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Title: Pregestational diabetes in Pregnancy: complications, management, surveillance and mechanisms of disease - a review

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What do we know?

- Diabetes in pregnancy is associated with increased risks to the woman, the fetus and the neonate.
- The prevalence of pre gestational is increasing world wide.

What does this add?

- Mechanisms of congenital anomalies and impaired fetal growth, including epigenetic modifications, changes in gene expression in critical developmental pathways, and oxidative stress are summarised

- Strategies for aneuploidy screening and monitoring for fetal wellbeing should be modified in women with diabetes

Abstract
Diabetes is an increasingly common diagnosis among pregnant women. Pregestational diabetes is associated with an increase in many adverse pregnancy outcomes, which impact both on the woman and her fetus. The models of pregnancy care for women with diabetes are based largely on observational data or consensus opinion. Strategies for aneuploidy screening and monitoring for fetal wellbeing should be modified in women with diabetes. There is an increasing understanding of the mechanisms by which congenital anomalies and disorders of fetal growth occur, involving epigenetic modifications, changes in gene expression in critical developmental pathways, and oxidative stress. This knowledge may lead to pathways for improved care for these high risk pregnancies.

Keywords: Diabetes, Environment, Fetal Surveillance, Fetal & Placental Pathology, Maternal Serun Screening, Fetal Ultrasound, Fetal Imaging

Introduction

Diabetes in pregnant women is increasingly common. Depending on the demographics of the population, and the screening process used, 5-16% of the pregnant population have gestational diabetes (GDM), and around 1% have type 1 or type 2 diabetes [1, 2]. The complications of pregnancies with type 1 diabetes including increased perinatal mortality, congenital anomalies, fetal growth restriction, preterm birth, caesarean section and macrosomia are well known, and these risks are equally likely in women with type 2 diabetes [3-6].

Ultrasound has an important role to play in diagnosis and management of pregnancies complicated by pregestational diabetes. In this review we will discuss the epidemiology, mechanisms of diabetes on congenital anomalies, the use of ultrasound in managing diabetic pregnancies in terms of assessing fetal growth and well being and the specific concerns in aneuploidy screening in diabetic pregnancies.

Diabetic embryopathy

Risk factors and epidemiology

Diabetes plays an increasing role in the number of children born with congenital anomalies [7]. Pregestational diabetes has repeatedly been demonstrated to be a risk factor for increased rates of birth defects, with greater than 10 fold risk for defects including neural tube defects, holoprosencephaly, major cardiac anomalies, exomphalos, bilateral renal agenesis. Sacral agenesis, or caudal regression syndromes is classically associated with pregestational diabetes, with odds ratios in case control studies of up to 80 fold, however, the majority of babies with caudal regression are born to women without diabetes [8-11].

Multiple papers have demonstrated the association between poor periconceptional control of diabetes and increased rates of fetal anomalies. The risk increases over the baseline population when the HbA1c reaches 6.9%, and when HbA1c is over 10.4%, the rate of major anomaly can be over 10%. In some series, at low HbA1c levels, there is no reported increase in congenital anomalies over the background population, but this is not found in all reports [12, 13].

Mechanisms

The mechanisms by which prenatal exposure to maternal diabetes significantly impacts fetal growth and development is complex and multifactorial. It includes epigenetic modifications, changes in the expression of genes involved in critical developmental pathways, and increased oxidative stress (reviewed in Basu and Marquez-Valdez [14, 15]). In this regard, animal models of diabetes in pregnancy have been particularly useful and necessary.

Genes

There is increasing evidence demonstrating maternal diabetes can change genes involved in the signalling and metabolic pathways that are essential for embryogenesis including folate metabolism, oxidative stress, apoptosis and proliferation [16, 17]. Microarray analysis has been used to identify genes and pathways in mice embryos exposed to diabetes [16]. For example, a study by Pavlinkova et al. identified 126 genes that were changed in diabetes-exposed embryos relative to controls [16]. They included genes involved in transcriptional regulation, signal transduction, oxidative stress, lipid metabolism, metal-ion homeostasis, protein catabolism, and proliferation. These genes have well described roles in neurological and cardiac development.

Maternal diabetes also increases the risk of congenital anomalies of the kidney. Several signalling pathways have been implicated in the impairment of nephron function and structure associated with exposure to maternal diabetes, including increased apoptosis [18] and repression of Wnt/β-catenin and Notch signalling [19].

Studies from humans and animal models have clearly shown that folate is required for normal embryogenesis. In mice, neural tube defects induced by abnormalities in maternal folic acid metabolism can be exacerbated by diabetes in pregnancy [20]. Folic acid supplementation can prevent congenital malformations in the offspring of diabetic mice [21], and in humans [22, 23].

Oxidative stress

Animal model of diabetes in pregnancy have demonstrated an imbalance in nitric oxide (NO) and reactive oxygen species (ROS) in the development of fetal anomalies [14]. During embryogenesis in maternal diabetes, ROS generation is amplified in concert with decreased expression and activities of the main ROS scavenging enzymes (i.e. antioxidants) including superoxide dismutase (Sod1) and glutathione peroxidase (Gpx). Oxidative stress directly damages the DNA damage and causes protein/lipid oxidation. In addition, it can have indirect effects on multiple cellular pathways such as apoptosis, proliferation and inflammation. In addition to increased ROS, the bioavailability of NO is reduced which leads to endothelial dysfunction. Reductions in NO occur as a result of increased ROS, eNOS uncoupling and/or reduced chromatin accessibility at eNOS locus.

In mice, the occurrence of fetal malformations in diabetic pregnancy can be reduced by reducing oxidative stress (e.g. the antioxidant N-Acetylcysteine) and increasing nitric oxide production (e.g. the tetrahydrobiopterin Sapropterin which improves eNOS function)[24, 25]. However, clinical trials in human pregnancy have shown unexpected adverse outcomes including an increase in the incidence of IUGR [26]. The human trials were not in women with diabetes, and were not powered for uncommon congenital anomalies.

Epigenetic

Epigenetic alterations, such as DNA methylation (which primarily occurs on CpG dinucleotides) and histone modification, have been implicated in regulating the expression of genes involved in growth and development [27]. Only a few studies have reported on the epigenetic modifications that may occur during embryogenesis in pregnancies complicated by pre-existing diabetes. In a transgenic rat model, a diabetic pregnancy caused epigenetic changes in a gene important for cholesterol metabolism, Srebf2 (sterol regulatory element binding transcription factor 2)[28] . Specifically, CpG hypermethylation of the Srebf2 promoter in the fetal brain and the liver was associated with decreased Srebf2 gene expression. In mice, with diabetes induced by STZ, hypermethylation of the

IGF2 gene in fetuses was associated with lower birth weight [29]. Maternal diabetes in pregnancy has also been shown to alter the histone acetylation of genes known to cause neural tube defects in embryos and neural stem cells [30, 31].

Early anomaly screening

The pregestational diabetes population is well placed to benefit from recent advances in early diagnosis of fetal anomalies because of the higher risk in these pregnancies, compared to women without diabetes. Among the most common major anomalies in women with pre pregnancy diabetes are cardiovascular and neural tube defects, and these are potentially amenable to early diagnosis by ultrasound. Early diagnosis of anomalies has a number of medical and psychological benefits [32-34]. Early diagnosis is important for access to termination of pregnancy in jurisdictions where access is gestation dependent, and in providing choice between medical and surgical procedures. For women who choose to continue the pregnancy, early diagnosis enables earlier planning of place of delivery, and potentially access to more information.
Systematic review of the detection of major structural anomalies at 11 to 14 weeks has shown that in high risk groups, 61% of major structural anomalies can be detected, and in lower risk groups, 45%. These data however, are not directly applicable to women with diabetes as in many of the low risk cohorts, aneuploid fetuses were included, and in the high risk cohort, many of the pregnancies were included because the nuchal translucency was >3mm. Both of these subgroups have a very high rate of structural anomalies, and so it is likely that in a cohort with a lower a priori risk, such as women with well controlled pregestational diabetes, the detection rate will be lower. We are not aware of published data reporting detection rates of fetal anomalies in women with prepregnancy diabetes. The false positive rate was not reported in the majority of the included studies, and so is still a consideration when planning access to early diagnosis [35]. It should also be noted that despite the high levels of detection reported from these published studies, many in tertiary centres, population based detection of cardiac anomalies at mid trimester in the general population is still around 70% [36].

Medication

The majority of women with pregestational diabetes are treated with insulin in pregnancy. Oral hypoglycaemics also have a role in pregnancy as insulin sparing agents in women who are very insulin resistant, and due to unplanned pregnancies, many women will conceive while still taking oral hypoglycaemic agents. Traditional insulins are not thought to be teratogenic. There is some difficulty in assessing the risk of medications for treating diabetes due to the increased risk of congenital anomalies and other adverse pregnancy outcomes for women with diabetes, even if unexposed to medication.

The best studied oral hypoglycaemic is metformin. Metformin does not appear to be associated with an increased risk of birth defects. It has been used widely in management of polycystic ovarian syndrome, and so there are extensive published data on the safety profile. Large population based studies and metaanalysis have found no increase in congenital anomalies when metformin was used in a mixed group of women with or without diabetes, or when used for subfertility [37-39].

A small study compared the outcomes for women taking gliclazide compared with those of women taking metformin in pregnancy and was not able to determine any differences in congenital anomalies, birth weight, or neonatal hypoglycaemia [40]. There are very few safety data on many of the newer oral or long acting parenteral agents, and it is likely that these data will only emerge very slowly, as case reports of inadvertent exposure occur.

Many women now use modern insulin analogues instead of human insulin because of improved performance characteristics, including improved glycaemic control. A population based study, including approximately 1600 women, with outcomes corrected for baseline diabetic control using HbA1c, did not show any increase in birth defects in women with diabetes using insulin analogues, including insulin lispro, insulin aspart, insulin glargine and insulin detemir compared to using human insulin [41]. Previous smaller reviews had found similar results [42], and so use of these agents is considered acceptable.

Fetal growth

The commonest impact of pregestational diabetes on fetal growth is large for gestational age, occurring in 40 to 60% pregnancies [3, 4]. Less commonly, pregestational diabetes leads to fetal growth restriction, but this is infrequently seen unless the woman has significant vascular disease, as measured by her own complications of diabetes, including retinopathy, nephropathy or cardiovascular disease or comorbidities, such as hypertension.

Macrosomia in diabetes is thought to be caused by facilitated diffusion of glucose across the placenta, leading to transient fetal hyperglycaemia. Subsequent stimulation of the fetal pancreatic β cells results in fetal hyperinsulinemia, which has long been shown to be related to fetal growth and increased fat mass [43].

Estimation of fetal weight in women with prepregnancy diabetes is an important element of care. In order to examine fetal growth, serial ultrasounds are recommended every 4 weeks from 28 weeks' gestation [44]. The final growth scan should be performed at around 36 weeks' gestation to guide the timing and mode of birth. If there is suspected fetal growth restriction, particularly in the presence of maternal hypertension, past history of fetal growth restriction and/or diabetic nephropathy, more frequent or earlier initiation of scanning may be required.

One of the reasons to detect macrosomia is to try to predict shoulder dystocia. Shoulder dystocia is up to six times more common with infants of a diabetic mother than with infants at the same weight in a woman without diabetes [45, 46]. If the estimated fetal weight (EFW) at the time of birth is more than 4500g in women with pre-existing diabetes, the risk of shoulder dystocia is over 20% [47] and so the American College of Obstetrics and Gynecology recommends elective caesarean section in this setting [48]. It is estimated that 443 diabetic women with EFW >4500gm will need to have an elective caesarean section to avoid 1 permanent brachial plexus injury [49].

Ultrasound is expected to be have an error range of approximately 10-15% of the fetal weight, although this accuracy is less with longer time until delivery, maternal obesity, increasing gestational age, increasing birth weight and maternal diabetes in most reported series [50-53]. Accuracy of ultrasound in EFW in women with pregestational diabetes has been assessed in a number of small cohorts, however these also included women with gestational diabetes mellitus, who generally have milder disease [54-61]. The observed increased inaccuracy of ultrasound weight estimation in women with diabetes may be due to altered anthropometry and over representation of macrosomic fetuses. Ultrasound has been demonstrated to be less accurate in large fetuses, in some diabetic and non diabetic cohorts [52, 56], but not in others[62]. The altered anthropometry has been demonstrated both by ultrasound and postnatally. Measured sonographically, infants of diabetic mothers have been noted to have a larger abdominal circumference due to excess subcutaneous fat and liver size. Measured postnatally, infants of diabetic mothers have a higher ponderal index, compared to non diabetic macrosomic babies [63] and greater shoulder to head difference and chest to head difference than non diabetic babies of similar birthweight [64].

Alternatives to standard biometric measurement of head circumference, abdominal circumference and femur length to estimate fetal weight have been investigated. Measures including cord area, intraventricular septal thickness, shoulder diameter, soft-tissue thickness of anterior abdominal wall, 3D thigh volumes, upper arm, scapula and liver size have been reported to have small improvements in macrosomia detection [65-69]. These measurements may be difficult to reproduce in clinical practice and have generally not been validated in large studies. There may be additional clinical benefit in the use of other ultrasound measures, such as the level of fetal truncal asymmetry (abdominal circumference minus biparietal diameter) which correlates with the incidence and severity of shoulder dystocia [70]. Meta-analysis did not find sufficient evidence for improved detection of macrosomia using MRI compared to ultrasound [71].

Fetal well being

Women with pregestational diabetes continue to have a much higher perinatal mortality than women without diabetes; some of this is attributed to congenital anomalies, some to growth restriction and preeclampsia, but there is also a higher rate of unexplained stillbirth [72, 73]. Antenatal fetal monitoring, including CTG, assessment of amniotic fluid, maternal reporting of fetal movements and biophysical profile are widely used to try to mitigate this risk, although data to support the performance, timing, method or frequency of evaluation is largely observational.

Fetal Dopplers

Umbilical artery Doppler assessment has been shown to have a role in reducing perinatal mortality in high risk pregnancies, however these studies predominantly include growth restricted fetuses [74]. Umbilical artery resistance increases when there is placental infarction, or a small placenta, as is seen in growth restriction, however in the majority of diabetic pregnancies, the fetus is macrosomic, and so although widely used, its role is less clear in these pregnancies. The United Kingdom NICE (National Institute for Health and Care Excellence) guideline specifically advises against the use of fetal umbilical artery Doppler recording, fetal heart rate recording and biophysical profile testing in diabetes unless there is a risk of fetal growth restriction [44]. Middle cerebral artery Doppler has yet to

find its place in monitoring in nondiabetic pregnancies [75] and there are minimal data to support its role in diabetic pregnancies.

Amniotic fluid

Amniotic fluid measurement is used as a marker of fetal wellbeing. Amniotic fluid is increased in diabetic pregnancies [76]. This is thought to be due to macrosomia, which is associated with increased amniotic fluid in non-diabetic pregnancies, and with fetal hyperglycaemia, and subsequent increased osmotic load leading to a diuresis. Given this difference, consideration should be given to using an altered range to define normal amniotic fluid in women with pregestational diabetes, however again, the authors are not aware of a published reference range validated for this purpose.

Placental morphology

Several ultrasound parameters have been reported to assess placental function in women with pregestational diabetes [77-80]. Findings have been variable between the studies, and further investigation is needed before these techniques have a role in clinical care.

Aneuploidy screening

The presence of diabetes needs to be considered when calculating aneuploidy risk in women with diabetes using ultrasound and biochemistry. Several authors have demonstrated lower levels of PAPP-A in women with prepregnancy diabetes, and in 1 paper, a concomitant reduction in BHCG [81-84]. The authors suggest that adjusting for these changes would result in a decrease in both detection rate and false positive rate of the test. Only one of these papers distinguishes between type 1 and type 2 diabetes, and in these group, a difference in PAPP-A was only found in women with type 2 diabetes.

There are no published data on the performance of Non Invasive Prenatal Testing in women with diabetes, but the rates of low fetal fraction and need for redraw, or unsuccessful test are higher in obese women. Obesity and type 2 diabetes commonly coexist, and so it would be expected that in these women, a higher rate of failed test would also occur [85].

Preeclampsia screening

Clinical models for predicting severe, early onset preeclampsia have been used to target an at-risk population and are becoming more widely used in clinical practice. Models have been developed to screen for preeclampsia between 11-13 weeks' gestation, using factors such as maternal risk factors, mean arterial pressure, uterine artery pulsatility index, maternal serum PAPP-A, soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF). Recent randomised controlled trial data have demonstrated the benefit of screening and prescribing aspirin to those at high risk prior to 16 weeks of pregnancy, with a resulting reduction in early onset preeclampsia[86].

A consideration for the implementation of preeclampsia prediction using these methods is the cost, and access to high quality ultrasound. Evaluation in the non diabetic population has suggested that given the additional costs of screening, and the low cost and low side effect profile of prevention with low dose aspirin, it would be pragmatic to offer aspirin as intervention to all women without screening, which would provide improved outcomes at less cost [87]. Among women with pre-existing

diabetes in the ASPRE trial, the rate of early onset preeclampsia, before 34 weeks, was 1.3% in the screen negative group [86]. For these women, where the risk of early onset preeclampsia in the screen negative group is relatively high, the argument for universal aspirin in preference to screening is even more convincing.

Conclusion

Diabetes in pregnancy continues to pose increased risks for the women and for the fetus and neonate. Ultrasound plays an important role in the management of pregnancies in women with pregestational diabetes. There remain a number of important research questions in pregestational diabetes, including in prevention of fetal anomalies, fetal growth assessment and surveillance.

Data availability
No original data was generated in this literature review.

Ethics approvals
Ethical approval was not required.

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