Original Article

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Recurrent Pregnancy Wastage: Histology of Products of Conception

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ABSTRACT

Background: Histopathologic examination of products of spontaneous abortion is done to identify pregnancy-molar or ectopic. Also, in the perspective of recurrent abortion, additional diagnostic information can be obtained. We studied products of conception with the aim to find if it is of any value in recurrent pregnancy wastage.

Methods: Data was obtained from patients with the diagnosis of recurrent spontaneous abortion.The samples were examined macroscopically and microscopically by a competent histopathologist.

Results: Age of the patients ranged from 23-36 years. Majority of the recurrent abortions occurred during 10-15 weeks of gestation accounting for 41 (65.07%) cases. Recurrences ranged from third to fifth time loss contributing to 44 (69.84%), 14 (22.22%) and 5 (7.93%) cases respectively. Villous oedema of chorionic villi were seen in 30 (47.61%) cases. Abnormal vascularity in the form of complete avascularity of villi was observed in 8 (12.69%) cases. 50 (79.36%) cases showed fibrinoid degeneration. Amongst the 50 cases, 30 (60%) cases showed both perivillous and intravillous fibrin while 20 (40%) cases showed only perivillous fibrin deposition. 30 cases (47.61%) showed evidence of chronic villitis. The 30 cases were subdivided into "infectious villitis" and "villitis of unknown etiology" (VUE). Infectious villitis was seen in only 1 case (3.3%) which showed presence of toxoplasmal cysts and plasma cell infiltration. Deciduitis was observed in 31 (49.20%) cases. Decidual necrosis was seen in 23 (36.50%) cases. 3 (4.76%) cases of partial mole were diagnosed. 4 (6.34%) cases each of syncitial knots and villous infarction were seen. We did not encounter any cases of chronic intervillositis and chronic endometritis.

Conclusion: It is rational to perform histopathological examination routinely for all recurrentmiscarriages.

Keywords: *Recurrent, Abortion, Histology*

Introduction

Spontaneous abortion is defined by The United States Centers for Disease Control and Prevention and the World Health Organization as unintentional or unplanned termination of pregnancy before 20 weeks of gestation or when the weight of fetus or any products of conception is less than 500 gms [1]. Recurrent Pregnancy Loss (RPL) or Habitual Abortion is defined as "the occurrence of three or more clinically detectable pregnancy losses" prior to 20 weeks of gestation [2].

Spontaneous abortion is seen in about 10-20% of recognized pregnancies[3]. The etiopathogenesis of abortions can be understood by studying the pathology of spontaneous abortions[3]. We determined the various abnormalities of the chorionic villi (the main fetal part of the placenta serving as functional transport unit for oxygen as well as nutrition to the fetus) and the decidua in cases of recurrent spontaneous abortion.

Materials and Methods

The aim of our study was to look for the histopathological findings in products of conception of recurrent spontaneous abortion and to note if this information can be clinically useful.

This study was carried out in a tertiary care institute in the department of Pathology over a period of three years. A total of 63 cases which fulfilled the criteria of the definition of Recurrent Pregnancy Loss were included in the study. The samples of products of conception were obtained from patients admitted in our hospital in the Department of Obstetrics and Gynecology with the diagnosis of recurrent spontaneous abortion.

The samples were received in the form of fragmented bits in 10% formalin and were examined macroscopically by a histopathologist before being routinely processed and stained with Hematoxylin & Eosin stain. The sections were examined microscopically by the same histopathologist who performed the macroscopic examination. Special stains were done wherever necessary.

We tried to identify the different histopathological changes in chorionic villi and decidua in recurrent abortion.

Observations and Results

Demographic Features: A total of 63 cases were studied. The age of the patients ranged between 23-36 years. Majority of the recurrent abortions occurred during 10-15 weeks of gestation accounting for 41 (65.07%) cases.

Recurrences ranged from third to fifth time loss contributing to 44 (69.84%), 14 (22.22%), 5 (7.93%) cases respectively (Table 1).

Histological Changes in Chorionic Villi: Villous oedema of chorionic villi was seen in 30 (47.61%) cases. Abnormal vascularity in the form of complete avascularity of villi was observed in 8 (12.69%) cases.

50 (79.36%) cases showed fibrinoid degeneration (Fig. 1). Amongst the 50 cases, 30 (60%) cases showed both perivillous and intravillous fibrin while 20 (40%) cases showed only perivillous fibrin deposition.

30 cases (47.61%) showed evidence of chronic villitis. The 30 cases were subdivided into "infectious villitis" and "villitis of unknown etiology" (VUE). Infectious villitis was seen in only 1 case (3.3%) which showed presence of toxoplasmal cysts and plasma cell infiltration, hence diagnosed as toxoplasmosis (Fig. 2). Remaining 29 (96.66%) cases showed presence of chronic villitis without any associated infectious cause, hence, were classified under the heading of VUE.

Deciduitis was observed in 31 (49.20%) cases.

Decidual necrosis was seen in 23 (36.50%) cases.

In our study we diagnosed 3 (4.76%) cases of partial mole (Fig. 3) out of 63 cases.

4 (6.34%) cases each of syncitial knots and villous infarction were seen.

We did not encounter any cases of chronic intervillositis and chronic endometritis.

Table 1: Recurrences percentage.

Previous abortion	Number of cases	Percentage
2	44	69.84%
3	14	22.22%
4	5	7.93%
Total	**63**	**100**

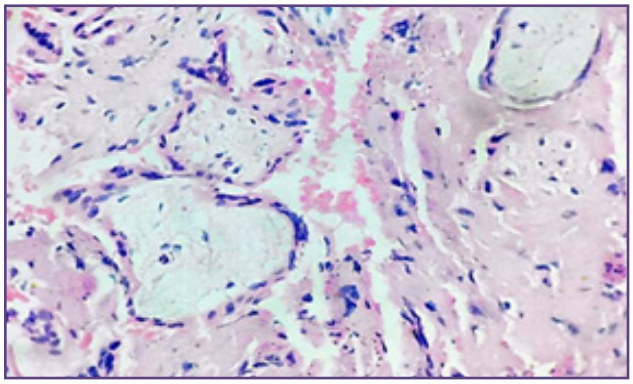

Fig. 1: Fibrinoid degeneration of chorionic villi (Hematoxylin and Eosin, 20X).

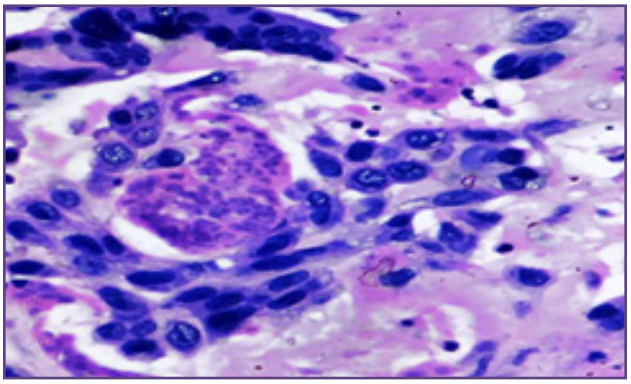

Fig. 2: Toxoplasmosis: Chorionic villous showing presence of toxoplasmal cyst(Hematoxylin and Eosin, 40X).

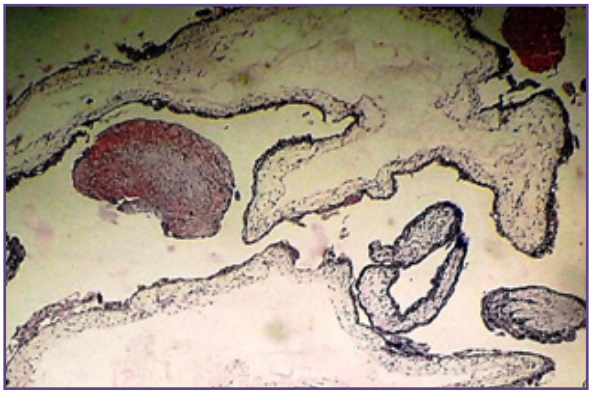

Fig. 3: A partial mole demonstrating severe villous oedema with cistern formation (Hematoxylin and Eosin, 10X).

Discussion

Histologic examination of products of conception which is done to confirm an intrauterine pregnancy and to exclude gestational trophoblastic disease forms an important component of patient management in cases of abortion [4]. Also, additional diagnostic information may be obtained.

We tried to identify the different histopathological changes in chorionic villi and decidua in recurrent abortion because of the insufficient data pertaining to the clinical importance of such histopathological examination in cases of recurrent abortion, a common and clinically important problem.

Demographic Features*:* In the present study, the age of the patients ranged between 23-36 years. Increased maternal age is thought of as a major risk factor for RPL. Spontaneous abortion was observed in 64.6% women aged 18–25 years and 16% women aged 30-40 years while 67.25 % maternal mothers were above 35 years of age when they gave birth to young mothers with RPL in one study where both maternal age and maternal mothers age were researched [5]. Therefore both advanced maternal age and advanced maternal mother's age should be considered a risk factor for RPL. Another study found that chromosomal abnormality rate increased significantly with maternal age [6].

Majority of the recurrent abortions occurred during 10-15 weeks of gestation accounting for 41 (65.07%) cases. One study documented a median gestational age of 7 weeks (range: 3-20) [7]. The vast majority of abortions occurred in the first trimester in another study [8].

Recurrences ranged from third to fifth time loss contributing to 44 (69.84%), 14 (22.22%) and 5 (7.93%) cases respectively. This was in concordance with a study [9] which reported first time loss in 48 % cases and fifth time loss in 7.5 % cases [9].

Histological Changes: Studies on recurrent spontaneous abortion have established that hydatidiform moles can be identified, villous dysmorphic features suggesting fetal aneuploidy and rare conditions like chronic histiocytic intervillositis (CHI) may be diagnosed on histologic examination of products of conception.

Chorionic villi were examined for villous oedema, abnormalities of vasculature, fibrinoid degeneration, chronic villitis, chronic intervillositis, syncitial knots, villous infarction and chronic endometritis. Molar pregnancy was also looked for. Decidual changes in the form of deciduitis and decidual necrosis were also noted.

Histological abnormalities in the chorionic villi were seen in 50 (79.36%) cases. Abnormal villi, which indicate fetal chromosomal abnormalities, were found in 62% of women with a recurrent abortion in one study[10].

Partial hydatidiform mole was diagnosed in 3 patients (4.76%). Studies researching on morphological examination of products of conception in recurrent abortion have shown that hydatidiform moles are definitely identified [4]. Diagnosis of hydatidiform mole has tremendous clinical importance because the patient has to be observed for persistent gestational trophoblastic neoplasia and may suffer from recurrent mole in subsequent pregnancies [4].

Ahlam [11] reported a case of six consecutive molar pregnancies. Recurrent abortions may uncommonly be due to familial hydatidiform mole syndrome in which the moles are recurrent and usually complete, of biparental more commonly than androgenetic origin [12].

Fibrinoid degeneration is the deposition of fibrinoid material initially external to basement membrane and later appearing in the villous stroma, derived from hemorrhages. The hemorrhage seeps through adjacent decidua and forms a membrane like sheet around chorionic villi. Red blood cells can be demonstrated in the fibrinoid material if carefully searched for [13].

50 (79.36%) of our cases showed fibrinoid degeneration. Amongst the 50 cases, 30 (60%) cases showed both perivillous and intravillous fibrin while 20 (40%) cases showed only perivillous fibrin deposition. Fibrin deposition was reported by Van Horn et al [14]. Massive perivillous fibrin deposition (MPFD) is associated with serious pregnancy outcome like recurrent abortion, fetal growth abnormalities and fetal death [15]. Three cases of primary antiphospholipid antibody syndrome (PAPS) attending a recurrent abortion clinic were studied. Partial or complete massive perivillous fibrous deposition (MPVFD) and maternal floor infarction (MFI) was seen in them and it was hypothesised that PAPS may be an influencing factor [16]. Another study noted similar findings of massive perivillous fibrin deposition in recurrent abortion [4].

30 cases (47.61%) showed evidence of chronic villitis. The 30 cases were subdivided into "infectious villitis" and "villitis of unknown etiology" (VUE). Infectious villitis was seen in only 1 case (3.3%) of recurrent abortion which showed presence of toxoplasmal cysts and plasma cell infiltration, hence diagnosed as toxoplasmosis. Remaining 29 (96.66%) cases showed presence of chronic villitis without any associated infectious cause, hence, were classified under the heading of VUE.

It is generally assumed that almost all congenital toxoplasma infections develop from a primary infection during pregnancy. 45% of the infants in women with primary infection during pregnancy develop congenital

toxoplasmosis. The rate of infection increases with gestation and is 17%, 25%, and 65% in the first, second, and third trimesters, respectively. Although infection is less likely in early gestation, fetal sequelae are the most severe when infection develops during this period [17].

Chronic villitis is most commonly seen in the third trimester, and is also seen in the second or first trimester. Approximately 10% of cases are associated with a known infectious etiology, close to 90% of these infectious villitides are due to cytomegalovirus and syphilis. In the vast majority of cases, no infectious etiology can be identified and the inflammation is termed villitis of unknown etiology (VUE). In some women, VUE appears to have no clinical significance. In others, the disorder gets progressively worse in subsequent pregnancies and is associated with recurrent pregnancy loss. Also, chronic villitis with increased perivillous fibrin deposition is more frequently associated with recurrent loss.

In a retrospective study, recurrent villitis was seen in ten out of 59 patients in whom placental villitis was diagnosed. The ten patients had 41 pregnancies totally and a pregnancy wastage of 60 per cent. There was increased fetal loss in all trimesters of gestation and postnatally, along with fetal growth retardation and premature delivery[18]. Massive chronic intervillositis (MCI) is associated with an adverse pregnancy outcome and poor fetal growth. Characteristic histology shows infiltration of the maternal intervillous space by chronic inflammatory cells and fibrin, without associated chronic villitis. A patient with 10 spontaneous abortions with repetitive massive chronic intervillositis in four of five gestations occurring in all three trimesters has been reported [19]. Chronic histiocytic intervillositis (CHI) affect about 1 in 200 pregnancies [4]. Chronic histiocytic intervillositis (CHIV) is an uncommon but important cause of recurrent abortion with loss occurring at later gestational ages sometimes [20]. We did not encounter any case showing chronic intervillositis.

Chronic endometritis has been reported and identified immunohistochemically in 9.3% patients [21]. We did not encounter any case of chronic endometritis.

Deciduitis and decidual necrosis were seen in 31 (49.20%) cases and 23 (36.50%) cases respectively. Decidual necrosis and acute and chronic inflammation were seen in antiphospholipid pregnancies[14]. Infarction and syncytial knot formation were also noted [14]. We encountered 4 (6.34%) cases each of syncitial knots and villous infarction.

Although pathologic evaluation and ultrasound are the most common tests done in a miscarriage, neither can confirm the chromosomal status of the developing embryo. Thus, in every case of miscarriage, especially when there are developmental anomalies, chromosomal analysis of the miscarriage should be performed. Knowing the chromosome results of the miscarried embryo/fetus is important, particularly for parents struggling with fertility or recurrent miscarriage.

Conclusions

In our study we diagnosed 3 cases of partial mole out of 63 cases, Thus, it should be emphasized that importance of histopathological assessment of the products of conception is not just to confirm that pregnancy was established but it is an important tool to rule out serious pathologies like molar pregnancies that necessitate special follow-up protocol and appropriate further management.

We diagnosed 47.61 % cases of chronic villitis in which one case was diagnosed as toxoplasmosis. This is of significant importance in patients with recurrent and habitual abortions, so as to establish a probable cause and to manage future pregnancies. Some of these findings may be associated with specific genetic aberration as most early spontaneous abortions are associated with genetic anomalies.

Such examination remains clinically indicated because it may allow the identification of important specific aetiological entities.

Thus a comprehensive multidisciplinary approach to miscarriage with a combination of clinical, genetic, pathological, and ultrasound examination of miscarriage can help identify and describe the cause of miscarriage and efforts should be made to use new technologies such as RT–PCR to maximize the future clinical information yield from these specimens.

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