High blood sugar levels and BMI linked to stillbirth in mothers with diabetes

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High maternal blood sugar levels and BMI are risk factors for stillbirth in mothers with diabetes, according to a new study in *Diabetologia* (the journal of the European Association for the Study of Diabetes), with

babies at the lowest and highest weights being most at risk. Mothers with pre-pregnancy diabetes are at a four to five times increased risk of stillbirth—with no improvement seen over recent years, in contrast with decreasing stillbirth rates seen in the general obstetric population.

Furthermore, the level of the mother's blood sugar emerged as a key risk factor for increased risk of stillbirth. Overall, while one third of stillbirths in mothers with diabetes occur close to term and might be influenced by policy on delivery, the majority occur before 37 weeks and finding better ways of detecting babies at risk will be critical.

Maternal obesity, advanced maternal age and smoking are known to be important modifiable risk factors for stillbirth in the general population, as is restricted fetal growth. However, data on pregnancies complicated by diabetes are more limited. Previous studies have indicated that suboptimal maternal blood glucose levels, microvascular complications and poor preparation for pregnancy are associated with stillbirth in mothers with diabetes—however traditional risk factors noted in the general population are less well documented for mothers with the condition.

This study, carried out by Dr. Robert Lindsay and Dr. Sharon Mackin, of the Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK and colleagues, analysed data from mothers diagnosed with pre-pregnancy diabetes to help define maternal and fetal characteristics associated with stillbirth. Timing of stillbirth was also analysed to examine the potential for strategies around routine delivery.

Maternity records obtained from the Scottish Morbidity Record 02 (SMR02) - a database containing clinical information on all birth episodes across Scotland including maternal and infant demographics, pregnancy/birth complications and delivery details—were linked with data from Scottish Care Information-Diabetes (SCI-Diabetes), a

database containing patient demographics and clinical information on diabetes diagnosis, complications and management. Data on infants delivered at or beyond 24 weeks from April 1998 to June 2016 from SMR02 were linked with data from SCI-Diabetes, identifying mothers diagnosed with types 1 or 2 diabetes before delivery. In keeping with accepted legal definitions, stillbirth was defined as birth of an infant, at or after 24 weeks of pregnancy, who at time of delivery did not breathe or show signs of life.

The study considered various potential risk factors: maternal blood sugar levels (from glycated haemoglobin (HbA1c) measurements taken before and during pregnancy); the mother's BMI, again from measurements taken during routine diabetes clinic appointments; and infant birthweight and in particular whether infants fell into the categories of large for gestational age (LGA) or small for gestational age (SGA) by nature of being within the top or bottom 10% of babies in terms of weight. The Scottish Index of Multiple Deprivation (SIMD) 2012 score was used to consider material deprivation, with mothers allocated to geographical area by postcode at time of delivery—each area having a score based on multiple indicators of material deprivation. To assess the possible effects of differences in clinic to clinic care, outcomes relating to different heath board and size of delivering hospital were examined.

The study identified 5392 singleton babies born to 3847 mothers with diabetes—3778 babies to 2582 mothers with type 1 diabetes; and 1614 babies to 1265 mothers with type 2 diabetes. Stillbirth rates were 16.1 per 1000 births in type 1 and 22.9 per 1000 births in type 2, compared with 4.9 per 1,000 births in the general population,

In keeping with other studies, the authors found that maternal blood glucose level is the key modifiable risk factor for stillbirth. Women with type 1 diabetes who suffered stillbirth were seen to have higher average blood glucose levels at all stages of pregnancy. For type 2 diabetes, a

different pattern was noted—in that pre-pregnancy blood glucose levels, rather than levels during pregnancy, appeared to be a more important predictor of stillbirth.

The authors note that in clinical practice, where input on blood sugar control as part of pre-pregnancy counselling would be of particular importance to mothers with type 2 diabetes, the uptake of such counselling is generally lower than in type 1 diabetes. They suggest that "overall efforts to improve blood glucose levels before and during pregnancy remain central." Another risk factor for stillbirth in mothers with type 2 diabetes was high maternal BMI. Maternal obesity, the authors note, is itself an independent risk factor for stillbirth, contributing to higher rates of preeclampsia, congenital abnormalities and fetal overgrowth.

In the general obstetric population, fetal growth restriction, whereby the unborn baby is smaller than it should be, is the strongest indicator of stillbirth risk. Likewise in the current study, absolute risk of stillbirth was highest in SGA infants (smaller than gestational age), particularly for type 1 diabetes. Similarly, LGA infants (larger than gestational age) are also at risk in the general population, and for type 2 diabetes this finding was mirrored here. Fetal overgrowth relates to maternal hyperglycaemia in later pregnancy—in this study it was noted that, even for mothers with the lowest blood glucose levels, the child's birth weight was considerably higher than that of the general population.

Optimal timing of delivery in diabetes remains controversial, the authors note. Many medical authorities recommend routine early delivery for mothers with diabetes—recent NICE (National Institute for Health and Care Excellence) guidelines in England, for example, suggest delivery in the 37th or 38th week. Compared to the general population, an increased risk of stillbirth for women with diabetes is seen at all stages of pregnancy, but previous studies have shown that at full term the higher

risk is at least five-fold. In this study a third of the stillbirths occurred at term. "It would seem then that earlier delivery would be a sensible approach," say the authors. "However, because of potential issues with early delivery -including respiratory distress syndrome as a result of inadequate lung development—we suggest that the increased risk of neonatal morbidity needs to be more formally explored before recommendations for optimal timing of delivery are made, particularly where mothers are managing to obtain almost normal blood glucose levels."

Unexpectedly, within this study a high proportion of stillborn infants (81%) were male among the mothers with type 2 diabetes. Previous studies indicate that male foetuses are more vulnerable in utero, with an increased risk of stillbirth of about 10% comparted to female infants. This current study, however, revealed stillbirth rates four times higher in male infants than in females for type 2 diabetes. However, the authors caution overall numbers were low and it would be useful to see similar data in other populations. The authors suggest that this might be explained by a combination of a higher metabolic demand, known to occur for male foetuses in the later stages of pregnancy, combined with a vulnerability caused by male foetuses having smaller placentas, and hence less compensatory reserve.

For both type 1 and type 2 diabetes, distributions of age, number of pregnancies, smoking rates and deprivation scores were similar in mothers regardless of whether the pregnancy ended in stillbirth or livebirth. Reassuringly, the authors note, there were likewise no significant differences in stillbirth rates when data were analysed by health board area or delivery hospital size, indicating that variations in clinic to clinic care are not a risk factor in stillbirth.

In conclusion, this study, of over 5000 infants over 18 years, considering a range of potential risk factors, has clearly shown that maternal blood

sugar levels and BMI are the main modifiable risk factors associated with stillbirth in women with diabetes. Mortality rates are highest for infants born small for their gestational age, but large infants are also at increased risk. "Achievement of near normal blood sugar levels remains key to reducing risk," the authors suggest, recommending "methods of supporting women to improve blood glucose levels in pregnancy, along with programmes to optimise weight before pregnancy." As stillbirth risk is high at full term, the authors recommend that "until more accurate assessment of risk during pregnancy becomes available, earlier delivery may be considered an attractive option."

More information: undefined undefined et al. Factors associated with stillbirth in women with diabetes, *Diabetologia* (2019). DOI: 10.1007/s00125-019-4943-9

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