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GESTATIONAL DIABETES MELLITUS LEAD TO HISTO PATHOLOGICAL CHANGES IN PLACENTA IN NORTH INDIA

[*1]Dr. Rakesh Kumar Shukla, [2]Dr. R. K Srivastava, [3]Dr. Anil Kumar, [4]Dr. Archana Mishra

[*1]Ph.D Scholar, Department of Anatomy, Rama Medical College, Kanpur, UP, INDIA
[2]Principal & Guide, Rama Medical College, Kanpur, UP, INDIA
[3]Assistant Prof. Central Research Lab, Rama Medical College, Kanpur, UP, INDIA
[4]Lecturer, Department of Biochemistry, MLN Medical College, Allahabad, UP, INDIA

Abstract: **Gestational diabetes mellitus (GDM) is a common metabolic complication in pregnancy affecting the maternal and foetal wellbeing.**
Aim: - The aim of this original research article is to investigate the histological changes in placenta of GDM and control women.
Method: - This study was done in Rama Medical College & Hospital Kanpur. Placenta sample from 50 cases of GDM and 150 of control women collected and histological changes studied.
Result: - In this study, the histological changes revealed that Fibrin was in 78% of GDM. Calcification was seen in 42% of GDM. Infarction was found in 4% of GDM. Chorioamnionitis was in 18% of GDM, but in control the histological changes revealed Fibrin in 40%, Calcification was 25.3%, Infarction was 4% and Chorioamnionitis was in 32%.
Conclusion: - Gestational diabetes mellitus causes significant histological changes but chorioamnionitis remains insignificant.

Keywords: **GDM, Gestational diabetes mellitus, Placenta, Fibrin, Calcification, Infarction, Chorioamnionitis.**

1. INTRODUCTION

Placenta is circular, discoid organ. The development of this is directly affected by the maternal health conditions. It also affects the intra-uterine status of the foetus. It is a structure where maternal and foetal tissues come in direct contact. It also suggests the immunological acceptance of foetal graft by the mother. Placenta is a potent endocrine, immunologic and metabolic organ. It is also responsible for nutrition, respiration and excretion for the foetus (Datta, 2007)[1].

Diabetes mellitus (DM) is one of the major actual public health issues consisting of chronic hyperglycaemia which can damage body organs and systems (Karamanou et al, 2016)[2]. Gestational diabetes mellitus (GDM) is the most common metabolic disorder of pregnant women with an estimated prevalence ranging from <1% to 28%. However, in the countries where universal screening is recommended, the percentage of pregnant women screened ranges from 10% to >90% (Jiwani et al, 2012)[3].

The prevalence of GDM in women in Asian countries is between 3.0-21.2%. The risk of developing GDM for South-Asian women is higher than the South East Asian and the East-Asian women (Chu et al, 2009; Yuen and Wong, 2015)[4,5].

Among different ethnicities, also mother and child outcomes have important variations. Newborns from Pacific Island countries have higher rates of macrosomia. However, children with Chinese backgrounds have lower adverse outcomes (Yuen and Wong, 2015)[5].

Aim and Objectives:

The aim of study was to observe histopathological changes in placenta of gestational diabetes mellitus pregnancy and control pregnancy in north Indian population.

2. MATERIAL AND METHODS

Study site:

The study was conducted in the Department of Anatomy and Gynecology, Rama Medical College & Hospital Kanpur.

Study population:

Placentas of full-term and preterm pregnancy were collected from labor room of Rama Hospital, Rama Medical College Kanpur of all reproductive age. Placentas of Gestational diabetes mellitus (GDM) and control women's were studied for histological changes.

Study design:

Case-control

Sample size:

50 cases of GDM and 150 as a control included in the study.

Study duration:

Thirty months plus Six months of course work.

Inclusion criteria:

- Gestational Diabetes mellitus

Exclusion criteria:

- Pre-existing Diabetes mellitus (IDDM-Type 1)
- Pre-existing Diabetes mellitus (NIDDM-Type 2)
- Chronic hypertension
- Essential hypertension
- Chronic renal disease (renovascular)
- Coarctation of aorta
- Pheochromocytoma
- Thyrotoxicosis
- Connective tissue disease-systemic lupus erythematosus
- Twins pregnancy

Methods:

Pregnant women were diagnosed with GDM under the standard protocol of Diabetes in Pregnancy Study Group India (DIPSI) and WHO. In the antenatal clinic, a pregnant woman after undergoing preliminary clinical examination had given a 75 g oral glucose load, irrespective of whether she had fasting or nonfasting state and without regard to the time of the last meal. A venous blood sample was collected at 2 hours for estimating plasma glucose by the GOD-POD method. GDM was diagnosed if 2-hour PG is ≥ 140 mg/dL.

Gestational weeks for Screening Recommended:

Following the usual recommendation for screening between 24 weeks and 28 weeks of gestation, the chance of detecting unrecognized type 2 diabetes before pregnancy (pre-GDM) is likely to be missed. If the 2-hour PG is > 200 mg/dL in the early weeks of pregnancy, she may be a pre-GDM and A1C of ≥ 6.5 is confirmatory. A pregnant woman found to have normal glucose tolerance (NGT), in the first trimester, should be tested for GDM again around 24th–28th weeks and finally around 32nd–34th weeks.

Methodology followed for Histological Examination:

- Two cm wedge of tissue required for histopathology from

a. Maternal & fetal surface 2 cm from periphery

b. Maternal & Fetal surface from centre

- Tissue packed in disposable cassettes with proper labeling.

Processing:

- Tissue processing were done under automated tissue processing machine, the Thermo Scientific™, Excelsior AS^{TM}

Embedding:

- Embedding done using automated Tissue-Tek TEC Machine.
- Placed the base mould over Tissue-Tek for 2 hrs.

Freezing:

- Paraffin blocks were stored at 0^0C 2hrs for 30 minutes.

Trimming:

- Trimming was usually done at thickness between 10 and 30 µm with the help of Leica RM 2125 RT microtome.

Section Cutting:

- Used the adjusting knob on the right side of the Leica RM 2125 RT microtome front panel to select the 5-micron section thickness.

Hot Water Bath:

- Picked the ribbon gently to the MAC tissue floater hot water bath and attached a single floating film of paraffin at the midway of the slide.

Deparaffinization:

- This is done by placing the slide over Macro Scientific slide warming table at 60^0C for 20 min.

Staining:

- This is done by automated tissue strainer Tissue-Tek DRS.

Cover Slip:

- Slide covered by cover slip and prepared for microphotography.

Histological appearances of placentas assessed for:-

- Fibrin deposition, Calcification, Infarction and Chorioamnionitis.

Microphotography:

- Microphotography done with Magnus theia – I trinocular digital microscope.
- Slide observed at 100X and 400X.

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Microphotographs:

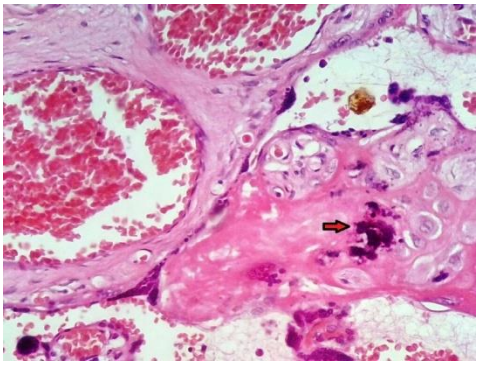

Fig. 1: Microphotograph of Peripheral Fetal Surface In GDM. Showing Areas of Calcification. H-E Stain at 400X.

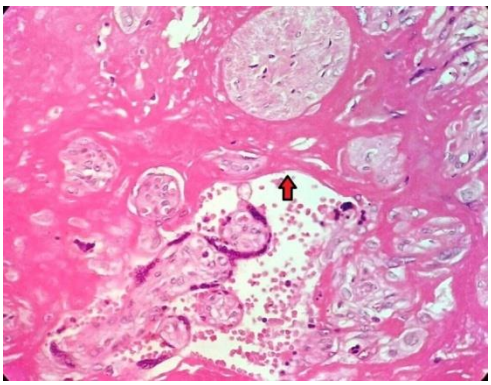

Fig. 2: Microphotograph of Peripheral Fetal Surface In GDM showing area of intervillous fibrin deposition. H-E Stain at 400X.

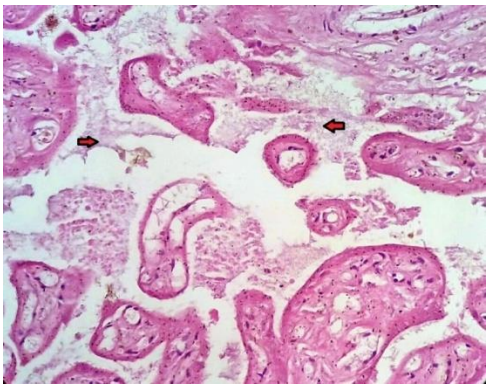

Fig. 3: Microphotograph of Central Fetal Surface In GDM Showing areas of inter villous necrosis. H-E Stain at 400X.

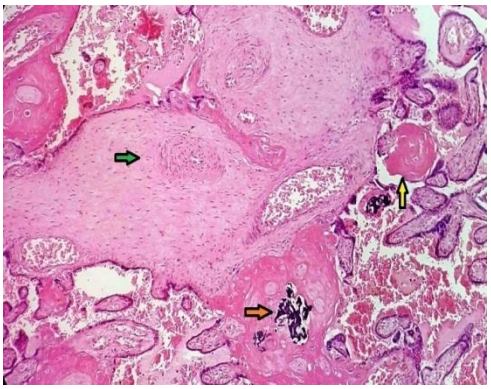

Fig. 4: Microphotograph of Peripheral Maternal Surface In GDM Showing areas of calcification (orange arrow), fibrin (yellow arrow) And fibrosis (green arrow). H-E Stain at 400X.

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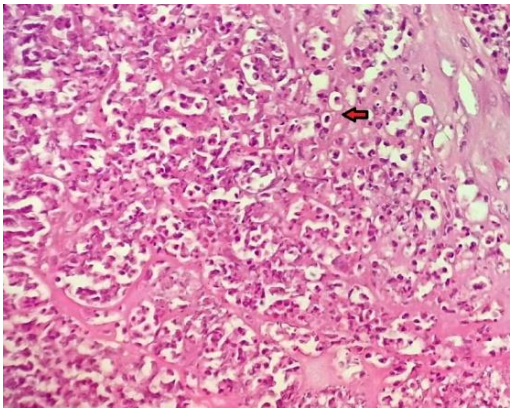

Fig. 5: Microphotograph of Central Maternal Surface in GDM showing areas neutrophilic infiltration coressponding to chorioamnionitis. H-E Stain at 400X

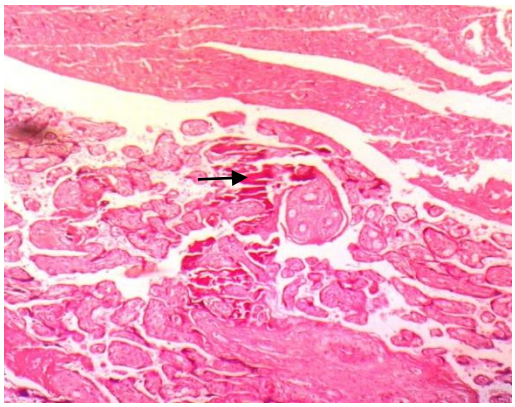

Fig. 6: Microphotograph of Peripheral Maternal Surface Showing Calcification in Control. H & E Stain at 100X

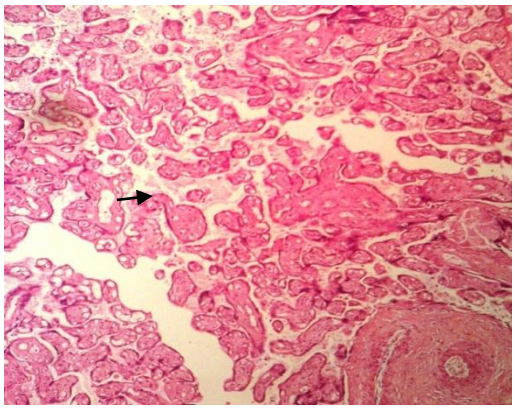

Fig.7: Microphotograph of Central Maternal Surface Showing Fibrin Deposition In Control. H & E Stain at 100X

3. OBSERVATIONS AND RESULTS

The present study was undertaken to find out the histological changes in the placenta of GDM and Controls women. A total of 50 cases of GDM and 150 controls were included in the study.

TABLE I: Comparison of maternal age among the groups

Groups	**Age in years (Mean±SD)**
GDM	31.28±1.99
Controls	28.44±3.03
p-value[1]	0.09

[1]ANOVA test

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TABLE II: Comparison of OGTT between the groups

Groups	OGTT (mg/dl) (Mean±SD)
GDM	186.50±15.02
Controls	97.15±10.05
p-value[1]	0.06

[1]ANOVA test

TABLE III: Comparison of parity among the groups

Parity	GDM (n=50)		Controls (n=150)		p-value[1] GDMvs Controls
	No.	%	No.	%	
Nullipara	2	4.0	28	18.7	0.0001*
Primipara	9	18.0	34	22.7	
Multi para	39	78.0	88	58.7	

[1]Chi-square-test, *Significant

TABLE-IV: Comparison of histological changes among the groups

Deposition	GDM (n=50)		Controls (n=150)		p-value[1]
	No.	%	No.	%	GDMvs Controls
Fibrin					
Yes	39	78.0	60	40.0	0.0001*
No	11	22.0	90	60.0	
Calcification					
Yes	21	42.0	38	25.3	0.0001*
No	29	58.0	112	74.7	
Infarction					
Yes	2	4.0	6	4.0	0.0001*
No	48	96.0	144	96.0	
Chorioamnionitis					
Yes	9	18.0	48	32.0	0.09
No	41	82.0	102	68.0	

[1]Chi-square-test,*Significant

4. DISCUSSION

In the present study, In this study, the mean age of GDM cases was 31.28±1.99 years. Ana et al (2012)[6] reported the mean age of the GDM women being 28.5±5.71 years. The mean age of controls in the present study was 28.44±3.03 years.

Maternal age is proven risk factor for GDM. But there is no consensus on the age after which there is significantly increased the risk of GDM. In the literature, the lowest cut off is ≥25 years as recommended by the American Diabetes Association.

In the present study, In GDM, 78.0 % multipara, 18.0 % primipara and 4.0% nullipara cases found in this study. Ana et al (2012)[6] found that there was a higher proportion of multigravida than secundigravida and primigravida women (23 cases [37.1%], 11 cases [17.7%], and 9 cases [14.5%], respectively) among women with GDM.

In the present study, OGTT was significantly (p=0.0001) higher among GDM (186.50±15.02) patients compared to controls (97.15±10.05).In a study (Havagiray et al, 2016)[7] found that OGTT was significantly higher in GDM cases compared to control.

In GDM, many biologic and molecular mechanisms of regulating glucose levels are involved. It has been demonstrated that inadequate decrease of the renal threshold for glucose (RTG) that is determined by the nephron's reabsorption capacity, play a role in the development of GDM. In fact, glucose is reabsorbed through sodium glucose transporters in

the proximal tubules. During pregnancy, the renal glucose reabsorption capacity reduces because of decreased glucose transporter expression leading to lower glucose elimination (Klein et al, 2014)[8].

Histological studies have revealed apparent fibrinoid necrosis and vascular lesions such as chorangiosis, and thickening of the basement membrane more frequently in placentas from pregnancies complicated by GDM. When compared with normal placentas. In other studies, poorly controlled GDM placentas have shown villous edema, fibrin deposit in the syncytiotrophoblast, and hyperplasia of cytotrophoblast. These changes have been less distinct in placentas from well-monitored diabetic mothers and hardly observed in normal cases (Gauster et al, 2011)[9].

In this study, the histological changes revealed that Fibrin was in 78% of GDM. Calcification was seen in 42% of GDM. Infarction was found in 4% of GDM. Chorioamnionitis was in 18% of GDM. Ana et al (2012)[6] demonstrated that the assessment of an association between GDM and placental changes showed that all 43 women with GDM (100%) demonstrated some sort of change in either the foetal or maternal placental surface. The most common placental changes included in study are calcification (19; 44.1%), fibrin (11; 25.6%), and placental infarction (1; 2.3%) on the maternal surface; and fibrin (35; 81.4%), calcification (4; 9.3%), and hematoma (1; 2.3%) on the foetal surface. There were no placental changes in the maternal surface in 12 cases (28%) and on the foetal surface in three cases (7%). Majumdar et al (2005)[10], studied 50 PIH cases and 50 control and found mean Infarcted area 16.5 ± 4.6, mean Calcification 33.3± 3.15 and mean Fibrinoid necrosis 11.3±2.3 in PIH and Mean Infarcted area 3.77 ± 1.87, mean Calcification 4.125± 1.15 and mean Fibrinoid necrosis 3.13±1.87 in control.

In this study, the histological changes revealed that Fibrin was in 40% of controls. Calcification was seen in 25.3% of controls. Infarction was found in 4% of controls. Chorioamnionitis was in 32% of controls. In a study (Ranga et al, 2017)[11], infarction was 6.7% of controls; Calcification was in 23.3% of controls.

5. CONCLUSIONS

- The mean age of GDM and controls was 31.28±1.99 and 28.44±3.03 years respectively.
- Primipara was in 18% of GDM and 22.7% of controls.
- OGTT was significantly (p=0.0001) higher among GDM (186.50±15.02) patients compared to controls (97.15±10.05).
- Fibrin was higher in GDM than controls.
- Calcification was higher in GDM than controls.
- Infarction was found in same percentage in GDM and controls but lowers than other histological changes.
- Chorioamnionitis was statistically insignificant (p>0.05).

Gestational diabetes mellitus cause significant histological changes in the placenta that affects foetal and maternal well-being. This study is helpful for those who are concerned for mother and child health.

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