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Placental pathology in relation to the White's classification of diabetes mellitus

Abstract The objective of this study was to investigate various macroscopic and microscopic features of the placenta in pregnancies complicated by diabetes according to White's classification. A total of 148 placentas were studied. Sixty-five were from control patients and 83 from diabetic mothers. The diabetic mothers were further divided into three groups according to White's classification. There were 40 cases in White's group A and 36 cases in White's group B. There were 7 cases in White's groups C and D combined. Advanced maternal age and grandmultiparity were significantly higher in White A, White B and White C&D compared to the normal group. Mean weight of the mother was higher in White group A and group B compared to the control group and group C&D. The placental weight and neonatal weight were increased provided the diabetes was not complicated by vascular disease. With accompanying vascular disease the placental weight and neonatal weight were reduced compared to the controls. As a result of increased perinatal jeopardy the rate of operative delivery was higher in diabetic mothers. No major difference was observed in microscopic changes of placentas in different groups according to White's classification and the normal group.

Keywords Diabetes · Pregnancy · Placenta · White's classification

Introduction

Diabetes mellitus is one of the most common endocrine disorders that can complicate pregnancy. Congenital abnormalities, stillbirth, macrosomia and intrauterine growth restriction are common complications associated with diabetes in pregnancy. With the implementation of treatment programs emphasizing normalization of maternal glucose levels and better techniques to assess fetal well-being and maturity, fetal and neonatal mortality have now become uncommon events in those pregnancies complicated by diabetes mellitus.

Macroscopic and microscopic placental pathologies in pregnancies complicated by diabetes are so extensive and varied that reported observations sometimes appear contradictory [18]. The differences in these reports may be attributed to the degree of severity of diabetes and differences in gestational age at delivery.

During pregnancy diabetes may show different clinical pictures and cause various complications in the mother and the fetus; hence, in this study the diabetic mothers have been divided into different groups according to the White's classification [20]. The aim of our study was to investigate the various macroscopic and microscopic features of the placenta in pregnancies complicated by diabetes according to White's classification. Various maternal and fetal characteristics were studied as well.

Materials and methods

This study was performed in the Maternity Hospital of Kuwait (MHK) from June 1999 to June 2000. MHK is the largest hospital in Kuwait serving combined care of Obstetrics and Gynaecology with a capacity of 500 beds, and an average of 12000 deliveries per year. All patients gave their informed consent prior to their inclusion in the study.

White's classification [20] of maternal diabetes is summarized as follows: Class A (Gestational diabetes/abnormal glucose tolerance test which reverts to normal within a few weeks after delivery. No insulin required); class B (Onset of diabetes after 20 years of age, less than 10 years duration, no vasculopathy); class C (Duration of diabetes 10–19 years, onset after 10 years of age, minimal vasculopathy); class D (Duration of diabetes 20 years or more, onset before 10 years of age, vasculopathy); classes F, R, H (Diabetes with nephritis, retinitis proliferans and heart disease respectively). Eighty-three placentas of pregnancies with maternal diabetes mellitus classified according to White were included in the study. There were 40 cases in White's A group and 36 cases in White's group B. There were 7 cases in White's group C and D combined.

Sixty-five placentas from a control group of healthy, non-diabetic women were selected retrospectively. Mothers with compli-

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cations such as pre-eclampsia, anaemia, placental abruption and intrauterine growth restriction were not included in this group. These women gave birth at term (37–42 weeks gestation) to healthy children.

Macroscopic and microscopic examination of the placentas

Each placenta received was cleaned and grossly examined as described by Salafia and Vintzileos [14]. Features looked for during gross examination were: extraplacental membranes (adherent blood clot, color, transparency, site of rupture, insertion, amnion nodosum, velamentous vessels, chorionicity); umbilical cord (length, diameter, vessel number, true knots, insertion, angioma, allantoic and omphalomesenteric remnants); chorionic plate (color and transparency, dimensions and shape, vascular pattern, subarachnoid thrombi) maternal surface (completeness, adherent blood clot, placental indentation, calcifications); villous parenchyma (infarction, intervillous thrombosis, chorioangioma, maternal floor infarction, perivillous fibrin deposition, pallor).

For microscopic examination a minimum of four sections (umbilical cord, membrane roll and two full thickness sections 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 Vintzileos [14]. The pathological changes which were sought were dysmaturity, maternal floor infarction, intravascular thrombosis, villitis, infarction, funisitis, chorioamnionitis and calcification. The placentas were weighed without the cord.

Maternal floor infarction is characterized by deposition of fibrin in the decidua basalis. This extends into the intervillous space entrapping chorionic villi, which become avascular ans 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 infarct were considered to be positive in this study.

Statistical methods

The χ^2 test or Fischer's exact test were used to establish association between categorical variables. The student's t-test was used to compared means. One way analysis of variance (ANOVA) was used to compare means in more than two groups.

Results

Maternal and fetal characteristics

Mean maternal age was significantly higher in White A (32.4±5.3), White B (33.4±5.1) and White C & D (30.5±8) compared to the control group (28.5±5.8) ($p<0.0001$, by ANOVA). The percentages of mothers in different age groups are shown in Table 1. The percentage of grandmultipara (parity >4) was higher in White's groups A, B and C&D compared to the control group as shown in table 1. Mean weight of the mother was higher in White group A (79.5±17.2) and group B (79.5±15.2) compared to the control group (70.1±13.9) and group C&D (69.5±14.2) (Table 1). Table 1 also shows that a greater number of heavier mothers (>75 kg) were present in White A and B groups.

The percentage of mothers undergoing cesarean sections was higher in the diabetic mothers compared to the control mothers as shown in table 1. Mean birth weights of babies were greater in White's A group compared to other groups ($p<0.05$, by ANOVA) (Table 2).

Placental characteristics

Placental weight was significantly higher in White A and White B groups compared to control group ($p>0.01$ and 0.05, respectively) (Table 3). Mean length of the umbilical cord was significantly higher in White group A than the control group. Mean placental surface area and perimeter in White groups A and B were higher than in control group (Table 3). Mean placental perimeter and placental length were significantly higher in White's group B than the control group (Table 3). There was no significant association of microscopic features of placenta in the normal and other groups (Table 4).

Table 1 Maternal age, weight, parity and mode of delivery in different groups

Maternal characteristics	Normal (n=65)	White A (n=40)	White B (n=36)	White C&D (n=7)
Maternal age				
< Than 20 years	5 (7.7)	1 (2.5)	0	0
20–30 years	37 (56.9)	13 (32.5)	12 (33.3)	4 (57.1)
> Than 30 years	23 (35.4)	26 (65)	24 (66.7)	3 (42.9)
Mean±SD	28.5+5.8	32.4+5.3	33.4+5.1	30.5+8.0
Maternal weight				
< Than 75 kg	35 (53.8)	11 (27.5)	8 (22.2)	3 (42.9)
≥ Than 75 kg	30 (46.2)	29 (72.5)	28 (77.8)	4 (57.1)
Mean±SD	70.1+13.9	79.5+17.2	79.5+15.2	69.5+14.2
Parity				
P_0	26 (40)	5 (12.5)	3 (8.3)	3 (42.9)
P_{1-4}	36 (55.4)	24 (60)	24 (66.7)	2 (28.6)
P>4	3 (4.6)	11 (27.5)	9 (25)	2 (28.6)
Delivery mode				
Vaginal	59 (90.8)	35 (87.5)	26 (72.2)	5 (71.4)
Operative	6 (9.2)	5 (12.5)	10 (27.8)	2 (28.6)

n ( ) numbers of cases (percentage)

Table 2 Fetal characteristics in different groups

Fetal characteristics	Normal (n=65)	White A (n=40)	White B (n=36)	White C&D (n=7)
Gestational age				
< Than 37 weeks	7 (10.8)	2 (5)	7 (19.4)	2 (28.6)
≥ Than 37 weeks	58 (89.2)	38 (95)	29 (80.6)	5 (71.4)
Mean±SD	38.5±3.1	38.9±1.8	37.7±2.4	36.0±4.9
Sex of the fetus				
Male	31 (47.7)	27 (67.5)	11 (30.6)	3 (42.9)
Female	34 (52.3)	13 (32.5)	25 (69.4)	4 (57.1)
Birth weight				
≤ 2500 gm	9 (13.8)	3 (7.5)	4 (11.1)	1 (14.3)
2501–4000 gm	53 (81.5)	31 (77.5)	27 (75)	6 (85.7)
> Than 4000 gm	3 (4.6)	6 (15)	5 (13.9)	0
Mean±SD	3176±785	3580±600	3348±739	2933±1115
Apgar score at 1′				
≤ Than 7	22 (33.8)	8 (20)	15 (14.7)	2 (28.6)
> Than 7	43 (66.2)	32 (80)	21 (58.3)	5 (71.4)
Mean±SD	7.2±2.0	7.5±1.4	7.2±1.5	7.5±0.8
Apgar score at 5′				
≤ Than 7	6 (9.2)	2 (5)	3 (8.3)	1 (14.3)
> Than 7	59 (90.8)	38 (95)	33 (91.7)	6 (85.7)
Mean±SD	8.4±2.2	8.9±0.7	8.6±1.4	8.7±0.8
Admission to NICU				
Not Admitted	56 (81.2)	35 (87.5)	25 (69.4)	6 (85.7)
Admitted	9 (13.8)	5 (12.5)	11 (30.6)	1 (14.3)
Neonatal outcome				
Alive and well	52 (80)	35 (87.5)	24 (66.7)	6 (85.7)
Dead	3 (4.6)	0	1 (2.7)	1 (14.3)
Alive with sequele	9 (13.8)	5 (12.5)	9 (25)	0
Alive with congenital abnormality	1 (1.5)	0	2 (5.6)	0

n ( ) number of cases (percentage)

Table 3 Macroscopic placental features in different groups

Placental features	Normal (n=65)	White A (n=40)	White B (n=36)	White C&D (n=7)
Height	1.75±0.5	1.92±0.4	1.82±0.6	1.76±0.5
Weight[a]	518.30±145.2	585.59±118.2	577.3±137.7	557.67±209.1
Length[b]	17.53±2.5	17.91±2.1	18.7±2.4	17.30±2.9
Breadth	14.88±2.5	15.70±1.9	15.6±2.3	15.70±3.1
Surface area[c]	260.26±65.2	282.39±53.5	292.5±69.4	278.60±91.8
Volume[d]	453.68±184.0	550.87±147.7	525.3±209.2	504.4±227.3
Perimeter[e]	64.15±8.9	66.97±6.9	68.5±8.1	66.0±11.9
Cord length[f]	43.15±16.0	56.28±16.5	47.7±17.8	45.83±18.9

Numbers are mean±standard deviation
[a] Normal vs A&B; $p<0.01$ & <0.05 by students t-test)
[b, c, e] (Normal vs B; $p<0.05$ by student t-test
[d] Normal vs A; $p<0.01$ by student t-test
[f] Normal vs A; $p<0.0001$ by student t-test)

Table 4 Microscopic placental features in different groups

Placental features	Normal (n=65)	White A (n=40)	White B (n=36)	White C&D (n=7)
Maternal floor infarction	2 (3.1)	1 (2.5)	1 (2.8)	0
Intravascular thrombosis	1 (1.5)	1 (2.5)	1 (2.7)	0
Placental inflammation	18 (27.7)	8 (20)	7 (19.4)	3 (50)
Placental infarction	21 (32.3)	14 (35)	11 (30.6)	2 (33.3)
Placental dysmaturity	5 (7.7)	6 (15)	2 (5.6)	3 (50)
Placental calcification	27 (41.5)	8 (20)	7 (19.4)	2 (33.3)
Funisitis	1 (1.5)	1 (2.5)	1 (2.7)	0
Chorio-amnionitis	1 (1.5)	2 (5)	2 (5.6)	1 (16.7)

n ( ) number of cases (percentage)

Discussion

Our results showed that advanced maternal age and grandmultiparity were important factors that were associated with all the diabetic groups according to White's classification. Mothers in the White's group A and B weighed more than the control group; however, the mean weight of the mothers in White's group C&D did not differ significantly from the control group. This could be due to the fact that obesity is a risk factor for gestational diabetes (White's group A) and that most patients in White's group B have type II diabetes mellitus (non-insulin dependent or adult onset diabetes) which is also associated with obesity. Whereas mothers in White's groups C&D are mostly tpye I diabetic (insulin dependent or juvenile diabetes).

In pregnancies complicated by diabetes the major concerns are fetal distress and potential for birth trauma associated with macrosomia. Therefore, both preexisting and gestational diabetes increase the risk for cesarean delivery. In our study the percentage of operative delivery was higher in the White group A (12.5%), White group B (27.8%) and White group C&D (28.6%) than the control group (9.2%). Studies have reported that diabetic women give birth to their children at an early gestational age [2, 11, 17]. The average gestational age in White's group C&D was lower than the control group ($p<0.06$). Gestational age at birth in White's groups A and B did not differ significantly from the control group. The lower gestational age at delivery in White's group C&D could be iatrogenic. Such patients often need termination of pregnancy because of complications such as poor glycemic control, intrauterine growth restriction or abnormal results of tests for fetal well-being.

The macroscopic appearance of placental tissue usually reflects the severity of diabetes. In cases of gestational diabetes and pregestational diabetes without maternal vasculature disorder, the placenta is larger and heavier than in normal pregnancy [4]. This is mainly due to an increase in cell number as indicated by the DNA content. The size of the cell remains unchanged [3, 21]. In more advanced stages of pregestational diabetes, frequently associated with intrauterine growth restriction, placenta seems to be smaller [21]. In our study, the birth weight of babies born to mothers in the White group A and B were heavier than the control group and White's group C&D. Similarly the placental weights of mothers in White's group A and B were significantly higher than the control group and White's group C&D. Thus, placental weight and neonatal weight appeared to be influenced by the duration and severity of vascular complications of diabetes.

One of the most consistently reported microscopic finding in placentas from diabetic mothers is the immaturity of chorionic villi [5, 6]. Accelerated maturation has been described in some large placentas from diabetic mothers [12, 15]. Immature villi, normal villi and villi of advanced maturity can be observed from region to region in normal and abnormal term placentas [7, 9, 16]. There-fore, features of maturity can only suggest but are not diagnostic of diabetes [13]. Studies have shown that retarded maturation of terminal villi in gestational diabetes is less pronounced than in overt diabetes [19]. In our study 15% of placentas from White group A showed dysmaturity as compared to 42.9% of the placentas in the White group C&D, however, this was not statistically significant (Table 3). This could be due to the small number of placenta with placental dysmaturity in each group.

Another common finding in the diabetic placenta is fetal artery thrombosis the cause of which remains unknown [8]. We found no significant difference in cases with intravascular thrombosis in the control group (1.5%) compared to other groups. This could be explained by the fact that we had a small number of patients in White's groups C&D (7 patients) and this group are more likely to manifest this findings. Also, patients in this group delivered at an earlier gestational age.

The frequency of villitis varies in different countries. In our study it was 21.7% in all the diabetic groups combined as compared to 7.6% in Australia, 9.0% in Canada, 13.6% in England, 33.8% in Argentina and 6.0% in U.S.A. [10]. However, in our study there was no significant difference in the incidence of villitis in the control group and the other groups. Villitis is frequently associated with pre-eclampsia, intrauterine growth restriction, maternal auto-immune disease and recurrent spontaneous abortion. This finding is not specific for diabetes and is, therefore, equally distributed among the cases and controls.

The reported frequency of maternal floor infarction ranges from 0.09% to 0.5%. It is associated with a high rate of fetal mortality and intrauterine growth restriction [1]. Although we reported only severe cases, the frequently of maternal floor infarction in our study was 3.1% in the control group, 2.5% in White A group, and 2.8% in White group B. There was no case of maternal floor infarction in White's groups C&D. In spite of the fact that the frequency of maternal floor infarction in our study is higher that that previously reported we did not have any case of intrauterine fetal death among the diabetic patients. This could be a reflection of better testing of fetal well being and successful obstetrical intervention at an earlier gestational age.

Studies have shown that placental infarcts are common in placentas from pregnancies complicated by diabetes [13]. Driscoll states that the number of infarcts is increased if the maternal diabetes is severe (e.g. White's classes D, F, R) but not otherwise [5], In our study we found infarction in 35% of placentas in White group A, 30.6% in White group B, 33.3% in White groups C&D and 32.3% in the control specimens. These findings correlate with what was reported in previous studies.

In conclusion, the placental weight and neonatal weight were increased provided the diabetes was not complicated by vascular disease as seen in White groups A and B. With accompanying vascular disease (White groups C&D) the placental weight and neonatal weight

were reduced compared to the controls. As a result of increased perinatal jeopardy the rate of operative delivery was higher in all the White's classification groups compared to the control group. No major difference was observed in microscopic changes of placentas in different groups according to White's classification and the control group.

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