Original Article

Placental Pathology in Spontaneous Abortions: A Study with Review of Literature

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ABSTRACT

Introduction: 'Retained products of conception' are quite a frequent specimen received for histopathological examination. Apart from confirmation of pregnancy, a careful examination can provide some additional information about the cause or the conditions associated with abortion.

Methods: A total of 53 cases were studied over a period of 1 year (from June 2014 to May 2014). The specimens were received in formalin, kept for fixation and stained with Haematoxylin and Eosin.

Results: Thirty out of fifty-three cases showed significant positive findings. Maternal perfusion defects were the most common (80%); of which, ischemia related defects were the most frequent ones (87.5%). The other findings included maternal floor infarction, chronic histiocyticintervillositis and persistent muscularization of basal plate arteries. Fetal perfusion defects constituted of three cases (10%) in which avascular villi were seen in two cases and chorangiosis was seen in one case. One case each of partial mole, complete mole and gestational trophoblastic neoplasm was also found in the study.

Conclusion: The present study highlights few of the histopathological findings observed in such specimens, which might help in predicting future pregnancy outcome and in planning the family accordingly.

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Introduction

Spontaneous abortions are quite prevalent. The initial pathologic assessment is used to confirm the presence or absence of pregnancy tissue and identification of a molar pregnancy. However the pathologists have strived to add more than a diagnosis of products of conception. A careful histopathological examination offers an understanding of aetiology and pathogenesis of abortions, thereby helping in risk assessment for the neonate and in reproductive planning in the family.[1] In this study we focus on determining the various abnormalities of maternal perfusion, fetal perfusion and chorionic villi in routine samples of spontaneous abortions which might help in determining the aetiology of abortion and in planning further pregnancy.

Materials and Methods

The study was carried out on all the specimens received as 'Retained products of conception' in our department over a period of one year (June 2014 to May 2015). A total of 53 cases were received, out of which 30 cases showed significant pathological findings. The pathological findings were divided as maternal perfusion defects (MPDs), foetal perfusion defects (FPDs) and others. The remaining 23 cases were either unsatisfactory or showed no specific finding and were excluded from the study. All specimens were fixed in formalin and stained with haematoxylin and eosin stain. The slides were then examined under the microscope.

Results

Out of the 30 cases studied, the majority were first trimester abortions (19). 8 cases were second trimester abortions and only 3 cases were third trimester abortions. 24 cases showed MPDs. Only one case showed FPD and gestational trophoblastic tumor each. Out of the MPDs, ischemia related changes were found to be the most frequent ones (21 cases) of which acute ischemia comprised of 13 and chronic ischemia comprised of 9 cases. One case showed both acute and chronic ischemic changes. The remaining 3 cases were of maternal floor infarction (MFI), chronic histiocyticintervillositis (MCI) and gestational trophoblastic tumor each. In the category of FTDs, two cases were encountered which showed avascular villi and one case showed chorangiosis. One case each of partial and complete mole was also noted.

Discussion

Placenta is an organ with circulation from the mother and foetus. Hence a histopathological examination must be carried out for aetiologies from both.[2] The maternal side disorders that affect the conceptus are numerous and have important foetal sequelae or recurrence risk. Few of them are infarcts, ischemia, chorangiosis, maternal floor infarction (MFI) and massive chorionic intervillositis.

Infarcts: They occur due to ischemic damage to the placenta seen histologically as collapsed villi with empty intervillous space and undergoing necrosis. In addition to infarcts which are really absent maternal perfusion, there are findings which correspond to chronic ischemic damage to placenta. These include small villi, large syncytial knots and absence of midsized villi.[3]Acute infarcts show villous crowding, increased perivillous fibrin deposition and ghost villi. They are found much more commonly in patients with hypertension or preeclampsia.[4]In our study acute infarcts were seen in 13 cases (50%) and chronic ischemia was seen in 7 cases (26.9%). One case (3.84%) showed both acute and chronic ischemic changes. Figure 1a and 1b show changes in chronic ischemia and acute ischemia (infarct) respectively.

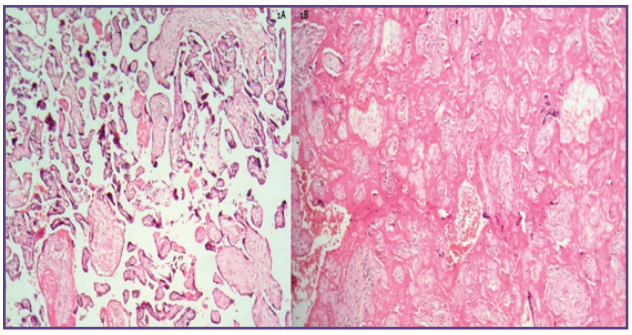

Fig. 1a: Low power view showing hypermature small sized villi with increased syncytial knots. (H&E 100X). Figure 1b: Low power view showing infarct necrosis with ghost villi and increased perivillous fibrin. (H &E 100X).

Maternal Floor Infarction (MFI): It is characterised by markedly increased perivillous fibrin and extracellular matrix fibrinoid surrounding distal villi with large number of associated intermediate trophoblast cells. The entrapped villi may become infarcted due to diminished perfusion. [4] .Fibrinoid material is derived from haemorrhages. The haemorrhage seeps through adjacent decidua and forms a membrane like sheet around chorionic villus. In some cases it may be due to maternal thrombophilia leading to increased fibrin deposition at the villous maternal-fetalinterface. In addition, compromised villous trophoblast integrity exposes tissue factor and activates the clotting cascade locally on the villous surface. Grossly, the placenta is firm and marbled.It has been found to be associated with autoimmune diseases, preeclampsia, thrombophilias, increased risk of renal tubular dysgenesis,[5] cystic renal dysplasia[6] and anti fetal rejection.[7]It is also associated with IUGR, prematurity, diabetes, Rh-incompatibility recurrent abortion, preterm delivery, fetal death, adverse

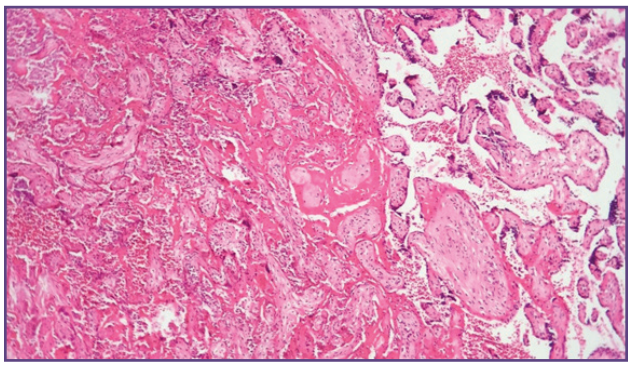

Fig. 2: Low power view showing normal villi (right side) and increased perivillous fibrin deposition around distal villi with trophoblasts (left side). (H&E 100X).

neurodevelopmental outcome, CNS injury and elevated levels of maternal serum alpha fetoprotein.[8-10] We found one case of MFI histologically showing increased perivillous fibrin around distal villi with areas of infarct.

Chronic (Histiocytic) Intervillositis also called as Massive Chronic Intervillositis (MCI): is a striking finding in which the maternal space is filled by CD68 positive histiocytes with admixed or nodular increase in fibrin.[2]The absence of villous inflammation and large number of histiocytes in chronic intervillositis distinguishes this lesion from chronic lymphohistiocyticvillitis with perivillous extension and fibrin deposition. The intensity of intervilloushistiocytic burden increases with gestational age. It is known to be caused by maternal T lymphocytes, predominantly CD-8 positive, that inappropriately gain access to the villous stroma. Fetal antigen presenting cells (Hofbaeur cells) expand and are induced to express class II major histocompatibility complex molecules. Maternal monocyte –macrophages in the perivillous space likely amplify the immune response .This lesion is more commonly seen in spontaneous abortions especially in first trimester and is rare in later pregnancy. It has reportedly the highest recurrence risk and causes fetal death.[11, 12]It is a strong risk factor for neonatal encephalopathy and cerebral palsy. MCI can also be observed in malaria infection. However, the histiocytes contain material pigment and show no villous damage. [11]Parant et al[12] has classified MCI into two histological levels of severity, viz moderate and severe. We report one case of MCI which falls in moderate category showing focal intervillouslymphohistiocytic inflammatory infiltrate with mild fibrinoid deposition (Figure 3a and 3b).

Marchaudon et al[13] observed a very substantial increase in alkaline phosphatase levels in MCI associated with an immune phenomenon. Mekinian et al have suggested an autoimmune association such as antiphospholipid syndrome.[14]

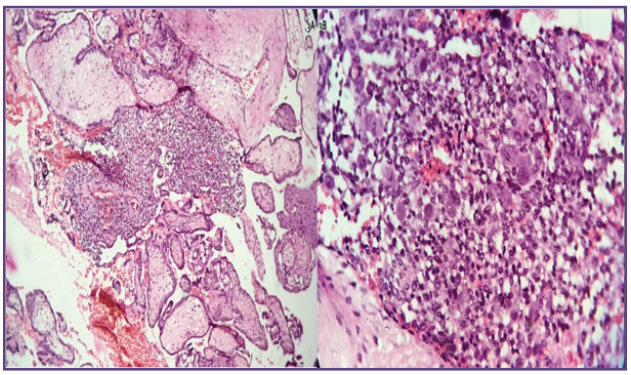

Fig. 3a: Low power view showing a focal collection of lymphocytes and histiocytes in the intervillous area. (H&E 100X). Figure 3b: High power view showing histiocytes, lymphocytes with admixed trophoblastic cells. (H&E 400X).

Another feature of maternal vascular perfusion defect is persistent '**Muscularization of Basal Plate Arteries**' also called as failure of physiological transformation which means failure of extra-villous trophoblast invasion of the maternal spiral arterioles. This results in persistent vaso-reactivity to circulating vasoactive mediators decreasing the blood flow into intervillous bed. The end result is chronic ischemia and villous infarcts.[2] The term physiological transformation is used to describe the disappearance of normal muscular and elastic structures of arteries and their replacement by fibrinoid material in which trophoblasts are embedded. Preeclampsia and fetal growth retardation have been found to be strongly associated with failure of spiral artery remodelling[15] because it results in the failure of development of a low resistance arteriolar system which dramatically decreases the blood supply to the growing fetus. In preeclampsia, invasion of the uterine spiral arteries is limited to proximal decidua with 30% to 50% of the spiral arteries escaping endovascular trophoblast remodelling.[16] Maternal and fetal complications associated with preeclampsia include abruption, renal failure, IUGR, preterm delivery and death. Kam et al[17] have stressed upon the role of trophoblast in the physiological change in decidual spiral arteries. According to them, the likely sequence of events leading to remodelling is that first the interstitial trophoblasts home to the spiral arteries and destroy the vessel media as a priming process which is subsequently followed by migration of endovascular trophoblasts down the arterial lumen causing destruction of endothelial cells accompanied by deposition of fibrinoidnaterial. Figure 4a shows physiologically transformed decidual arteries showing endovascular and interstitial trophoblastic infiltration in vessel wall. Figure 4b shows thickened untransformed spiral arterioles.

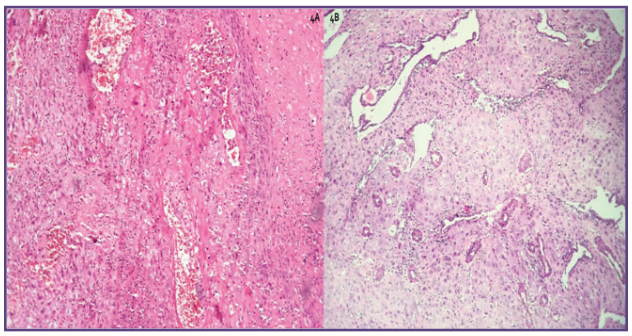

Fig. 4a:Low power view showing endovascular trophoblastic remodeling in decidual arterioles. (H&E 100X). Figure 4b: Low power view showing persistent muscularization of decidual arterioles. (H&E 100X).

In our study, we found one such case showing lack of physiological transformation.

The fetal perfusion defects: affecting the conceptus are 1) Fetal thrombotic vasculopathy, 2) Hemorrhagicendovasculitis, 3) Recanalization of stem vessels, 4) Chorangiosis. The end result of long standing fetal vascular occlusion is avascular villi. (Figure 5)

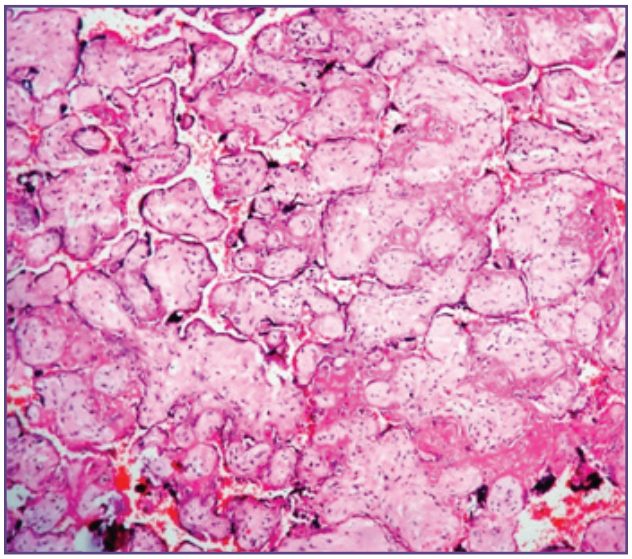

Fig. 5: Low power view showing avascular term villi with hyalinised stroma. (H&E 100X)

They appear as collagenized pink villi without intravillous vessels.Initially the collagen is soft which later gets condensed and hyalinised. The term is reserved for the group with 15 or more affected terminal villi per section. The finding is well described in preeclampsia and diabetic pregnancies Scattered foci of avascular villi (and/or villous stromal vascular karyorrhexis) could be used to describe less severe cases.[18]Stromal fibrosis of terminal villi is a consequence of regression after intrauterine fetal death or is a result of impairment of placental circulation due to different causes. Ceratinforms of fibrosis may develop via stromal edema (e.g. diabetes mellitus, blood group incompatibility, immunological disorders).

Hemorrhagicendovasculitis is a distinctive histopathological finding of damage to endothelium of villous vessels resulting in extravasation of fetal red blood cells and recanalized stem vessel lumens. Obstruction to fetal vascular blood flow results in IUGR, neurologic injury, cardiac failure, oligohydramnios and fetal death. [19, 20] We found two cases of intrauterine death showing avascular villi consistent with fetal transfusion defects.

Chorangiosis: Chorionic villi rarely contain more than five capillaries in a term placenta. Villous hypervascularity in which individual terminal villi contain an excessive number of vessels has been called as chorangiosis by Altshuler,[21] who has defined it as the presence of more than 10 capillaries per villous in 10 medium power fields in at least 3 non infarcted areas of placenta. Chorangiosis has to be differentiated from chorangioma, chorangiomatosis, placental congestion and ischemia. Chorangioma and chorangiomatosis are commonly seen before 32 weeks of gestation and involves proximal elements of villous structures whereas chorangiosis is a diffuse process commonly seen after 37 weeks of gestation involving the terminal villi and having numerous capillaries with intact basement membrane. [22] Placental congestion shows a numerically normal vasculature and ischemic placenta shows shrinkage of villi with hyper-maturation. The pathogenesis of chorangiosis is thought to be hypoxic stimulus which causes excessive villous capillary and connective tissue proliferation.[21] In our study, we found one case of chorangiosis. (Figure6).

We also found one case each of partial mole, complete hydatiform mole and gestational trophoblastic neoplasm

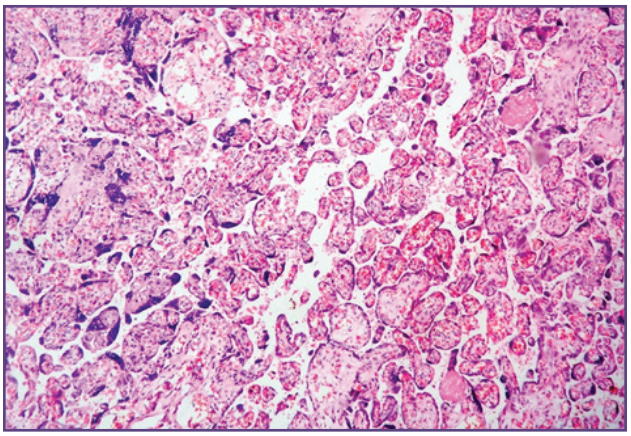

Fig. 6: Low power view showing hypervascular term villi. (H&E 100X)

Table 1.The findings in all the 30 cases.

No.	Age (yrs)	Obstetric History	POG of present pregnancy	Time of previous abortion (if any)	Histological findings	Diagnosis
1.	27	G4P1A3	2 months	2 month	Infarct necrosis with ghost villi	Findings are consistent with acute ischemic damage to placenta
2.	27	G3P2A1	11 weeks	-	Hypermature villi with increased syncytial knots and empty intervillous space	Chronic ischemic damage to placenta
3.	23	G2P0A2	7 weeks	2 months	Villous crowding with increased perivillous fibrin deposits	Acute ischemic damage
4.	32	G3P2A1	8 weeks	-	Villous crowding with increased perivillous fibrin deposits	Acute ischemic damage
5.	24	G1P0A1	11 weeks	-	Infarcted ghost villi with increased fibrin	Acute ischemic damage
6.	36	G5P4A1	4 months	-	Infarcted ghost villi with increased fibrin	Acute ischemic damage
7.	20	G1P0A1	11 weeks	-	Hypermature villi with increased syncytial knots and empty intervillous space	Chronic ischemic damage
8.	36	G6P2A4	3 weeks	2 months	Infarct with ghost villi and increased fibrin deposits	Acute ischemic damage to placenta
9.	22	G1P0A1	16 weeks	-	Proliferation of trophoblasts with atypical features in a background of necrosis, haemorrhage, infiltrating muscle bundles. No villi seen.	Gestational trophoblastic tumor (?choriocarcinoma / PSTT)
10.	26	G2P1A1	3 months	-	Hypermature villi with sclerosis along with intervening infarcted areas	Both acute and chronic ischemic damage
11.	27	G2P1A1	10 weeks	-	Areas of increased perivillous fibrin, trophoblastic cells and infarct	Maternal floor infarction
12.	40	G9P7A2	15 weeks	2 months	Hypermature villi with increased syncytial knots and sclerotic villi	Chronic ischemic damage
13.	26	G1P0A1	24 weeks	-	Infarcted villi only. No viable area	Acute ischemic damage
14.	23	G1P0A1	8 weeks	-	Hypermature villi with increased syncytial knots	Chronic ischemic damage
15.	25	G1P0A1	10 weeks	-	Persistent muscular layer around spiral arterioles in decidua	Lack of physiological transformation of decidual arteries
16.	36	G5P4A1	4 month	-	Ghost villi with increased fibrin	Acute ischemic damage
17.	27	G3P2A1	8 weeks	-	Infarct with ghost villi and increased fibrin	Acute ischemic damage
18.	40	G5P3A2	7 weeks	10 weeks	Ghost villi with increased fibrin	Acute ischemic damage
19.	35	G2P1A1	11 weeks	-	Increased syncytial knots and sclerotic hypermature villi	Chronic ischemic damage

No.	Age (yrs)	Obstetric History	POG of present pregnancy	Time of previous abortion (if any)	Histological findings	Diagnosis
20.	25	G3P1A2	10 weeks	8 weeks	Sclerotic hypermature villi and empty intervillous spaces	Chronic ischemic damage
21.	26	G2P1A1	18 weeks	-	Sclerotic hypermature villi and empty intervillous spaces	Chronic ischemic damage
22.	35	G2P1A1	7 weeks	-	Collection of histiocytes and lymphocytes in the intervillous space	Chronic (histiocytic) intervillositis
23.	35	G1P0A1	9 weeks	-	Large areas of infarct with ghost villi	Acute ischemic damage
24.	25	G2P1A1	39 weeks (IUD)	-	Occluded vessels in stem villi with avascular villi	Hemorrhagicendo-vasculitis
25.	28	G1P0A1	6 weeks	-	Areas of infarct with ghost villi	Acute ischemic damage
26.	26	G1P0A1	20 weeks	-	Areas of infarct with ghost villi	Acute ischemic damage
27.	25	G3P1A2	11 weeks	12 weeks	Both normal and hydropic villi with trophoblastic proliferation	Partial mole
28.	33	G4P3A1	13 weeks	-	Large hydropic villi with cistern formation and circumferential trophoblastic proliferation	Complete hydatiform mole.
29.	30	G4P2A2	27 weeks	24weeks	Avascular villi	Consistent with fetal transfusion defects
30.	24	G1P0A1	34 weeks	-	Villi with increased number of capillaries filled with blood	Chorangiosis

(GTN) (?choriocarcinoma / ?PSTT) in our study. Microscopically, partial mole showed both normal and hydropic villi (Figure 7) whereas complete mole showed only hydropic villi with cistern formation and circumferential trophoblastic proliferation. The two established risk factors associated with it are extremes of maternal age and prior molar pregnancy. Compared to women aged 21-35 years, the risk of complete mole is 1.9 times higher for women both >35 years and <21 years as well as 7.5 times higher for women >40 years. Prior hydatidiform mole predisposes to another molar pregnancy. The risk of repeat molar pregnancy after 1 mole is about 1%, or about 10-20 times the risk for the general population. Complete hydatidiform moles undergo early and uniform hydatid enlargement of villi in the absence of an ascertainable fetus or embryo, the trophoblast is consistently hyperplastic with varying degrees of atypia, and villous capillaries are absent. Approximately 90% of complete moles are 46, XX, originating from duplication of the chromosomes of a haploid sperm after fertilization of an egg in which the maternal chromosomes are inactive. The other 10% of complete moles are 46, XY, or 46, XX, as a result of fertilization of an empty ovum by 2 sperm (dispermy). Partial hydatidiform moles show fetal tissue, chorionic villi with focal edema, scalloping and prominent stromal trophoblastic inclusions, a functioning villous circulation, as well as focal trophoblastic hyperplasia with mild atypia only. Most partial moles have a triploid karyotype (usually 69, XXY), resulting from the fertilization of an apparently normal ovum by 2 sperm.[23]

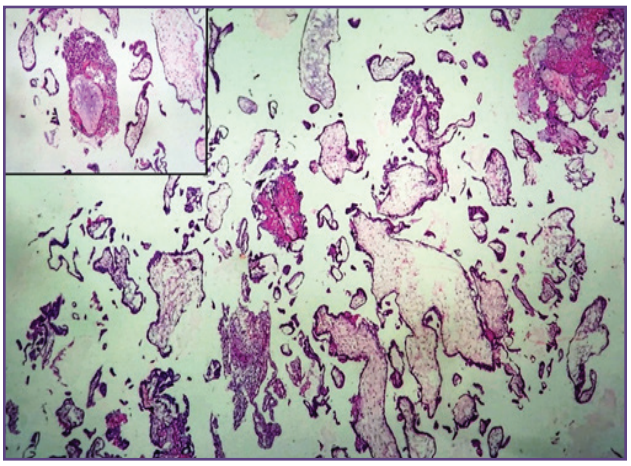

Fig. 7: Scanner view showing both normal and hydropic villi. (Inset showing circumferential trophoblastic proliferation in a hydropic villus). (H&E 40X)

GTN showed complete absence of chorionic villi and presence of atypical cytotrophoblasts and syncytiotrophoblasts in a background of necrosis and haemorrhage. An occasional mitotic figure was also identified.

Conclusion

Ischemia in maternal transfusion defects has been found to be the most common disorder affecting placenta in spontaneous abortions. We stress upon careful sampling and inspection of all products of conception in cases of spontaneous abortion and report any significant pathological finding which predicts the nature of future pregnancies and fetal outcome so that a required intervention, planning, counselling may be done at the right time.

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