Impaired gestational glucose tolerance

Its effect on placental pathology

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ABSTRACT

Objective: The aim of this study was to investigate several macroscopic and microscopic features of placenta in cases with impaired gestational glucose tolerance.

Methods: Seventy-five gm World Health Organization criteria for the diagnosis of gestational diabetes and impaired gestational glucose tolerance were followed during the period June 1999 through to June 2000, at the Maternity Hospital of Kuwait. Macroscopic and microscopic examinations of 95 placentas were carried out. Sixty-five were from the control patients and 30 were from cases with impaired gestational glucose tolerance.

Results: Mean maternal age, maternal weight and parity was significantly higher in the impaired gestational glucose tolerance (IGGT) group compared to the control group. Mean birth weight of the baby was significantly higher in the IGGT group compared to the control group. Mean placental weight and the percentage of the cesarean delivery was higher in the IGGT group but did not reach the level of significance. There was no significant association between the microscopic features of the placenta in the control and IGGT groups.

Conclusion: Impaired gestational glucose tolerance is related to increased neonatal and placental weight, which may lead to a higher number of cesarean deliveries, stressing the similarity between impaired gestational glucose tolerance and gestational diabetes mellitus. More stringent criteria may be necessary to define gestational diabetes. Microscopic features of placenta both in the control and IGGT groups did not show any significant difference.

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Since pregnancies complicated by diabetes are associated with an increased risk of maternal and fetal morbidity, the Third International Workshop Conference on Gestational Diabetes and American Association has recommended the routine screening of all pregnancies for gestational diabetes.[1] Important complications of diabetes are congenital abnormalities, unexplained sudden intrauterine fetal death (IUFD), macrosomia and intrauterine growth retardation. Improvement in the fetal assessment, neonatal care and the metabolic management of pregnant women has significantly reduced the incidence of perinatal mortality and morbidity. Maternal diabetes is associated with extensive placental abnormalities such as placentomegaly, infarcts, dysmaturity, angiopathies, abnormalities of the basement membrane and abnormalities of placental villi such as hydrops, fibrosis and increased glycogen content. The most consistent of these features is the enlargement of the placenta, which is usually associated with fetal macrosomia. A linear relationship between the placental weight and fetal weight has been documented throughout early and late human gestation, and at birth.[2-4]

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Table 1 - Maternal characteristics in the 2 groups.

Maternal characteristics	Control 65	IGGT 30	*p* value
Maternal age			
<20 years	5 (7.7)	1 (3.3)	<0.05*
20-30 years	37 (56.9)	9 (30)	
>30 years	23 (35.4)	20 (66.7)	
Mean	28.5 ± 5.8	32.4 ± 6.0	<0.01**
Maternal weight			
<75kg	35 (53.8)	7 (23.3)	<0.01*
≥75kg	30 (46.2)	23 (76.7)	
Mean	70.1 ± 13.9	80.3 ± 17.5	<0.01**
Parity			
P_0	26 (40)	3 (10)	<0.0001*
P_{1-4}	36 (55.4)	16 (53.3)	
P>4	3 (4.6)	11 (36.7)	
Chronic disease			
None	56 (86.2)	23 (76.7)	NS*
PIH	4 (6.2)	3 (10)	
Chronic BP	4 (6.2)	2 (6.7)	
PET	0	1 (3.3)	
Sickle cell	0	1 (3.3)	
SLE	1 (1.5)	0	
Delivery mode			
Vaginal	59 (90.8)	26 (86.7)	NS*
Operative	6 (9.2)	4 (13.3)	

*p value by chi-square
**p value by student t test
BP - blood pressure
PIH - pregnancy induced hypertension
PET - positron-emission tomography
SLE - systemic lupus erythematosus

Table 2 - Fetal characteristics in the 2 groups.

Fetal characteristics	Control 65	IGGT 30	*p* value
Gestational age			
<37 weeks	7 (10.8)	2 (6.7)	NS*
≥37 weeks	58 (89.2)	28 (93.3)	
Mean	38.5 ± 3.1	38.8 ± 1.7	NS*
Sex of the fetus			
Male	31 (47.7)	8 (26.7)	NS*
Female	34 (52.3)	22 (73.3)	
Neonatal weight			
<2500 gm	9 (13.8)	2 (6.7)	NS*
2501-4000 gm	53 (81.5)	24 (80)	
>4000 gm	3 (4.6)	4 (13.3)	
Mean	3176 ± 784	3563 ± 615	<0.05**
Apgar score at 1'			
≤7	22 (33.8)	7 (23.3)	NS*
>7	43 (66.2)	23 (76.7)	
Mean	7.2 ± 2.0	7.4 ± 1.5	NS**
Apgar score at 5'			
≤7	6 (9.2)	1 (3.3)	NS**
>7	59 (90.8)	29 (96.7)	
Mean	8.4 ± 2.2	9.0 ± 0.5	<0.05**
Delivery mode			
Vaginal	59 (90.8)	26 (86.7)	NS*
Operative	6 (9.2)	4 (13.3)	
NICU admission			
Not admitted	6 (86.2)	26 (86.7)	NS*
Admitted	9 (13.8)	4 (13.3)	
Neonatal outcome			
Alive and well	52 (80)	25 (83.3)	NS*
Dead	3 (4.6)	0	
Alive with sequele	9 (13.8)	5 (16.7)	
Alive with congenital abnormality	1 (1.5)	0	

*p value by chi-square test, ** p value by student t test
NICU - neonatal intensive care unit

During the Fourth International Conference on Gestational Diabetes held in 1997, the diagnostic criteria were revised (cut off for 75 gm glucose load test were <5.3 mmol /L for fasting and <8.5 mmol /L for 2-h).[5] The clinical significance of impaired glucose tolerance remains unclear. Should people who are found to have impaired glucose tolerance be followed up, and what treatment, if any, should they receive? Few studies have shown that patients with impaired glucose tolerance are associated with increased rates of unfavorable perinatal outcomes.[6-8] Most of the previous studies were concerned with the placental changes in diabetic pregnancies. This study was setup to investigate several macroscopic and microscopic features of the placenta in cases with IGGT.

Methods. The Maternity Hospital of Kuwait (MHK) is the largest hospital in Kuwait serving combined care of obstetrics and gynecology with a capacity of 500 beds, and an average of 12,000 deliveries per year. During the period from June 1999 through to June 2000 we have followed 75 gm revised diagnostic criteria recommended on the occasion of the Fourth International Conference on Gestational Diabetes held in 1997 for the diagnosis of gestational diabetes and impaired glucose tolerance. All pregnant patients attending the sunday clinic who were not known to be diabetic were subjected to 75 gm glucose tolerance test between 24-28-weeks. All those patients who had impaired glucose tolerance were put on a special/restricted diet by a dietitian. Their blood sugar profiles were regularly carried out. Those patients whose blood glucose was not controlled on diet alone were tested for insulin need (2-h postprandial blood glucose >120 mg/dl), and positive cases were put on insulin accordingly. All these patients regularly had their blood sugar profiles and had their full antenatal care in MHK and their files were identified with a special sticker. Nurses were instructed to collect the placentas of these patients in special plastic bags and transfer them to the Faculty of Medicine for further study. A total of 95 placentas were studied. Sixty-five placentas were from the control patients and 30 were from cases with (IGGT).

Macroscopic and microscopic examination of the placentae. Each placenta received was cleaned and grossly examined as suggested by Salafia and Vintzileus.[9] For microscopic examination a

Table 3 - Macroscopic placental features in the 2 groups.

Macroscopic placental features	Control (65)	IGGT (30)	*p value
Placental height	1.75 ± 0.49	1.900 ± 0.42	NS
Placental length	17.53 ± 2.50	17.79 ± 2.09	NS
Placental breadth	14.88 ± 2.45	15.61 ± 1.90	NS
Placental surface area	260.3 ± 65.2	278.5 ± 53.8	NS
Placental volume	453.7 ± 184.0	540.9 ± 157.8	<0.05
Placental perimeter	64.15 ± 8.89	66.48 ± 6.80	NS
Cord length	43.15 ± 16.04	53.8 ± 17.76	<0.01
Placental weight	518.3 ± 145.2	572.8 ± 114.4	NS

IGGT - impaired gestational glucose tolerance
*p value by student t test

Table 4 - Microscopic placentral features in the 2 groups.

Microscopic placental features	Control (65)	IGGT (30)	*p value
Maternal floor infarction	1.75 ± 0.49	1.900 ± 0.42	NS
Intravascular thrombosis	17.53 ± 2.50	17.79 ± 2.09	NS
Placental inflammation	14.88 ± 2.45	15.61 ± 1.90	NS
Placental infarction	260.3 ± 65.2	278.5 ± 53.8	NS
Placental dysmaturity	453.7 ± 184.0	540.9 ± 157.8	<0.05
Placental calcification	64.15 ± 8.89	66.48 ± 6.80	NS
Funistis	43.15 ± 16.04	53.8 ± 17.76	<0.01
Chorio-amnioitis	518.3 ± 145.2	572.8 ± 114.4	NS

*p value by chi-square test, NS - not significant
IGGT - impaired gestational glucose tolerance

minimum of 4 sections (umbilical cord, membrane roll and 2 full thickness section cut perpendicular to the placental plate) were examined. In addition sections from abnormal areas seen on gross examination were similarly submitted for processing. The slides were examined for lesions as shown in the appendix modified from Salafia and Vintzileus.[9] The placenta was weighed without the cord. The pathological changes, which were sought were dysmaturity, maternal floor infarction, intravascular thrombosis, villitis, infarction, funisitis, chorioamnionitis and calcification. Maternal floor infarction is characterized by the deposition of fibrin in the decidua basalis. This extends into the intervillous space entrapping chorionic villi, which become avascular and sclerotic. In this study the deposition of fibrin in the decidua basalis, which forms the core change in maternal floor infarction was evaluated semi quantitatively and graded as mild, moderate or severe. Only the severe cases of maternal floor infarction were considered to be positive in this study.

Statistical methods. The Chi square test or Fischer's exact test were used to find association between categorical variables. The student's t-test was used to compare means. The value $p<0.05$ was used as cut off level for significance.

Results. The mean maternal age and weight were significantly higher in the IGGT group compared to the control group (**Table 1**). The percentage of grandmultiparity was also higher in the IGGT group (**Table 1**). **Table 2** shows that the mean birth weight was significantly higher in the IGGT group (3563gms) compared to the control group (3176gms) ($p<0.05$). The percentage of operative delivery was higher in the IGGT group than the control group but the difference was not statistically significant. Neonatal outcome did not show any significant difference in the control and the IGGT groups. The mean umbilical cord length was significantly higher in the IGGT group compared to the control group. The mean placental weight was also higher in the IGGT group compared to control group, but the difference was not statistically significant (**Table 3**). **Table 4** shows the microscopic placental features in the 2 groups. There was no significant association between the microscopic features of placenta in the control and the IGGT groups.

Discussion. The percentage of pregnancies with diabetes mellitus was 4.8% in 1997 in the Maternity Hospital Kuwait. Out of these diabetic pregnancies 9.9% had gestational diabetes, 15.3% had impaired glucose tolerance test in pregnancy and 74.8% had pregestational diabetes. The perinatal mortality related to all the diabetic pregnancies was 21.3 per 1000 in the Maternity Hospital Kuwait.[10] Previous studies have shown that maternal age, weight and parity are important factors that are associated with diabetic pregnancy.[11,12] Our results show that patients with IGGT are also associated with older age, obesity and grandmultiparity. Our study was designed to see if the infants of women with minor abnormalities of glucose metabolism not diagnostic of gestational diabetes are at risk of adverse perinatal outcome. Due to the increased perinatal jeopardy, the rate of

cesarean section is increased in diabetic mothers. In our study the percentage of operative delivery was higher in the IGGT group (13.3%) than in the control group (9.2%), but the difference was not statistically significant. Studies have reported that diabetic women give birth to their children at an early gestational age.[4,13,14] There was no significant difference in the mean gestational age of the IGGT and the control group in our study. One of the important perinatal concerns in the offspring of mothers with gestational diabetes is excessive fetal growth, which may result in birth trauma. The mean neonatal birth weight was significantly higher in the IGGT group (3563 gms) compared to the control group (3176 gms), which stress the similarity between IGGT and GDM. Weights of normal placentas range from 400-550 grams and those from pregnancies complicated by diabetes often exceed 650 gms.[4,13-15] In our study the mean placental weight (572.8 gms) was higher in the IGGT group compared to the control group (518.3 gms) but the difference was not statistically significant. Placental weight was significantly correlated to neonatal weight. This placentomegaly and fetal macrosomia is likely due to the growth promoting effects of insulin and possibly other hormones.[15,16] Mean length of the umbilical cord was also greater in the IGGT group. Placental abnormalities associated with maternal diabetes are so extensive and varied that the reported observations sometimes appear contradictory.[15] Discrepancies in these reports may be due to placentas from women with diabetes of variable severity and from pregnancies of different gestations. Placental abnormalities described in diabetes include, placentomegaly, infarcts, dysmaturity, angiopathies, abnormalities of the basement membrane and abnormalities of placental villi such as hydrops, fibrosis, increased glycogen content. Our results do not show any significant difference in the microscopic features of placentas in the IGGT and the control groups.

In conclusion our results indicate that even a limited degree of maternal hyperglycemia is related to the advanced maternal age, grand multiparity and increased maternal weight. Impaired gestational glucose tolerance is also associated with increased neonatal weight and increased placental weight which may lead to a higher incidence of cesarean delivery stressing the similarities between IGGT and GDM. It is therefore suggested that more stringent criteria may be necessary to define gestational diabetes. There was however no major difference observed in the light microscopic features of the placenta and the neonatal outcome. Further studies involving a larger surveying population are currently in progress to find a probable association between IGGT and perinatal outcome.

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