestational diabetes (GDM).

The prevalence of diabetes in pregnancy is at an exponential rise throughout the world including South Asia, particularly due to increase in prevalence of both obesity and diabetes in women of childbearing age. Two out of every five women in the reproductive age have diabetes, which accounts for over 60 million women worldwide.[1] International Diabetes Federation (IDF) estimates that in 2015, 20.9 million (16.2%) of live births to women had some form of hyperglycaemia in pregnancy. Among them 85.1% were estimated to be due to gestational diabetes, 7.4% due to other types of diabetes first detected in pregnancy and 7.5% due to diabetes detected prior to pregnancy. According to IDF, Gestational diabetes (GDM) develops in one in 25 pregnancies worldwide. In India alone, an estimated 4 million women have GDM.[1]

Before the discovery of insulin in 1921, more than 100 cases of mothers with Diabetes had been reported, who were presumed to be type 2 DM patients, and the infant mortality rates were more than 90% at that time. As late as 1980s also, females with Diabetes were counseled against pregnancy due to significantly adverse offspring outcomes. Near normoglycaemia achieved and maintained throughout the pregnancy has resulted in much better perinatal mortality rates comparable with normal population during last few decades.[2]

The main objective of this review is to elaborate on offspring outcomes as a result of in utero exposure to adverse metabolic environment and the impact of therapy for Diabetes on foetal development.

Pathogenesis of Gestational Diabetes Mellitus

In comparison to healthy women, women with GDM demonstrate reduced insulin responses to nutrients.[3,4] When insulin levels and responses are expressed relative to degree of insulin resistance, a prominent deficiency in pancreatic β-cell function can be identified in women with prior GDM.[5] Therefore most of women with GDM have β-cell dysfunction that occurs on a background of chronic insulin resistance already present before pregnancy.[6,7] Not only the obese but also lean women who develop GDM, show distinct resistance to insulin mediated glucose disposal and suppression of glucose and fatty acid production.[3] Many other defects, such as diminished expression of Peroxisome proliferator-activated receptor gamma (PPARγ), alterations in the insulin signaling pathway and reduced insulin-mediated glucose transport have been found in skeletal muscle and fat tissue of women with GDM.[7]

Recently, it has also been proposed that events leading

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to the development of GDM are triggered by antigens which are present in the foetus itself. Human leukocyte antigen-G (HLA-G), which usually protects the foetus from immune attack, interacts between nuclear factor-κB and it is postulated to be the key in the events leading to GDM development. Other causes of DM in pregnancy include type 1 & 2 DM, maturity-onset diabetes of the young (MODY) that are likely to represent cases of symptomless pre-existing diabetes, first detected by routine glucose screening during pregnancy.[7]

Offspring Outcomes

Exposure to adverse metabolic status during intra uterine life results in adverse offspring outcome: congenital malformations, cardiometabolic derangement, cognitive impairment, overweight and obesity in adult life. Poor metabolic factors including uncontrolled hyperglycaemia and consequent foetal hyperinsulinaemia play the key role in pathogenesis.

Teratogenecity Associated with Diabetes

Pre-existing Diabetes with poor metabolic control during organogenesis is strongly associated with 3-4 fold higher risk of major congenital anomalies.[8] Pathogenesis of foetal malformations associated with Diabetes is not well understood, but thought to be multifactorial and associated with exposure to nutrient excess/deficiencies and to toxic metabolites during organogenesis. Gestational Diabetes, which is diagnosed beyond 24 weeks of gestation by definition, well beyond the time of organogenesis, is also associated with variable higher risk of malformations according to level of hyperglycaemia[8]. Women with GDM, who were diagnosed to have DM at early postpartum testing, probably have had unrecognized type 2 DM and their rate of major congenital malformations(4-5%) were comparable with mothers with pre-existing DM. It is thought that teratogenecity in GDM is associated with unrecognized metabolic derangement since early stages of pregnancy in this group.[9] Hyperglycaemia, hypoxia, ketones, excess oxygen free radicals resulting in disruption of intracellular signaling pathways are thought to be connected with genotoxicity and cytotoxicity leading to congenital malformations at birth, miscarriages and still births. There is increasing evidence in the field of epigenetic factors with relation to pathogenesis of these malformations.[10] It has been further recognized that congenital malformations correlate with body mass index of women with Diabetes.[10] The major malformations are seen in following systems: cardiovascular, nervous system, gastro intestinal system, urinary tract, facial and musculoskeletal systems as shown in Table.

Perinatal Complications

Perinatal complications of a Diabetic pregnancy includes macrosomia, hypoglycaemia, respiratory distress, hyperbilirubinaemia, polycythaemia, congenital malformations, cardiomyopathy and sudden infant death.

Respiratory distress syndrome: Respiratory distress syndrome (hyaline membrane disease) is a fatal complication, which is seen six fold more frequently in newborns of women with hyperglycaemia than in non diabetic women.[12] Foetal hyperinsulinaemia and/or hyperglycaemia cause impaired production of surfactant due to the inhibition of differentiation of type 2 epithelial cells resulting in delay in pulmonary maturation.

Neonatal Hypoglycaemia: Newborns of mothers with diabetes develop hypoglycaemia immediately after the section of the umbilical cord due to sudden deprivation of maternal glucose supply, which is further aggravated by hyperinsulinaemia of the foetus. Anticipation of this condition in a newborn delivered to a diabetic mother is important for early recognition of this severe complication.[13]

Hypocalcaemia and Hypomagnesaemia: Deprivation of maternal nutrient flow can also lead to hypocalcaemia and hypomagnesaemia in the newborn

Table: Congenital Malformations associated with Diabetes.[10,11]

Cardiovascular system	Transposition of great arteries, Ventricular septal defect, Atrial septal defect, Tetrology of Fallot, Coarctation of Aorta, Single umbilical artery, Hypoplastic left ventricle, Cardiomegaly
Central Nervous system	Open neural tube defects, Holoprosencephaly, Absent corpus callosum, Arnold-Chiari anomaly, Schizencephaly, Microcephaly, Macrocephaly, Agenesis of olfactory tracts, Hydrocephaly
Gastro Intestinal system	Pyloric stenosis, Duodenal atresia, Microcolon, Anorectal atresia, Omphalo-enteric cyst/fistula, Hernias
Urinary tract	Renal agenesis, Renal cysts, Hydronephrosis, Duplication of ureter, Ureterocele, Uterine agenesis, Hypoplastic vagina, Micropenis, Hypospadias, Cryptorchidism, Hypoplastic testes, Ambiguous genitalia
Musculoskeletal system	Caudal dysgenesis, Craniosynostosis, Costovertebral anomalies, Limb reduction, Club foot, Contractures, Polysyndactyly
Other	Cleft palate, Cleft lip

within the first few hours of life which can cause neuromuscular excitability, convulsions, apnoea and even death.[14,15]

Polycythemia/Hyperbilirubinaemia: Long standing hyperinsulinaemia, hypoxia and placental insufficiency which occur as a consequence of poor glycaemic status, lead to an increased foetal erythropoiesis. When these extra red blood cells are haemolysed, hyperbillirubinaemia results, which is two-fold more common in newborns of mothers with diabetes compared to non diabetes.[16]

Cognitive Development Delay

It has been found that maternal diabetes in pregnancy was associated with offspring cognitive mal-development. High or fluctuating concentrations of glucose and potential ketonaemia account for altered brain structure in-utero.[17] This is also contributed by pleiotropic effects of genes shared by mother and offspring that are related to both risk of diabetes and IQ, shared familial environmental exposures such as socioeconomic position, educational attainment, levels of physical activity and nutrition.

Offspring Adiposity and Long Term Metabolic Complications

Significant proportion (15-45%) of offsprings of Diabetic mothers are macrosomic, which accounts for 3-fold higher rate than for normal controls.[18] Maternal obesity is also an independent risk factor for macrosomia.[19] According to modified Pedersen's Hypothesis, maternal hyperglycaemia resulting in foetal hyperinsulinaemia and increased glucose utilization together with increased foetal fat and protein deposition leads to macrosomia with unique pattern of overgrowth with thicker upper extremity skin folds, which augments the risk of shoulder dystocia.[18] Many studies including the Hyperglycaemia Adverse Pregnancy Outcome Study (HAPO) have supported the relationship of maternal hyperglycaemia, foetal hyperinsulinaemia with foetal weight.[20,21]

Studies have shown that DM in pregnancy is associated with metabolic disturbances in offspring at later life: obesity, metabolic syndrome and insulin resistance.[22] Offspring of Pima Indian women exposed to pre and gestational Diabetes were larger at birth as well at any age and developed more diabetes compared to offspring of non diabetic women.[23] Exploring perinatal outcome among children (EPOCH) study showed that exposure to GDM in utero results in obese children with visceral adiposity with highest growth velocity around puberty.[24] This association is likely to be multifactorial, including genetic and shared pre and postnatal environment factors and their interactions. Adverse "metabolic memory" created through foetal programming is thought to be one of the underlying mechanisms.[22] Further, genetic changes taking place through epigenetic mechanisms at multiple foci of foetal epigenome within this adverse environment leads to transgenerational transmission of GDM, increasing the risk of GDM in female offspring.[18]

Therapies for Diabetes/GDM in Pregnancy and the Offspring

The main target of management of Diabetes/GDM in pregnancy is a healthy offspring. This focuses on maintenance of near normoglycaemia and avoidance of hypoglycaemia. Several treatment modalities exist, including medical nutrition therapy, insulin and oral agents, where safety of the offspring is the major target. Insulin is the first line medication, requiring close titration with self monitoring of blood glucose throughout the pregnancy for better glycaemic control without hypoglycaemia. All insulins are categorized under pregnancy class B, except insulin glargine, glulisine and degludec which are in class C.[25] Glucose crosses the placenta freely, but insulin does not, unless it is immunogenic and bound to IgG antibodies. Diabetes fetopathy is thought to be the result of foetal hyperinsulinaemia; therefore exogenous insulin used in treatment should not cross the placenta, while achieving maternal glycaemic targets. Human insulin is proven to have better offspring outcomes when compared to animal insulins.[2] Many studies have compared human insulin with insulin Lispro, Aspart and found that these analogues attenuate post prandial hyperglycaemia, reduce hypoglycaemic events with proven offspring safety with low immunogenicity in gestational as well as pregestational Diabetes. Further studies are underway to explore the long term safety of these analogue insulins. Use of long acting insulin analogues still carries safety concerns such as possible teratogenicity, alterations in binding capacity to IGF-1 and insulin receptors, which might play a role in embryo implantation and many other placental functions and immunogenicity in the absence of strong evidence from randomized clinical trials or long term prospective studies.[2]

Type 2 Diabetes and gestational Diabetes are strongly linked with insulin resistance. Therefore theoretically, Metformin is an ideal first line medication. Many studies including MiG trial, the largest trial published in

this aspect, showed Metformin, when compared with insulin results in less maternal weight gain, less severe neonatal hypoglycaemia, but more preterm deliveries with no significant difference between neonatal outcome.[26] Considerable research done on polycystic ovarian syndrome (PCOS) patients exposed to Metformin around the time of conception and during pregnancy also yields significant offspring safety data on Metformin use in pregnancy.[27] MiG TOFU (offspring followup) at 2 years showed better fat distribution pattern in offspring exposed to Metformin during their intrauterine life, reassuring the clinicians using Metformin. But whether this will translate into a true insulin sensitive pattern will be probably answered to some extent with future MiG TOFU results.[28] Despite its possible advantages and patient preference, Metformin has failed as a single agent to maintain near normoglycaemia in majority of patients with GDM as well type 2 DM.

Glibenclamide when compared to insulin as well as Metfomin has shown to result in more maternal and neonatal hypoglycaemia and macrosomia, which is two fold higher. Though reports from Langerhan et al show no significant foetal transfer of glibenclamide, other researchers have debated this and claimed possible Glibenclamide transfer as an additional causative factor for foetal hyperinsulinaemia and macrosomia in addition to proven neonatal hypoglycaemia.[29,30]

Therapies should be selected to achieve near normoglycaemia avoiding hypoglycaemia, paying concern to their safety for better offspring outcome.

Conclusion

Hyperglycaemia; pre-existing Diabetes or Gestational Diabetes Mellitus is an increasingly encountered metabolic disorder in pregnancy. Unfavourable glycaemic control and other metabolic parameters during pregnancy are associated with foetal, neonatal and long-term complications in the offspring. Preconception glycaemic and metabolic control, as well as early identification and control of hyperglycaemia during pregnancy are the key strategies to improve outcomes in the offspring. Long term follow up studies are required to assess the long-term impact of adverse maternal environment on these 'metabolically challenged offspring'. In addition further evidence is required on the impact of intervention with regular monitoring and primordial prevention including healthy lifestyle and weight monitoring strategies to mitigate long-term metabolic consequences in the offspring.

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