

Infants of diabetic mothers

A cohort study

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ABSTRACT

الأهداف: تحديد ما حدث للمواليد الذين ولدوا بمستشفى قوى الأمن بالرياض، المملكة العربية السعودية، لأمهات لديهن مرض السكري ومقارنة المضاعفات التي لوحظت لديهم مع فئة المواليد الآخرين ممن ليس لدى أمهاتهم داء السكر.

الطريقة: هذه الدراسة التعرض المحتملة المتزامنة لمواليد حديثي الولادة في مستشفى قوى الأمن، الرياض، المملكة العربية السعودية للأمهات اللاتي لديهن داء السكر خلال الفترة من يناير 2011م ونوفمبر 2011م.

النتائج: أجريت الدراسة على 601 مولود كان بينهم 319 مولودا ليس لدى أمهاتهم داء السكر و 282 مولودا لدى أمهاتهم داء السكر. كان معدل المضاعفات بين مواليد الأمهات المصابات بداء السكر عالياً بدرجة ذات أهمية؛ ومعدل فترة بقائهم بالمستشفى أطول مقارنة مع فئة المواليد الآخرين الذين لا تعاني أمهاتهم من داء السكر. كذلك أوضحت الدراسة عدم وجود اختلاف في معدل المضاعفات لدى المواليد الأمهات المصابات بداء السكر مسبقاً قبل الحمل ومعدل المضاعفات لدى المواليد الأمهات تطور لديهن داء السكر الحاملي (أثناء الحمل).

الخلاصة: أوضحت هذه الدراسة أن النساء الحوامل المصابات بداء السكر تزداد لدى أجنتهن نسبة المخاطر وكذلك المضاعفات والعوامل المرضية للمواليد بعد الولادة بوقت قصير. ويبدو أن ذلك يتعلق بدرجة السيطرة على نسبة سكر الدم لدى الأم قبل وأثناء فترة الحمل. إن هذه المعدلات العالية للمخاطر والمضاعفات لدى مواليد الأمهات المصابات بداء السكر، وبشكل خاص التشوهات الخلقية الرئيسية، تستدعي اهتمام كافة الأطراف المعنية لتكثيف الجهود للسيطرة على نسبة سكر الدم لدى النساء قبل الحمل وأثناء فترة الحمل، واتباع التدابير والاحتياطات المتوفرة للوقاية ومنع حدوث المضاعفات والتشوهات الخلقية بين هؤلاء المواليد.

Objectives: To determine the outcome of infants born to diabetic mothers at Security Forces Hospital, Riyadh, Saudi Arabia, and compare the complications seen in these infants with infants of non-diabetic mothers.

Methods: This is a concurrent prospective cohort study of a population of newborn infants delivered at Security Forces Hospital, Riyadh, Saudi Arabia for diabetic mothers between January 2011 and November 2011.

Results: A total of 601 infants were enrolled in the study consisting of 319 infants of non-diabetic mothers, and 282 infants of diabetic mothers. Infants of diabetic mothers showed significantly higher rates of associated complications and prolonged hospital stay reflected in their admission to the neonatal intensive care when compared with infants of non-diabetic mothers. There was no difference in rate of complications between infants of gestational diabetics and pre-gestational diabetics.

Conclusion: Our study showed that diabetic pregnancies are associated with an increased incidence of neonatal complications. These seem to be related to the degree of maternal glycemic control. The higher rates of complications among our infants of diabetic mothers, particularly major congenital malformations call for those involved in the care of diabetic mothers to consolidate their efforts to facilitate early booking in specialist clinics.

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Recently, a number of publications have raised concern about the rising prevalence of diabetes mellitus in Saudi Arabia. The International Diabetes Federation has named Saudi Arabia among the top 10 countries with the highest prevalence of diabetes.¹ This rising trend in the incidence of diabetes in the Kingdom has been noticed by other researchers who attributed it to changing socio-economic status naming gender and high income as the significant risk factors.^{2,3} Women were reported to have an overall prevalence that was twice that for men. Our hospital records show that 20% of pregnant patients followed in obstetric clinics are diabetics, reflecting this high prevalence rate. Population-based studies^{4,5} from different countries have shown that complications among infants of diabetic mothers are high. In these studies, complications reported included congenital malformations, macrosomia, respiratory distress syndrome, hypoglycemia, polythycemia, and hyperbilirubinemia. In these studies, the risk of congenital malformations is reported to range from 2-10 times that of the normal population, while macrosomia is said to occur in 20-30% of infants of diabetic mothers. With these data and the high prevalence of diabetes in the Kingdom, we thought it would be appropriate to look at our pregnant diabetic women to determine the magnitude of the problem that diabetes might impose on them and their offspring. Determining the risk of congenital malformations was important in this group because other risk factors such as obesity and consanguinity are common in Saudi Arabia. Therefore, our objective was to determine the outcome of infants born to diabetic mothers at the Security Forces Hospital, Riyadh, Saudi Arabia, and to compare the complications occurring in these babies with those found in infants of non-diabetic mothers.

Methods. This concurrent prospective cohort study was carried out at the Security Forces Hospital in Riyadh, Saudi Arabia, from January 2011 to November 2011. At the Security Forces Hospital all diabetic pregnant women are followed in the obstetric clinics by a team consisting of a diabetologist, obstetrician, feto-maternal obstetrician, and dietician. The maternal diabetic population consisted of mothers with either pre-gestational diabetes, established before pregnancy, or gestational diabetes, discovered during pregnancy. Pre-gestational diabetics are advised on follow up to seek medical advice before they conceive to achieve glycemic control and have their glycosylated hemoglobin (HbA1C) checked. All pre-gestational diabetics are treated by insulin. However, we noticed that most pre-gestational diabetics report to the clinics after they

have conceived. During pregnancy, the pre-gestational diabetics are followed according to their glycemic control, and we do not determine their HbA1C. The plan to deliver pre-gestational diabetics depends on maturity of fetus and its size, previous history of intra-uterine death, and previous repeat cesarean section, or associated obstetric disorder. None of the pre-gestational diabetics had other complications of diabetes.

The diagnosis of gestational diabetes in our hospital is based on a 2-hour 75 grams oral glucose tolerance test. The diagnosis is established if 2 plasma glucose levels exceed the thresholds of a fasting glucose concentration of 95 mg/dl (5.2 mmol/l) and a 2-hour glucose concentration of 155 mg/dl (8.6 mmol/l). Gestational diabetics are managed with diet to start with, but insulin is usually added if the plasma glucose cannot be controlled below 120 mg/dl (6.7 mmol/l). Since serum proteins change significantly during pregnancy, we do not use HbA1C as a follow up marker because it is a protein.

At the time of delivery, the babies' data were entered prospectively into a database including type of maternal diabetes, length of gestation, route of delivery, Apgar score, gender, growth parameters, and any abnormal findings. On follow up, further complications occurring were recorded. Babies born to non-diabetic mothers with no other medical disorders were considered as controls and were recruited at the same period. Non-diabetic mothers with other medical disorders before or during pregnancy, which may affect their newborns were excluded. Primary outcome measures included congenital malformations, prematurity, respiratory disorders, macrosomia, traumatic birth injuries, hypoglycemia, hypocalcemia, hyperbilirubinemia, and sepsis. Secondary outcome measures included length of stay in the neonatal intensive care unit (NICU) and mortality.

Statistical analysis. Categorical data were summarized as absolute numbers and percentages. Continuous data were summarized as means and standard deviations (SD) or medians with inter-quartile ranges (IQR). Comparisons between groups for categorical variables were carried out using chi-square test or Fisher exact test, while the student T test, or Mann-Whitney test was used for continuous variables. Odds ratio with 95% confidence intervals (CI) were used to quantify the strength of association between study outcomes and exposure. All analyses were performed using SAS/STAT software (SAS Institute Inc., Cary, NC, USA). The hospital research committee and Hospital Ethics Committee approved the study.

Results. A total of 601 babies were enrolled. Of these, 319 babies were born to non-diabetic mothers while 282 babies were infants of diabetic mothers. Of infants of diabetic mothers, 153 were born to mothers with gestational diabetes while 129 were born to mothers with pre-gestational diabetes. Table 1 shows the characteristics of these babies. There were no significant differences between the 2 groups. The route of delivery showed no significant difference between the 2 groups, and the rates of elective and emergency cesarean were similar in the 2 groups. All the primary outcome measures were significantly increased in the infants of diabetic mothers when compared with infants of non-diabetic mothers (Table 2). More infants of diabetic mothers behaved as functionally premature infants (26.7%) compared with 19% of infants of non-diabetic mothers ($p=0.031$). Respiratory distress was found in

70% of infants of diabetic mothers compared with 43.9% in infants of non-diabetic mothers ($p<0.001$). Hypoglycemia and traumatic injuries are also shown to be higher in infants of diabetic mothers ($p=0.003$). Major congenital malformations were 3 times more common in infants of diabetic mothers compared with infants of non-diabetic mothers ($p<0.001$). These occurred as neural tube defects ($p=0.022$), congenital heart disease ($p<0.001$), and caudal dysplasia ($p=0.131$). Secondary outcome measures showed that infants of diabetic mothers were more likely to have longer hospital stay when admitted to the NICU than infants of non-diabetic mothers ($p<0.001$). However, those admitted with the complications of respiratory distress, hypoglycemia, hypocalcemia, and traumatic injury did not show an increase in mortality. Hypoglycemia occurred more frequently in infants of pre-gestational diabetics than

Table 1 - Characteristics of infants of diabetic and non-diabetic mothers (N=601).

Characteristics	Cases (diabetic mothers) n=282	Control (non-diabetic mothers) n=319	P-value
Gestational age (weeks), mean ± SD	36.95 ± 3.983	37.39 ± 3.67	0.161
Length (cm), mean ± SD	48.15 ± 5.270	48.70 ± 4.53	0.168
Weight (Kilograms), mean ± SD	2.71 ± 0.8266	2.71 ± 0.747	0.976
Head circumference (cm), mean ± SD	33.11 ± 3.128	33.12 ± 2.57	0.971
Cord PH, mean ± SD	1.90 ± 3.180	1.69 ± 3.06	0.430
Apgar Score 1 mint, mean ± SD	7.97 ± 1.368	8.19 ± 1.425	0.049
Apgar score 5 mint, mean ± SD	9.16 ± 0.881	9.17 ± 0.933	0.883
Delivery			0.064
Spontaneous vaginal delivery, n (%)	141 (50.0)	159 (49.8)	
Elective cesarean section, n (%)	116 (41.1)	133 (41.7)	
Emergency cesarean section, n (%)	24 (8.5)	18 (5.6)	
Ventouse, n (%)	1 (0.4)	9 (2.8)	

Table 2 - Comparison of outcome of infants of diabetic and non-diabetic mothers.

Outcome and complications	Cases (diabetic mothers) n=282	Control (non-diabetic mothers) n=319	Odds ratio	95% Confidence interval	P-value
Outcome					
Expired, n(%)	6 (2.1)	10 (3.1)	0.67	0.24-1.87	0.448
Length of stay (days)	14.74±22.54	9.08±16.625			
Median (IQR)	7 (8)	3 (8)			<0.001
Complications					
Congenital malformation, n (%)	36 (12.8)	12 (3.76)	3.74	1.91-7.34	<0.001
Congenital heart diseases, n (%)	21 (7.5)	5 (1.6)	5.07	1.88-13.68	<0.001
Central nervous system (neural tube defects) (%)	5 (1.77)	0 (0)			0.022
Caudal dysplasia	2 (0.712)	0 (0)			0.131
Preterm low birth weight, n (%)	75 (26.7)	61 (19.1)	1.54	1.05-2.26	0.031
Traumatic injury, n (%)	10 (3.6)	1 (0.3)	11.73	1.49-92.25	0.003
Respiratory, n (%)	199 (70.8)	141 (43.9)	3.10	2.21-4.35	<0.001
Sepsis, n (%)	33 (11.7)	14 (4.4)	2.89	1.51-5.53	0.001
Hypoglycemia, n (%)	51 (18.1)	31 (9.7)	2.06	1.27-3.32	0.003
Hyperbilirubinemia, n (%)	41 (14.6)	45 (14.1)	1.04	0.65-1.64	0.866
Hypocalcemia, n (%)	7 (2.5)	1 (0.3)	8.12	1.03-367.26	0.0452

Table 3 - Comparison of outcome of infants of pre-gestational and gestational diabetics.

Outcome and complications	Pre-gestational diabetics n=129	Gestational diabetics n=153	Odds ratio	95% Confidence interval	P-value
Outcome					
Expired, n (%)	4 (3.1)	2 (1.3)	2.40	0.43-13.32	0.417
Length of stay, (days)	17.10 ± 26.92	12.72 ± 17.81			0.025
Median (IQR)	8 (10)	7 (6.0)			
Complications					
Congenital malformation, n (%)	15 (11.6)	21 (13.8)	0.82	0.40-1.67	0.584
Congenital heart diseases, n (%)	12 (9.3)	9 (5.9)	1.63	0.66-4.00	0.283
Central nervous system malformation, n (%)	2 (1.1)	3 (1.9)	0.70	0.16-2.98	0.730
Caudal dysplasia	1 (0.8)	1 (0.7)			0.902
Preterm low birth weight, n (%)	32 (24.8)	43 (28.3)	0.83	0.49-1.42	0.511
Traumatic injury, n (%)	5 (3.9)	5 (3.3)	1.18	0.33-4.18	0.791
Respiratory, n (%)	91 (70.5)	108 (71.1)	0.97	0.58-1.63	0.925
Sepsis, n (%)	15 (11.6)	18 (11.8)	0.98	0.47-2.03	0.956
Hypoglycemia, n (%)	34 (26.4)	17 (11.2)	2.84	1.50-5.38	0.001
Hypocalcemia, n (%)	6 (4.7)	1 (0.7)	7.36	0.87-61.99	0.051
Hyperbilirubinemia, n (%)	15 (11.6)	26 (17.1)	0.63	0.32-1.26	0.195

infants of gestational diabetics ($p < 0.001$). However, all other complications did not show significant differences between infants of pre-gestational diabetics and infants of gestational diabetics (Table 3).

Discussion. Recently, many publications from Saudi Arabia have shed light on the rising prevalence of diabetes mellitus in the population. Al-Nozha et al² indicated that one subject in 4 above the age of 30 is reported to have diabetes in Saudi Arabia. These reports have highlighted the magnitude of the problem of diabetes in the Saudi community and its impact on society.³ The group of women in the reproductive age is one of the groups of the society where the burden of diabetes exerts its toll on both the mothers and their babies. Population studies^{4,5} from different parts of the world have emphasized the significant perinatal and neonatal morbidities associated with diabetic pregnancies. Our 2 groups of infants showed no significant difference in the route of delivery, Apgar score, cord pH, and growth parameters. In particular, we refer to the occurrence of similar rates of cesarean section between diabetic and non-diabetic pregnancies, which contradicts reports from other studies. Cesarean section in diabetic patients was indicated by previous cesarean section, history of previous intra-uterine fetal death, associated polyhydramnios, oligohydramnios, pre-eclampsia, and other obstetric complications. Non-diabetic patients were essentially normal mothers who had to have elective cesarean because of 2 or more previous cesarean sections, or abnormal fetal presentation. The presence of the associated complications of infants of diabetic

mothers was the reason for their admission to the NICU, and the prolonged period of their hospital stay. Infants of diabetic mothers had significant respiratory disease, which can be explained by the functional pulmonary immaturity observed in these babies. Of the metabolic abnormalities, hypoglycemia was the most important complication seen in infants of diabetic mothers. Hypoglycemia occurs due to poor maternal glycemic control resulting in maternal hyperglycemia with consequent hyperinsulinemia in the baby.

Traumatic injuries consisted of 2 cases of Erb's palsy, and the rest were large cephalohematomas and subgaleal hemorrhages. The weights of the babies with Erb's palsy were less than 4 kilograms and the palsy was not related to macrosomia. Subgaleal hemorrhage occurred during vacuum extraction. Macrosomia was not significantly increased in our infants of diabetic mothers. This is most likely due to elective delivery at 37-38 weeks gestation rather than good glycemic control of diabetes. Excluding congenital malformations all other complications for which infants of diabetic mothers had to be admitted to the NICU were not associated with mortalities, and the infants were discharged home with no further morbidities. This is a direct result of the improved care and management of these babies. Our data clearly show that major congenital malformations occurred more frequently in infants of diabetic mothers, and that they are now the most important cause of mortality and morbidity in our intensive care unit, where 70% of the mortality is due to major congenital malformations. The major congenital malformations in our study population were neural tube defects,

major congenital heart disease, and caudal dysplasia. Others have reported similar mortality rates and similar occurrences in the types of malformations as our cohort.^{6,7}

Weindling,⁶ and Yang et al⁷ in 2 different papers reported increased morbidity and mortality in infants of diabetic mothers. DeBoer et al,⁸ examining the memory performance in infants of diabetic mothers, drew attention to the fact that these infants ran a 20 times higher risk of CNS malformations, anencephaly risk 13 times higher, and spina bifida risk 20 times higher. The risk of caudal dysplasia is said to be 250 times higher in infants of diabetic mothers.^{9,10} In our study, caudal dysplasia was only seen in infants of diabetic mothers, but this did not rise to a significant level when compared with infants of non-diabetic mothers. However, caudal dysplasia was equally distributed between infants of pre-gestational and gestational diabetics. Similarly Wren et al¹¹ reported a higher risk of congenital heart disease in infants of diabetic mothers.

Since 20% of the women who are followed in our institution's obstetric clinics are pregnant diabetics, one can only emphasize the importance of anticipating the risks involved for both the mother and her baby.

The socioeconomic burden of major congenital malformations cannot be underestimated as these babies may need lifelong integrated health services to allow for their rehabilitation. From these data and other data that have been reported elsewhere, it is evident that diabetic pregnancies are associated with increased risk of fetal, neonatal, and long-term complications. The outcome seems to be related to the onset and duration of glucose intolerance during pregnancy and the subsequent glycemic control. Poor glycemic control and hyperglycemia lead to deleterious fetal effects throughout the pregnancy.⁵ Two types of fetal syndromes have been recognized depending on the time of exposure to maternal hyperglycemia. Diabetic embryopathy is said to occur when maternal hyperglycemia is encountered at the time of conception and first trimester leading to major birth defects and spontaneous abortions. Diabetic fetopathy occurs when the fetus is exposed to maternal hyperglycemia during the second and third trimesters resulting in fetal hyperglycemia, hyperinsulinemia, and macrosomia.

We further went on to analyze the occurrence of these complications in the infants of the 2 groups of diabetics; namely, pre-gestational and gestational. No significant differences were found when the complications were compared except for neonatal hypoglycemia, which occurred more frequently in infants of pre-gestational diabetics. Our pre-gestational diabetics were mainly

followed by serials of plasma glucose estimations, and HbA1C was measured before and during the first trimester in very few mothers who presented early. In those few pre-gestational diabetics, 71% had a high reading of HbA1C above the accepted range for diabetic patients, which would suggest poor glycemic control. Although all our pre-gestational diabetics are managed by insulin, the occurrence of significant neonatal hypoglycemia suggests that poor glycemic control and persistent maternal hyperglycemia are operative during the second and third trimesters as well leading to significant fetal hyperglycemia and hyperinsulinemia, and eventually neonatal hypoglycemia.

The occurrence of major congenital malformations at similar rates between the 2 groups of infants of diabetic mothers is an alarming indication of the inability to diagnose gestational diabetes before or early in pregnancy, and hence the inability to provide early glycemic control, which may help to reduce the malformations. Unfortunately, gestational diabetic mothers in our institution present to the clinic by the end of the first trimester or after, thus, missing the essential early glycemic control during the critical period at which congenital malformations develop. Several studies have tried to address the methods for early detection and identification of women with gestational diabetes.¹² Risk factors have been used to identify gestational diabetics before or early in pregnancy because several studies have indicated that glycemic control during embryogenesis is the main factor in the origin of malformations.¹³ The importance of primary care centers and preconception clinics is now well-recognized, but education and counseling families with risk factors for diabetes may yield better results in early identification of gestational diabetics. Since neural tube defects are seen more in babies of diabetic mothers, a point can be made for encouraging early provision of folic acid and health education at the primary care level for these mothers.¹⁴

Until other mechanisms other than poor maternal glycemic control are identified as factors in development of diabetic embryopathy, strict glycemic control before and during the first few weeks of pregnancy should be the sole important measure applied if we are to reduce the incidence of congenital malformations.

Study limitations. In our study, we did not refer to the fetal outcome of diabetic pregnancies in relation to the rates of abortion and intra-uterine fetal deaths because we considered them as separate entities that have to be addressed on their own.

In conclusion, our cohort has shown that infants

of diabetic mothers have a higher incidence of complications when compared with infants of non-diabetic mothers. Since diabetic women attending obstetric clinics at Security Forces Hospital comprise 20% of all pregnant women attending the clinics, this study has highlighted the importance of early attention to this group in order to minimize the significant risk of complications imposed on them and their fetuses by diabetes. Our cohort has also shown that the majority of diabetic women present after the pregnancy has been established. This requires efforts to stress the importance of early reporting to clinics so that we can reduce the complications of diabetes by early control of hyperglycemia. Of great concern in this study is the late diagnosis of gestational diabetes in our patients, which poses more threat to the occurrence of complications in the infants. Early diagnosis and identification of gestational diabetes are a necessity in our population of diabetic mothers.

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