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Histopathological study for the products of conception from a regional pathology laboratory in Southwestern Saudi Arabia: A 5-year retrospective study

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ABSTRACT

Introduction: Abortion is defined as the ending of a pregnancy before 20 weeks of gestation or the delivery of a fetus that weighs less than 500 grams. Histopathological examination of the products of conception (POC) can diagnose the underlying cause of abortion e.g., molar pregnancy and hydropic alterations. *Methodology:* Over a period of five years, from 2017 to 2022; a total number of 569 cases of first-trimester abortion curetted material were sent to the regional laboratory, Department of Histopathology, Al-Qunfudah, Saudi Arabia. Clinical data of each case, type of abortion, placental morphology, villus size, villus vascularity and histopathological findings of each POC sample were studied. *Results:* The mean age of the studied women was (32.74 ± 7.04 years), with a mean number of pregnancies of 4.68 ± 3.07 (range: 0 - 25). Out of the studied POC samples n=355 (62.4%) were incomplete abortions, while inevitable abortion was the least frequent type n=15 (2.7%). There was a significant relationship between fibrin, Arias-Stella, hydrophobic changes, and fibrosis with villus size (p= 0.005, 0.001, 0.001, and 0.013, respectively). Additionally, villus vascularity was significantly associated with the histopathology findings; fibrin, fibrosis, Arias-Stella, and hydrophobic changes (p= 0.001, 0.005, 0.001, and 0.001, respectively). *Conclusion:* Our findings support that most abortions might be due to chromosomal abnormalities suggested by the significant prevalence of small and hypo-vascularized villi in the studied POC. Routine histopathological examination of all POC is mandatory to rule out critical conditions such as molar or ectopic pregnancy.

Keywords: Histopathology, abortion, product of conception, villus size, villus vascularity, Saudi Arabia

1. INTRODUCTION

The World Health Organization (WHO) defines abortion as the termination of a pregnancy before to 20 weeks of gestation or the delivery of a fetus weighing less than 500 grams. An estimated 73 million abortions are recorded annually worldwide; this accounts for 61% of all unplanned pregnancies and 29% of pregnancies overall (Casey et al., 2017). In 2017, there were approximately 856,730 abortions in the United States or 20.7 per 1000 women aged 15–44 years. Abortion is the most frequent pregnancy complication, and over 80% of spontaneous abortions occur within the first 12 weeks (Kaur and Gupta, 2016). In their clinical work, obstetricians and gynecologists often see patients experiencing miscarriage during the first trimester (Clement et al., 2019). However, the fundamental cause is still unclear, the increased rates of spontaneous abortion are linked to genetic and embryonic chromosomal abnormalities (Ashour et al., 2020; Xu et al., 2022).

Fetal and placental development are coordinated; therefore, any abnormalities in fetal development will appear as differences in the placental tissue, then the uterus rejects the placenta because of its uneven development, which might lead to spontaneous abortions (Dai et al., 2019). Adverse reproductive outcomes, such as spontaneous miscarriage, are more common in older women, and the risk of miscarriage increases with maternal age i.e., a woman aged 40 or older has five to seven times the chance of a woman aged 20 to 24 to experience abortion (Cohain et al., 2017). Women who have experienced problems during a previous pregnancy are at a greater risk of experiencing complications during subsequent pregnancies (Chojenta et al., 2014). Even though miscarriages are relatively rare and unavoidable in human reproduction, a failed pregnancy's emotional and social toll can be substantial (Lens, 2021).

There has been much discussion and contention over whether routine placental morphological examination should be used to identify the cause of early pregnancy loss (Li and Marren, 2018). Treatment for patients with premature pregnancy failure must include the essential and routine histopathological analysis of the product of conception (POC) (Lama and Pariyar, 2021). Confirming the presence of an intrauterine pregnancy and ruling out undetected prenatal trophoblastic illness in the form of a partial or complete hydatidiform mole are the primary purposes of a routine histological investigation of the POC (Eiriksson et al., 2021). The underlying cause of the pregnancy loss might be gleaned from histopathology examination (Wiles et al., 2019). Undiagnosed pathologies, such as molar pregnancy and hydropic alterations that require a unique regimen for monitoring and treatment, might be uncovered through histological analysis of the POC (Han et al., 2020).

A histopathological examination is essential for diagnosing placental abnormalities; women over 30 are likelier to have a partial mole (Mangla and Kaur, 2022). Almost all studies examining placental histology as a predictor of karyotype have focused on early miscarriage (Sobhani et al., 2021). Recurrent spontaneous abortions have been linked to several placental pathological abnormalities, but the clinical utility of routine screening of POC has not been systematically investigated (Shah et al., 2018). Earlier studies have attempted to discover distinct villus morphological alterations that may suggest chromosomal abnormalities. Some researchers found that it is possible to connect villus morphology with chromosomal abnormalities or to distinguish between normal and aberrant karyotypes (Vişan et al., 2020).

Because of the local cultural issues that encourage consanguineous marriage, Al-Qunfudah governorate and its surroundings in southwestern Saudi Arabia became an endemic area for many hereditary diseases, e.g., hemoglobinopathies, mainly sickle cell anemia and thalassemia (Memish et al., 2011). However, no studies have evaluated the prevalence of abortion in this area, but we believe that the rate of abortions is high and is most probably related to chromosomal abnormalities. This study aims to assess the morphological and histopathological changes in (the placenta, POC) that occurred during the first trimester's different types of abortions in Al-Qunfudah governorate in southwestern Saudi Arabia.

2. METHODOLOGY

During a period of five years that extended from February, 1st, 2017 to March, 1st, 2022, a total of 569 cases of first-trimester abortion curetted material were sent to the regional laboratory, Department of Histopathology, Al-Qunfudah, Saudi Arabia, for histopathologic investigation were examined. Clinical history and demographic data were retrieved from the request forms and patients' records. The slides were stained with routine hematoxylin and eosin stain following the standard procedure, and Manson's trichrome stain was used to assess intra-villus fibrosis. Then, two separate pathologists examined the slides.

The findings checklist included seven parameters: "1" Villus size was categorized as small, intermediate, or large. "2" Villus vascularity was graded into four groups; grade 0= there were no villi or insignificant villus to be assessed, grade I= normal vascularity, all villus or at least nine out of ten villi showed 8-10 blood vessels per villus with nucleated RBCs, periphery (adjacent to trophoblast), or centrally, grade II-A= showed 5-8 blood vessels perivillus predominantly located periphery containing less

nucleated RBCs (mild hypoplasia), grade II-B= showed 3-4 blood vessels peri villus predominantly located periphery containing 1-2 nucleated RBCs (Severe hypoplasia), grade III= all villi were avascular, but few villi showed < 3 blood vessels perivillus with nucleated red blood cells (Alsibiani, 2014). "3" Perivillus fibrin deposition – present or absent. "4" Fibrosis, present or absent "5" Arias Stella Reaction present or absent. "6" Decidualized tissue present or absent. "7" Hydropic changes present or absent.

Inclusion Criteria

All samples of spontaneous first-trimester abortions ≤ 11 weeks gestational age were sent for histopathological evaluation at Al-Qunfudah regional pathology laboratory, during the 5 years period of the study (2017-2022).

Exclusion Criteria

Curetted samples of second or third-trimester abortions ≥12-week gestational age, or samples that showed insignificant histopathological findings (decidua without any signs of pregnancy).

Ethical approval

Before starting data collection, the required official approvals were obtained from the Local Committee for Bioethics and Medical Ethics at Umm Al-Qura University, Makkah, SA Approval No. (HAPO-02-K-012-2022-09-1192)

Statistical Management

The collected data were analyzed using the Statistical Package for Social Science software (SPSS) (IBM SPSS Statistics for Windows, Version 25.0, IBM Corporation, Armonk, New York). Quantitative data were analyzed and presented as descriptive statistics (mean±SD), while numbers and percentages were used for qualitative data. Chi-squared tests and Fisher's exact test were used to determine the relationships between type of abortions, villus size, and villus vascularization. P-values of less than 0.05 were considered significant.

3. RESULTS

This retrospective study included 569 POC collected in the regional laboratory, Department of Histopathology, Al-Qunfudah, Saudi Arabia, from 2017 to 2022. Women who had abortions aged, on average 32.74±7.04 years old. Their average number of births was 2.84± 2.52 (range: 0 - 21), while their mean number of pregnancies was 4.68±3.07 (range: 0 – 25), (Table 1). According to Table 2, out of the examined POC, 355 (62.4%) were incomplete abortions, with inevitable abortions being the least common form 15 (2.7%). Seven POC samples were diagnosed as gestational trophoblastic disease. Nearly, 63.4% of histopathologic findings were fibrin, while Arias-Stella represented 28.5% of the examined samples. Small villi were seen in 44.6%, while avascular villi represented 32.7% of the studied POC. Nearly, half of the missed abortions showed small villi, while intermediate and small villi were found in about 80% of the incomplete abortion samples. About 65% of missed abortion samples showed avascular and severe hypo-vascular villi; however, it was 40% in samples of inevitable abortion (Table 2, 3).

Regarding the relationship between the histopathological findings and the villus size among the studied POC, there was a significant relationship between fibrin, Arias-Stella, hydropic changes, and fibrosis with villus size (p-values of 0.005, 0.001, 0.001 and 0.013, respectively) (Table 4). Additionally, significant relationships were found between villus vascularity and the histopathologic findings; fibrin (p=0.001), fibrosis (p=0.005), Arias-Stella (p=0.001), and hydropic changes (p=0.001), (Table 5). Figure 1 shows the relationship between the histopathological findings and the types of abortion. Missed abortion showed significantly higher frequencies of fibrosis and gestational trophoblastic abortion showed the lowest fibrosis (p=0.046). Arias-Stella was significantly found with incomplete abortions compared to being infrequently met with trophoblastic abortion (p=0.034). However, no significant relations were found with the decidua or hydropic changes (Figure 1). Sections of the studied POC samples showed Arias-Stella reaction, hydropic changes, avascular villi, inter-villus fibrin deposition, and intra-villus fibrosis, (Figure 2).

Table 1 Clinical data and demographic of the studied women

Variable	Mean±SD (Range)	Category	Frequency (%)
Age/years	32.74±7.04 (16 – 49)	≤ 20	16 (2.8)
		21-30	211 (37.1)
		31-40	259 (45.5)
		≥ 41	83 (14.6)
Number of pregnancies	4.68±3.07 (0 – 25)	Once	50 (8.8)
		Twice	64 (11.2)
		3-5 times	187 (32.9)
		6-10 times	128 (22.5)
		More than 10 times	140 (24.6)
Number of births	2.84±2.52 (0 - 21)	None	197 (34.6)
		Once	85 (14.9)
		Twice	80 (14.1)
		3 times	56 (9.8)
		More than 3 times	151 (26.6)
Residence		Urban	217 (38.1)
		Rural	352 (61.9)
Totals		569 (100.0)	

Table 2 Frequency distribution of type of abortion, histopathological findings, villus size, and vascularity of the studied POC samples

Product of conception variables		Number=569	Percentage (%)
Type of abortion	Incomplete abortion	355	62.4
	Missed abortion	110	19.3
	Complete abortion	54	9.5
	Blighted	28	4.9
	Inevitable abortion	15	2.7
	Gestation trophoblastic disease	7	1.2
Histopathological findings	Decidua	563	98.9
	Fibrin	361	63.4
	Fibrosis	75	13.2
	Arias-Stella	162	28.5
	Hydropic changes	129	22.7
Villus size	Small	254	44.6
	Intermediate	196	34.4
	Large	59	10.4
	Absent	60	10.6
Villus vascularity	Avascular (Absent)	186	32.7
	Mild	100	17.6
	Severe	107	18.8
	Normal	83	14.6
	Cannot be assessed	93	16.3

Table 3 Relationship between type of abortion with both villus size and villus vascularity among the studied POC samples

Type of abortion Villus Parameters		Incomplete abortion n=355 (%)	Missed abortion n=110 (%)	Complete abortion n=54 (%)	Blighted abortion n=28 (%)	Inevitable abortion n=15 (%)	Gestation trophoblastic disease n=7 (%)	Total N=569 (%)
Villus size a	Absent	42 (11.8)	6 (5.5)	8 (14.8)	2 (7.1)	0 (0.0)	2 (28.6)	60 (10.6)
	Large	30 (8.5)	17 (15.4)	3 (5.6)	4 (14.3)	2 (13.3)	3 (42.8)	59 (10.4)
	Intermediate	124 (34.9)	33 (30.0)	25 (46.3)	10 (35.7)	3 (20.0)	1 (14.3)	196 (34.4)
	Small	159 (44.8)	54 (49.1)	18 (33.3)	12 (42.9)	10 (66.7)	1 (14.3)	254 (44.6)
Villus vascularity b	Avascular (Absent)	100 (28.2)	44 (40.0)	20 (37.0)	13 (46.5)	5 (33.3)	4 (57.2)	186 (32.7)
	Mild	66 (18.6)	13 (11.8)	6 (11.1)	7 (25.0)	6 (40.0)	2 (28.6)	100 (17.6)
	Severe	71 (20.0)	21 (19.1)	10 (18.5)	4 (14.3)	1 (6.7)	0 (0.0)	107 (18.8)
	Normal	49 (13.8)	20 (18.2)	9 (16.7)	2 (7.1)	3 (20.0)	0 (0.0)	83 (14.6)
	Can't be assessed	69 (19.4)	12 (10.9)	9 (16.7)	2 (7.1)	0 (0.0)	1 (14.3)	93 (16.3)

aFisher's exact test= 30.85 P-value= 0.009

bFisher's exact test= 38.62 P-value= 0.001

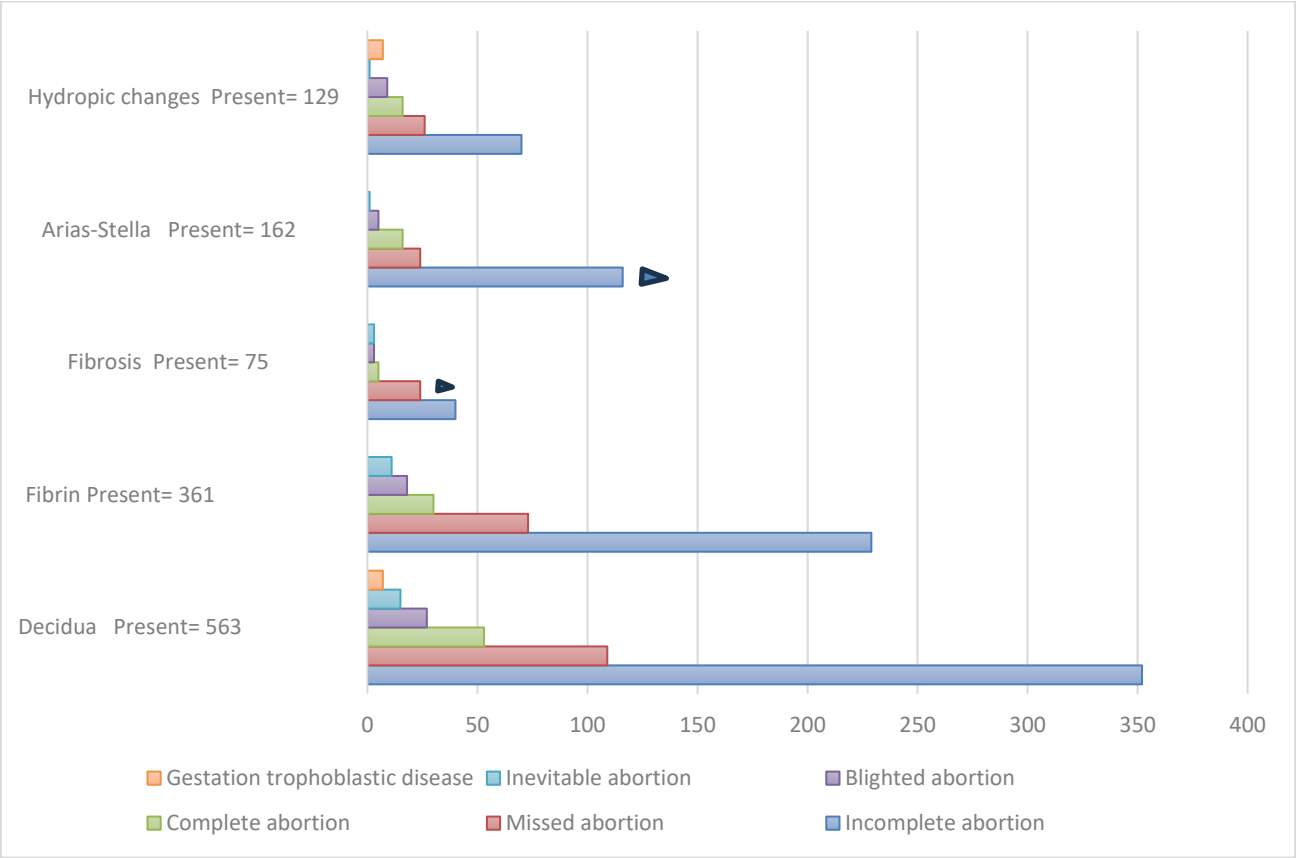
Table 4 Relationship between the histopathological findings and the villus size among the studied POC samples

Histopathological findings	Villus size				
	Absent	Large	Intermediate	Small	P-value
Decidua Present= 563 Absent= 6	59 (98.3) 1 (1.7)	58 (98.3) 1 (1.7)	194 (98.9) 2 (1.1)	252 (99.2) 2 (0.8)	0.874
Fibrin Present= 361 Absent= 208	25 (43.1) 33 (56.9)	39 (69.6) 17 (30.4)	131 (67.2) 64 (32.8)	166 (63.8) 94 (36.2)	0.005
Fibrosis Present= 75 Absent= 494	1 (1.7) 57 (98.3)	4 (7.1) 52 (92.9)	29 (14.9) 166 (85.1)	41 (15.8) 219 (84.2)	0.013
Arias-tella Present= 162 Absent= 407	52 (89.7) 6 (10.3)	10 (17.9) 46 (82.1)	39 (20.0) 156 (80.0)	61 (23.5) 199 (76.5)	0.001
Hydropic changes Present= 129 Absent= 440	0 (0.0) 58 (100.0)	37 (60.7) 24 (39.3)	70 (35.5) 127 (64.5)	22 (8.7) 231 (91.3)	0.001

Table 5 Relationship between the histopathological findings and the villus vascularity among the studied POC samples

Histopathological findings	Villus vascularity					
	Cannot be assessed.	Normal	Mild	Severe	Avascular (Absent)	P-value
Decidua Present= 563 Absent= 6	92 (98.9) 1 (1.1)	82 (98.8) 1 (1.2)	99 (99.0) 1 (1.0)	107 (100.0) 0 (0.0)	183 (98.4) 3 (1.6)	0.876
Fibrin Present= 361 Absent= 208	43 (46.2) 50 (53.8)	50 (60.2) 33 (39.8)	73 (73.0) 27 (27.0)	63 (58.9) 44 (41.1)	132 (71.0) 54 (29.0)	0.001
Fibrosis Present= 75	5 (1.4) 88 (94.6)	4 (4.8) 79 (95.2)	14 (14.0) 86 (86.0)	19 (17.8) 88 (82.2)	33 (17.7) 153 (82.3)	0.005

Absent= 494						
Arias-Stella Present= 162 Absent= 407	67 (72.0) 26 (28.0)	17 (20.5) 66 (79.5)	20 (20.0) 80 (80.0)	21 (19.6) 86 (80.4)	35 (18.8) 151 (81.2)	0.001
Hydropic changes Present= 129 Absent= 440	2 (2.2) 91 (97.8)	4 (4.8) 79 (95.2)	7 (7.0) 93 (93.0)	12 (11.2) 95 (88.8)	104 (55.9) 82 (44.1)	0.001



►: indicates significance where p-value is less than 0.05.

Figure 1 Relationship between the histopathological findings and the type of abortion among the studied POC samples

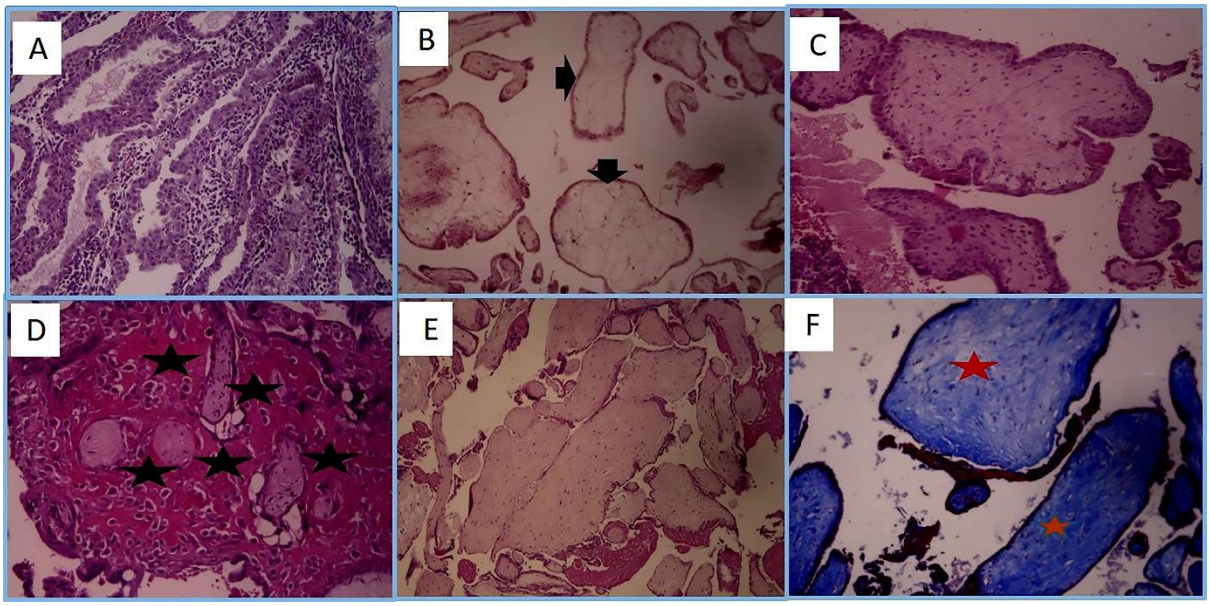


Figure 2 Histopathological findings of the studied POC samples: A. Areas-Stella reaction (20% H & E satin), B. Hydropic changes arrows (10x H & E stain), C. Avascular villi (10x H & E stain), D. inter-villus fibrin deposition blue star (20% H & E satin), E. intra villus fibrosis (10x H & E stain), F. intra-villus fibrosis red stars (10x Masson Trichrome stain)

4. DISCUSSION

Worldwide, abortion is an unpleasant outcome of pregnancy with many psychological and physical adverse effects (Coleman et al., 2017). This study assessed the morphological changes in 569 placenta and POC samples during the first trimester's abortion in the Al-Qunfudah governorate in southwest Saudi Arabia. The mean age of the studied women was (32.74 ± 7.04 years). This agrees with other studies that reported an increased risk of abortion with advanced maternal age (Thirukumar, 2019; Frick, 2021). Some chromosomal abnormalities showed corresponding morphological features. For example, trisomies showed small villi with decreased vascularity (Shetty et al., 2016). Normal villus of the first trimester must contain between 8 and 10 blood vessels. In this study, the avascular and severe hypo-vascular villi were seen in 51.5% of the studied samples, which agrees with the study done by Haque et al., (2004), who found decreased vessels in the chorionic villus of the first trimester.

Hypo-vascular and avascular villi indicate poor blood supply to the fetus, affecting fetal growth (Haque et al., 2004). In this study, fibrin around and between villi was seen in 361 (63.4%) of studded cases, similar to these findings reported by (Shilpa et al., 2018). The presence of fibrin jeopardizes the blood supply, leading to infracting the placenta. Histopathologic examination of product conception helps in treatment modality. Changes in villi and decidua need more morphological correlation with the result of molecular analysis to shorten the list of patients' needs in molecular studies (Makaju et al., 2015). Our study showed that fibrin and inflammation are the commonest outcomes in the histopathologic assessment of decidua; this agrees with other studies (Makaju et al., 2015; Raymond et al., 1999). In this study, a significant change in villi showed the presence of fibrin (63.4%), which is similar to a survey conducted by Raymond et al., (1999), who found that fibrin was present in 67% of cases.

In this study, after performing histopathological examination, seven POC samples were found to be molar pregnancy, which were sent earlier to the pathology laboratory while being labeled as incomplete abortion in the request forms for examination. These results strongly support the idea of submitting all POC to histopathologic examination since molar pregnancy needs watchful follow-up to detect any transformation to choriocarcinoma very early (Rashid, 2017). Similarly, another study showed that the histopathological examination could prove (22.2%) as hydatiform mole out of all the cases which were diagnosed by clinical assessment and ultrasound examination as missed abortions (Ohayi and Onyishi, 2020). The Royal College of Obstetricians and Gynecologists recommended histological examination of aborted tissue to confirm pregnancy and rule out an ectopic pregnancy or gestational trophoblastic disease (Dagdeviren et al., 2021).

Our study found that nearly 63% of histologic findings were fibrin, followed by Arias -Stella represented 28.5%, hydropic changes were (22.7%), and fibrosis was (13.2%), which is similar to the results described by Tasci et al., (2005), who reported fibrin, Arias-Stella, and hydropic changes were 60.4%, 25.2 and 14.3%, respectively. Another study found hydropic changes in 50% of studied POC and fibrosis in 30% (Hakvoort et al., 2006). The difference is probably due to the difference in the number of samples examined. The current study found strong correlations between villus vascularity and fibrin (P-value=0.001). In agreement with our

findings, a study by Hakvoort et al., (2006) stated that chorionic villus vascularization could be evaluated using the vascularization score system, which is an easy-to-use and reliable approach. The categorization can distinguish between normal and aberrant embryonic development, which helps determine the underlying reason for pregnancy loss (Hakvoort et al., 2006).

The villi in our study displayed numerous dysmorphic traits, including reduced vasculature per villus, aberrant trophoblastic growth, and hydropic alteration. Villus edema, inter-and peri villus fibrin deposition, inflammation, decidual alteration, and Arias Stella reaction were also noted. Abortion occurring between 8 and 10 weeks was significantly associated with decreased vessels per villi and hydropic changes. However, earlier-dated abortions were linked considerably with reduced patency of vessels, aberrant villus contour, ghost villi, and trophoblastic proliferation (Shetty and Narasimha, 2016). Since our study area is endemic for sickle cell disease and thalassemia and intermarried is highly prevalent, this can explain the high rate of abortion in this area, and many studies concluded that chromosomal abnormality is one of the significant causes of abortion (Klimczak et al., 2021).

5. CONCLUSIONS

Our findings support that most abortions might be due to chromosomal abnormalities suggested by the small and hypo-vascularized villi, which are significantly present in the studied POC in the current research. To rule out serious diseases like molar pregnancy and ectopic pregnancy, all products of conception must undergo routine histopathological screening. Evaluation of the morphological changes can offer vital information to direct molecular study that can help fully understand the causes and pathology of abortion.

Author contributions

Conceptualization: Omer Abdelbagi; methodology: Ibrahim Alshegifi, Omer Abdelbagi; software: Norah Alameri; validation, Hamad Alshegifi, Sultan Zaydi; statistical analysis: Ashraf Ewis; data curation: Sultan Zaydi and Abdulaziz Alsulbi —original draft preparation: Omer Abdelbagi and Asad Adam Abbas; writing, reviewing and editing: Mohamed Elhefny and Ashraf Ewis; supervision Omer Abdelbagi. All authors have read and agreed to the published version of the manuscript.

Ethical approval

This study was approved by the Local Committee for Bioethics and Medical Ethics at Umm Al-Qura University in Makkah. Approval No. (HAPO-02-K-012-2022-09-1192)

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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