Original Article

Indian Journal of Forensic Medicine and Pathology
Volume 13 Number 2, April - June 2020
DOI: http://dx.doi.org/10.21088/ijfmp.0974.3383.13220.3

Analysis of Histomorphological Spectrum of Stillbirth in Diabetic Pregnancies: An Autopsy Based Study in A Tertiary Care Teaching Hospital

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How to cite this article:
Anandraj Vaithy K, Rupal Samal, Venkatraghavan ATM, et al. Analysis of Histomorphological Spectrum of Stillbirth in Diabetic Pregnancies: An Autopsy Based Study in A Tertiary Care Teaching Hospital. Indian J Forensic Med Pathol. 2020;13(2):254–262.

Abstract

Background: Forensic Pathology remains a mainstay in diagnosing all forms of fetal death including stillborn and it is an indispensable tool in the process of evaluating the underlying cause of death. Diabetes mellitus (DM) being a common clinical condition with hyperglycemic state, it has a major impact on the growing fetus during gestation causing several morbidities including still birth. Histopathological evaluation of the systemic organs yields adequate information of the etiopathogenesis for the cause of death thereby aiding clinicians to proceed with further management and counselling to the parents

Methodology: The study was conducted between 2012 to 2020 covering 25 cases. The cases were categorized into 2 groups like Diabetes in Pregnancy (Type 1 & Type 2 DM) and Gestational Diabetes Mellitus (GDM). Complete clinical data including diabetic profile were documented. Routine fetal autopsy procedure was performed and the major systemic organs involved in metabolism like Liver, kidney, pancreas and lungs were weighed and analyzed for histomorphological changes**.**

Results: The study analyzed 25 cases which showed 5 cases each in Type 1 & Type 2 DM and 10 cases in GDM. Renal changes in fetuses were prominent in GDM compared to other groups. Histomorphological changes in the form degenerative features in liver, pancreas and lungs were more in common in GDM

Conclusion: Gestational Diabetes mellitus stays as a rampant condition leading to major cause for still birth compared to Type 1 & 2 DM. It had been evident that GDM is not an homogenous set of disease and a subset of conditions especially pre-existing but left undiagnosed could be a potential risk for growing fetal malformations with subsequent organ failure and stillbirth

Keywords: Fetal autopsy; Diabetes mellitus; Histomorphology; Still birth.

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Received on 08.04.2020, **Accepted on** 08.06.2020

Introduction

In the modern fraternity of medicine with many innovative interventional procedures for various disease conditions, fetal death still remains rampant and a formidable condition to deal for both Clinician and patients as well.[1,2] Fetal death is defined as 'a death that occurs before complete expulsion or medical interventional extraction of products of conception which is independent of gestational period and it is marked by no evidence signs of breathing, heartbeat, or signs physical mobilization of muscular movement.[3]

The incidence of fetal mortality is still on higher margin and it is denoted by[4]

$$\text{Fetal deaths} = \frac{\text{Number of fetal deaths encountered} \times 1000}{\text{Sum of live births and fetal deaths in a given number of population}}$$

Neonates and fetuses in India are highly vulnerable and it had been estimated that nearly one quarter of overall global deaths occurs in India which is highest among worldwide ratio constituting a sum of 0.80 million deaths per year.[5,6]

While many morbidities contribute to this high incidence, toxemic pregnancies is among the leading cause mostly attributed to maternal factors. Perinatal mortality is one among the consequent and it is applied as a tool to measure as the indicator of heath care status as a quanta due to the existing paucity of framework and guidelines in estimation of still births.[7]

World Health Organization (WHO) states still birth as 'loss of fetus that occurs post 20 weeks of gestational period subject to restriction to mothers with documentary evidence of biochemical confirmation of Gestational diabetes mellitus or condition of diabetes in pregnancy'.[1,8] There are several identifiable contributory factors for stillbirth which includes increased suboptimal glycemic index either in form of Gestational diabetes mellitus (GDM) or diabetes mothers in pregnancy (DIP); Maternal obesity, maternal smoking habits, gestational hypertension and subsequent pre-eclampsia, teratogenic medications (pre-conception) etc.[9,10]

Among the known factors GDM tops the table as a potential etiology for still birth in adjunction with other risks like lethal malformations, twin pregnancy and its associated morbidities, macrosomia, intrapartum hypoxia, intrauterine growth retardation, chromosomal abnormalities, maternal infections, low for gestational age, bad obstetric history and fetal medical conditions.[11,12]

Diabetes mellitus is defined as a spectrum of 'metabolic disorder characterized by high blood glucose levels owing to lack of adequate production or peripheral action of insulin in the body.[13,14] Gestational diabetes mellitus being the most commonly encountered medical related complication of pregnancy, WHO defines GDM as 'any grade of glucose intolerance which had been primarily recognized and proved by laboratory tests during time of pregnancy.[15,16] The prevalence of pre-existing DM in pregnancy (DIP) is just 1–1.5% whereas GDM accounts for a massive alarming figure of 9–25% of pregnancies in in India.[17,18]

Hyperglycemic state in utero in early pregnancy state is known to adversely impair organogenesis like renal, liver and pancreatic development.[18] Though radiological investigations are available to measure the organ damage, histopathological examination of organs of fetal autopsy stays as standard method of documenting the systemic organ damage occurred due to GDM.[19] A systemic analysis to work on the causes of still birth in GDM mothers identified systemic impairment of organs as major cause for still birth and its morbidities.[8,20]

Still birth and neonatal death seems to represent extremes of spectrum of morbidities, autopsy examination still remains as a nodal procedure of examination for integration of medical knowledge.[21,22] Various data available on GDM focusses only on clinical parameters and outcomes whereas in Indian context very sparse studies were carried out to analyze risks of GDM associated still birth in general population.[23,24] Systemic organs like liver, kidney, pancreas and lungs are known to be active metabolic and it is directly in association with DM related changes.[25] Hence the present study was conducted with a novel aim to analyze the histomorphological changes of renal, liver and pancreas on fetal autopsy in still birth from GDM mothers and propose guidelines on preventive measures and counselling to parents for subsequent pregnancies.

Materials and Methods

The study was conducted at Mahatma Gandhi medical college & Research Institute and all fetal autopsies performed during May 2012 to January 2020, was included for the study data collection. The study enrolled only cases which were directed to fetal autopsy at parents request after obtaining clear written consent and Institute Ethical clearance was obtained to collect data from medical records.

Inclusion criteria

Cases referred to routine fetal autopsy due to still birth from mothers having Diabetes/GDM at parents request to identify the underlying pathology

Exclusion criteria:

Intrauterine fetal death.

Data collection: Clinical and laboratory data collected was prescribed proforma which maternal

and pregnancy clinical details. Diabetes mellitus and Gestational diabetes was defined as per WHO guidelines and diabetic characteristic included type of diabetes (Type 1 Type 2); which were labelled as 'diabetes in pregnancy (DIP) and Gestational diabetes mellitus (GDM); HbA1c levels (preconception, early and late pregnancy levels), duration of diabetes, medication history and maternal smoking status. Still birth was defined as per WHO criteria and contributory (if any) were also documented.

All the procedures were carried out according to standard operating protocol. Anthropometric measurement was recorded by external examination. An 'I' incision was taken and en bloc dissection was done followed by internal examination of gross analysis of systemic organs. The organs were weighed, sectioned for further histopathological examination. The subjected tissue was processed by automated tissue processor, tissue blocks were prepared by paraffin embedded tissue blocks and stained with hematoxylin and eosin to analyze the microscopic features.

All the routine organs were analyzed as a routine evaluation and microscopical features of systemic organs like kidney, liver, pancreas and lungs which have major association and impact due maternal diabetes were documented in formatted proforma. The observed data were analyzed using descriptive statistics and the results were represented in terms of mean ± SD. In specifications, *p*-value was calculated and values <0.005 was taken to be significant

Results

A total of 25 cases of fetal autopsy which were referred to fetal autopsy by Clinicians at parents request were studied during the 7 years study which satisfied the inclusion criteria of still birth with GDM.

Most of the maternal age ranged between 23 to 27 among Type 1 & Type 2 DM whereas GDM majority of patients were elderly primigravida. HbA1c levels were reasonable under control in Type-2 DM compared to Type 1 DM in all the 3 trimesters. Whereas in case of GDM, HbA1C was in poor control in early pregnancy and was in control during later stages of pregnancies. As evident Type 1 DM were on insulin whereas Type-majority of cases (n = 4) were on oral medications. Still birth took place very early in case of Type 1 DM as early as 26 weeks and little later in Type 2 DM around 29 weeks of gestation. GDM still birth took place around 32 weeks of gestation. The general maternal clinical parameters and Diabetic characteristics were analyzed and the results were depicted in (Table 1).

Table 1: Analysis of clinical characteristics and Diabetic profile of the study parameters

Maternal parameters	Diabetes in Pregnancy (Type 1) (n = 5)	Diabetes in Pregnancy (Type 2) (n = 5)	GDM (n = 15)
Age (in years)	23 ± 3	25 ± 4	32 ± 2
Gravid status			
(i) Primigravida	04	03	08
(ii) Multigravida	01	02	06
Duration of diabetes	15 ± 3 years	5 ± 3 years	–
HbA1c levels			
(i) Pre-pregnancy	10 ± 2.2	6.3 ± 1.2	NA
(ii) Early pregnancy	8.2 ± 3.6	6.2 ± 1.6	8.1 ± 1.2
(ii) 3rd trimester	7.7 ± 2.7	5.7 ± 1.7	6.3 ± 1.6
Medication history			
(i) Insulin	07	01	–
(ii) Oral hypoglycemic drugs	–	04	
Gestational age at time of still birth	26 ± 3 weeks	29 ± 3 weeks	32 ± 4 weeks

Systemic organs were routinely evaluated under light microscopic observations for histopathological analysis. Renal changes was more commoner in GDM cases whereas equally common in Type 1 & 2 DM. similar findings were noted in systemic organs like liver, lungs and pancreas. Organs like kidney, liver pancreas and lungs were documented for histomorphological changes according to each diabetic category as shown in (Table 2).

Table 2: Histomorphological changes of systemic organs according to diabetic profile

Histomorphology of systemic organs	Type 1 DM (*n* = 5)	Type 2 DM (*n* = 5)	GDM (*n* = 15)
Kidney			
Glomerular changes-shrunken	02	01	08
Vacuolar degeneration	01	01	03
Hyalinization	–	01	03
Liver			
Distortion of architecture	01	01	07
Centrilobular necrosis	–	01	05
Lung			
Dilated alveoli & airspaces	01	01	07
Atelectasis	–	01	02
Fibrosis	–	–	04
Pancreas			
Decreased beta cells	01	01	07
Atrophied islet cells	–	01	04

In context to anthropometric measurements, kidney, liver and pancreas showed decreased in weight from their average expected weight in reference to gestational age as shown in (Table 3).

Table 3: Anthropometric values of systemic organs-weight (in grams)

Gestational age (in weeks)	Kidney weight (grams)			Liver weight (grams)			Pancreas weight (in grams)		
	DM 1	DM 2	GDM	DM 1	DM 2	GDM	DM 1	DM 2	GDM
26 ± 3 weeks	90 ± 10	120 ± 20	100 ± 20	120 ± 10	115 ± 20	110 ± 20	1.2. ± 0.2	1.1 ± 0.2	0.9 ± 0.02
29 ± 3 weeks	100 ± 15	125 ± 25	110 ± 20	130 ± 15	135 ± 25	115 ± 20	0.9 ± 0.3	1.2 ± 0.3	1.1 ± 0.02
32 ± 4 weeks	110 ± 15	130 ± 10	110 ± 15	140 ± 15	135 ± 10	115 ± 15	1.1 ± 0.2	1.4 ± 0.2	1.3 ± 0.2

Placenta being the nutrient supplying tissue to the growing fetus, placenta villi are more commonly affected with degenerative changes indicating hypoxia and its sequelae of morbidities. Various placental lesions noted in diabetic pregnancies are shown in (Table 4).

Table 4: Degenerative Changes in Placental &Villi on Histomorphology

Villous Lesions	Type 1 DM (*n* = 05)	Type 2 DM (*n* = 5)	GDM (*n* = 15)
Syncytial Knots	03	02	09
Villous Stromal Fibrosis	02	02	10
Fibrinoid Necrosis	02	03	11
Intervillous Hemorrhage	–	01	10
Membrane-Chorioamnionitis	02	03	11

Discussion

Autopsy being a dissection procedure, it still remains as focal point in imparting medical knowledge and providing critical parameters for quality assurance and effective implementation.[1,2] Therefore, medical knowledge of the gamut on underlying etiology of stillbirth in Indian demographical perspective is essential since it ensures appropriate facilities and guidelines to enhance the survival of growing fetus.[2,3]

The term 'Forensic Gynecology' refers mainly to medical cases and with regard to diagnostic aspects fetal autopsy for various indications serves as a major stay to identify underlying etiopathogenesis for fetal death, especially in case of still birth followed by Intrauterine deaths.[4] In recent times majority of parents opt themselves

for subjecting still birth fetus for autopsy studies for getting acknowledged with cause of death and get awareness and counselling for subsequent conceptions.[5,6]

The association between diabetes and its impact on pregnancy was first described Sir. Vincent in the year 1987 by conducting a case control studies.[7] After few decades, the incidence of stillbirth and congenial deformities heaped up to 4–6 times in diabetic associated pregnancies in Indian population.[7,8] In our hospital, the incidence of GDM and its associated morbidities was marginally higher compared to other domains.

Several studies had been commissioned to analyze the etiopathogenesis for higher incidence of GDM complications and most of the studies documented placental lesions followed by systemic organ dysfunction was the predominant cause for the alarming rate.[9] Interestingly, the rate of malformations was lower compared to rate of unexplained still births, thereby warranting need for additional studies in analyzing systemic organ pathology. In modern era after advent of many innovations, there was no decline in the rate of stillbirth in Diabetic cohort and it was still consistence in prevalence both in aspect of incidence and causes as well.[10,11]

The major reason of all abnormalities noted in diabetes in pregnancies (DIP) being sub-optimal glycemic control, HbA1c is considered as gold standard for assessing average blood glucose control in the preceding 5–11 weeks.[12] In recent times it had become as routine examinations irrespective of signs or history, that all antenatal women should undergo HbA1c tests especially in early to mid-gestation period.[13] In the present study, GDM cases showed poor control compared to Type 1 & 2 DM. The reason attributed is delayed presentation for undergoing blood tests and unawareness of the sequelae of complications. The observations are in concordance with prior studies done in the same geographic domain.[8]

In the present study, the anthropometric measurements in terms of weight showed that slight marginal increase in the weight than the expected average. The observations are in concordance with prior studies which postulates that existence of renal hypertrophy and hyper function as a compensatory mechanism. Since maternal hyperglycemic status triggers fetal hyperinsulinemia that eventually leads to enhanced glucose utilization, increased fat deposition and aminoacids production leading to hypertrophy of tissues. Recent studies have proposed that chemical mediators like insulin-like growth factors and fibroblasts growth factors may contribute for organomegaly in growing fetus of GDM.[14,15]

Histomorphological studies of kidney showed abnormal glomerular structural changes [atrophied glomeruli] as evidenced by gradient tubules to glomerular ratio, indicating retarded renal function of the growing fetus (Fig. 1).

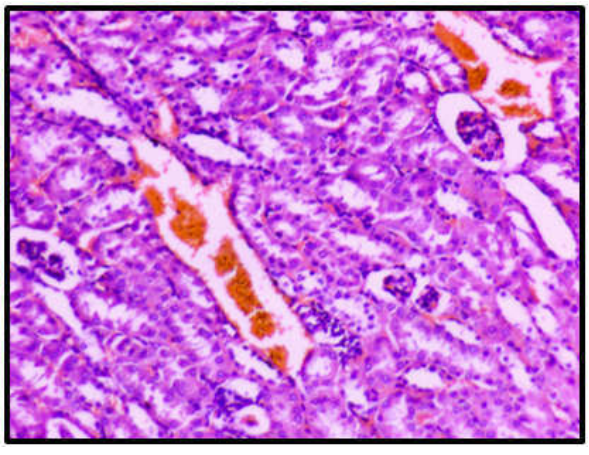

Fig. 1: Histomorphology of kidney showing shrunken glomeruli and decreased glomerular structures with congested vessels, H&E, 40X.

The glomeruli are shrunken in 8 cases (n = 15) pertaining to GDM fetuses followed by 2 cases in Type 1 & one case in Type 2 DM (n = 5 cases each). The observations are in concordance with previous studies.[15,16] The kidneys were also observed to be exposed to degenerative changes like vacuolation and hyalinization of the stroma and tubules (Fig. 2) with high incidence in GDM

followed by DIP concurring with prior studies done by Naik et al.[16] It was evident from the present study that renal pathology is more pronounced in fetuses of among GDM mothers compared to DIP. Eventually diabetic embryopathy affects other developing organs especially urinary tract system leading to congenital renal malformations, hydronephrosis and ureteric lesions. The reason attributed to high incidence of renal abnormalities in GDM is due to sub-optimal blood glucose level despite treatment modalities which led to loss of inadequate circulation of nephrons structure owing to the cause that renal blood vessels shrink with turbulent blood supply leading to glomerular shrinkage.[17,18] In 2 cases, tubular hypertrophy was observed which is explained by the fact that 'compensatory and adaptive 'mechanism. Thus renal pathology is a major concern in GDM as well as DIP with more alarming rate in former cases.

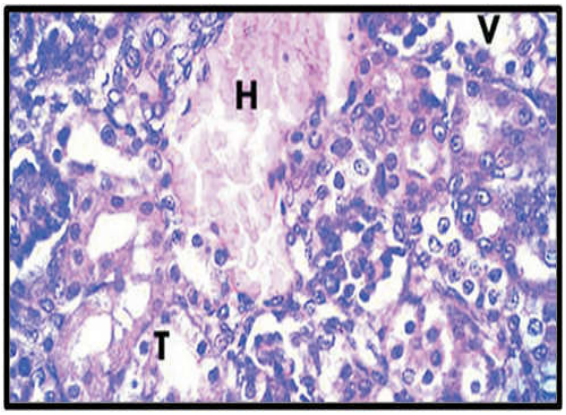

Fig. 2: Histomorphology of Kidney showing degenerative hyalinization (H), vacuolation (V), atrophic tubules (T), H& E, 40X.

Liver being a primary metabolic organ, it was subjected to many degenerative changes with high margin in fetus of GDM mother (12 cases, *n* = 15) compared to DIP. The pathological changes were denoted in the form of distortion of lobular architecture and necrosis indicating loss of blood supply (Fig. 3). Eventually all the metabolic activities are altered leading to systemic organ failure.[19,20] The observations were in concordance with previous Researchers that the mechanisms of reducing glucose output by liver, augments glucose uptake in the peripheral tissue since majority of GDM mothers were under Metformin treatment.[20,21]

Lungs being a major organ in pulmonary system, lung lesions were noted in the form of atelectasis and fibrosis more in GDM (13 out of 15 cases) followed by DIP leading to evidence of respiratory distress The reason for distress being inadequate circulation, prematurity and hypoplasia in the form decreased alveolar counts concurring with prior studies.[22] Microscopically, features showed irregularly dilated alveoli with septal fibrosis into the alveolar lumen (Fig. 4).

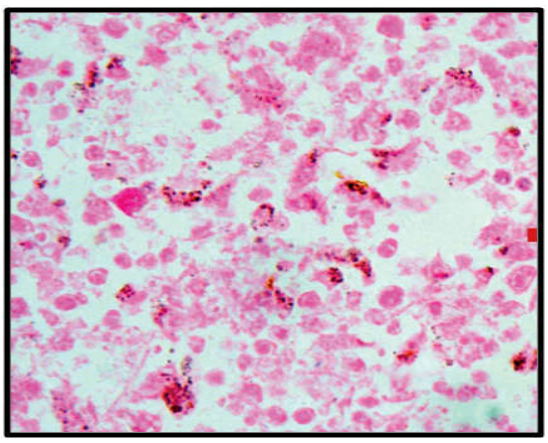

Fig. 3: Histomorphology of Liver Showing Complete Distortion of Architecture With Necrosis, H&E, 40X.

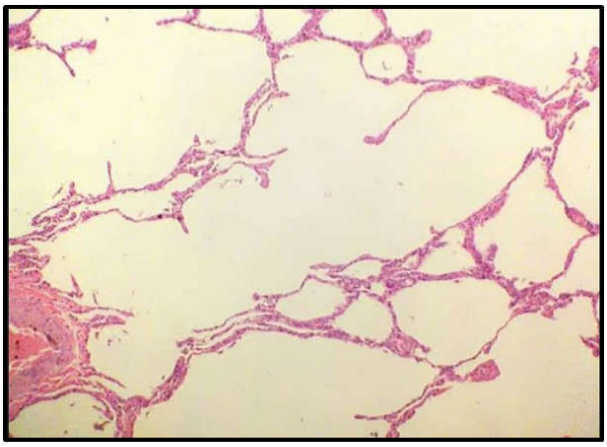

Fig. 4: Histomorphology of lung showing septations of alveoli and irregularly dilated alveolar spaces with evidence of atelactasis, H&E,4 0X.

Pancreas being an endocrine organ with primary function of secreting insulin from beta cells, our results showed decrease in the counts of beta cells and islet cells in the form of atrophy. The production of insulin denovo in fetuses in decreased more in GDM compared to DIP concurring with prior Research analysis.[23,24]

Placental being the dynamic gestational organ, it showed various degenerative changes in the forms of villous fibrosis, syncytial knots and hemorrhage. The gross weight of placenta was increased relatively to normal expected weight, Chorioamnionitis was predominantly noted in majority of cases in GDM & DIP indicating high prevalence of infections in diabetic pregnancies (Fig. 5).

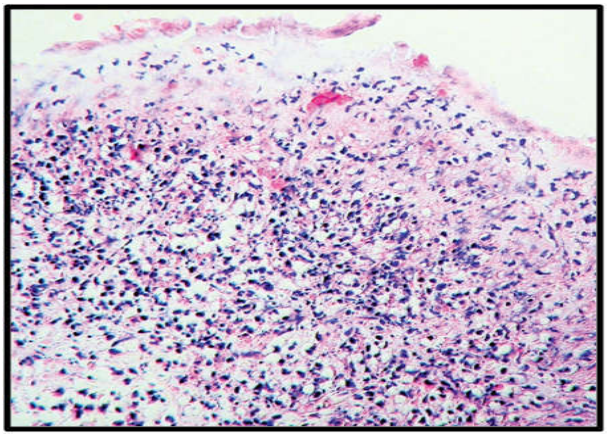

Fig. 5: Histomorphology of Acute chorioamnionitis with focal necrosis with dense neutrophilic infiltrates & cell debris with disrupted syncytial lining, H&E, 10X.

HbA1c

Hb1c being a gold standard method of assessing average glycemic control in diabetic patients for the preceding 70–110 days, it had been recommended that to do HbA1c tests at the time of conception and during the course of gestation as a follow up.[25] In the present study, HbA1c is sub-optimal among the GDM patients followed by Type1 cases and then Type 2 cases. The reason attributed for the spike in GDM is delayed presentation since majority of females do check their blood glucose as prima facie during early pregnancy only leading to difficulties in controlling in later period of gestation. Researchers had postulated that since most of the critical organogenesis would have elapsed by the time GDM or diabetes is detected, thus having an impact on growing fetus.[24,25] Recent studies had shown that, even tight control of glycemic index especially during pregnancy could have a role in

reducing risk of malformations though systemic morbidities occur in varying proportions.[25]

Critical appraisal of the study

Diabetic in pregnancy is mostly characterized by insulin resistance and also decreased secretion of insulin from pancreas and it stays as a major concern in causing congenital anomalies and fetal deaths especially with risk for still births. Diabetes remains as major factor for systemic organ failure. It had been evident that GDM is not an homogenous set of disease and a subset of conditions especially pre-existing but left undiagnosed could be a potential risk for growing fetal malformations with subsequent organ failure and still birth. The only limitation encountered in the study is lack of inadequate source for karyotyping and genetic analysis since the study was conducted in resource limited area.

Conclusion

Forensic Pathology being a nodal point of focus in picking up systemic organ failures which was left undiagnosed mortally. Fetal autopsy is a significant procedure in the domain of Forensic Gynaecology often picking up the cause of fetal death in still birth conditions. Diabetic pregnancies manifest as a serious and alarming challenge globally since the growing fetus is exposed to multiple morbidities like still birth due systemic organ failures, anomalies as evidenced in the present study. Fetal autopsy in adjunction with Histomorphology analysis of systemic organs aids the Obstetricians and Pathologists to arrive at a definite diagnosis for the cause of still birth. Feat death being an unfortunate event for the parents, Histomorphological analysis paves directions for genetic counselling and to entrust awareness among the parents for future planning of pregnancies.

Conflicts of Interests: None

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