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Original Research

Placental Chorangiosis: Clinical Risk Factors and Pregnancy Outcomes

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Abstract

Background: Placental chorangiosis is a response to fetal hypoxia, linked to be associated with maternal/fetal disorders and higher mortality rates. Therefore, this study aimed to explore the association of placental chorangiosis with specific maternal clinical risk factors, as well as its impact on pregnancy outcomes compared to pregnancies with normal placental conditions. **Methods**: This retrospective case-control study was conducted at King Saud University Medical City (KSUMC) between September 2018 and December 2021. A total of 78 pregnant women were included, and 26 cases of placental chorangiosis were identified and included in the study, which were randomly matched to 52 controls. The demographic data of maternal factors (age, body mass index (BMI), type of gestation, gravidity, and parity) and pregnancy outcomes (abortion, gestation age at delivery, mode of delivery, born alive or not, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at 1 and 5 minutes, birth weight, and mean placental weight) were retrieved from the patient's medical records, all placental histopathological examination were reviewed. Simple and multiple logistic regression analysis were used, and crude and adjusted odds ratios (ORs) and relative risk (RR) were reported with a 95% confidence interval (95% CI). **Results**: None of the potential maternal risk factors (age, BMI, type of gestation, gravidity, and parity) were statistically associated with chorangiosis. Chorangiosis, however, exhibit statistically significant associations with an increased number of abortions (RR: 21.59, 95% CI: 1.24–376.20, $p = 0.003$), intrauterine fetal death (IUFD; RR: 4.50, 95% CI: 1.53–13.25, $p = 0.004$), and low neonatal APGAR scores at 5 minutes (RR: 3.31, 95% CI: 1.22–9.01, $p = 0.029$). **Conclusion**: Placental chorangiosis is a rare pathological change in the placenta resulting from the interaction of several maternal and fetal disorders. When present, it can serve as an important indicator of chronic fetal hypoxia and predict poor obstetrical outcomes.

Keywords: placenta; placental chorangiosis; maternal morbidity; neonatal morbidity; mortality

1. Introduction

Older pregnant women are at higher risk of experiencing health problems before and after giving birth. Women who give birth at an advanced maternal age are more likely to develop gestational diabetes mellitus (GDM), hypertension (HTN), and preeclampsia, as well as experiencing preterm birth. Additionally, they have a higher chance of fetal morbidity and mortality [1]. Although the exact mechanism is not fully understood, there are several factors that have been attributed to adverse outcomes related to advanced maternal age, such as deteriorated maternal metabolism, impaired myometrial function, poor placental perfusion, and decreased placental influx of nutrients [2].

The placenta is a vital organ in pregnancy that provides oxygen and nutrients to the growing fetus. While it serves as a sensitive and specific indicator of a normal pregnancy, evaluating placental function poses challenges [3]. Placental abnormalities can indicate a decrease in the amount of oxygen the fetus receives. Fetal injuries, maternal HTN or diabetes mellitus (DM), infections, or problems with the umbilical cord may cause these abnormalities. Fortunately, the placenta usually responds to fetal hypoxia using compensatory mechanisms, such as the growth of new blood vessels in the chorionic villi, a process known as chorangiosis [4].

In 1984, Altshuler *et al*. [4] first described chorangiosis, which is defined microscopically as the presence of ten or more terminal villi containing ten or more capillaries in ten or more fields of three or more random non-infarcted areas of the placenta. In a normal third-trimester pregnancy, microscopic examination of the terminal chorionic villi generally reveals five or fewer cross-sections of fetal capillaries. However, in areas of chorangiosis, it can display up to twenty or thirty capillaries [4]. The reported incidence of placental chorangiosis is around 5–7% [5]. Several maternal and fetal conditions have been suggested to have an etiological role in developing chorangiosis, including pregnancy-induced DM, HTN, preeclampsia, higher al-

titudes, advanced maternal age, and umbilical cord abnormalities. Chorangiosis is also often linked to high fetal morbidity and mortality rates, reaching up to 42%, which may include stillbirths, fetal growth restriction (FGR), congenital malformations, cerebral palsy, and low Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores [6]. Furthermore, placental vascular abnormality has been studies and linked to abnormal and unexpected fetal acidemia at birth [7].

Petersen *et al*. [5] reported a higher rate of cesarean sections associated with chronic fetal hypoxia. Another complication of fetal hypoxia is a low pH level at birth (pH <7), which is associated with fetal acidemia due to impaired placental gas exchange and removal of metabolic wastes. This condition can lead to poor outcomes, including newborn brain damage [5,7].

This study aimed to explore the association of placental chorangiosis with several maternal clinical risk factors, such as maternal age, body mass index (BMI), gestation type, gravidity, and parity, as well as its effect on pregnancy outcomes compared to pregnancies with a normal placenta.

2. Material and Methods

Our retrospective case-control study was conducted at King Saud University Medical City (KSUMC), King Khalid University Hospital, between September 2018 and December 2021. The medical records for all pregnant women who received antenatal care services and delivered at our facility during the specified period were retrieved and reviewed. Patients with incomplete medical records were excluded. A total of 26 cases of pregnant women with placental chorangiosis were identified. Fifty-two matched consecutive cases of pregnant women with normal placentas were included as a control group. A patient information sheet was used to extract the demographic data from patients' files, including data related to potential risk factors such as maternal age, BMI, gestation type, gravidity, and parity. Pregnancy outcomes, gestational age, delivery mode, 1- and 5-minute APGAR scores, newborn birth weight, placental weight, and pH, were also recorded. According to Altshuler's criteria [4], the histopathological slides of all included placentas were reviewed for the diagnosis of chorangiosis [1–7]. Our study was approved by the Institute's Ethical Committee, College of Medicine, King Saud University IRB number: (E-20-4906).

We used Statistical Package for Social Sciences (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0, Armonk, NY, USA) for data entry and analysis. The outcome variables were expressed as numbers and percentages. The association between possible maternal risk factors and the occurrence of chorangiosis was analyzed using simple and multiple logistic regression. Crude and adjusted odds ratios (ORs) are reported with a 95% confidence interval (95% CI). The chi-square test or Fisher's exact test was used to study the association between chorangiosis and pregnancy outcomes. Relative risk (RR) 95% CI are reported for those outcomes. A p-value ≤ 0.05 was considered significant.

3. Results

Seventy-eight women were included in our study, out of which 26 cases were diagnosed with placental chorangiosis (33.3%) (Fig. 1), and 52 controls had normal placentas (66.7%). The mean age of all women was 31.32 (5.58) years (cases = 31.42 [5.92] years, and controls = 31.27 [5.40] years). The mean BMI of all women was 29.88 (5.15) kg/m^2 (cases = 30.66 [4.96] kg/m^2, and controls = 29.49 [5.25] kg/m^2). Most women in both groups had singleton gestations (84.62% among the cases and 90.38% among the control group). The median gravidity for the cases was 2.5 (range: 1–5) and 3 for the control group (range: 1.25–4). Similarly, the median parity for the cases was 1 (range: 0–3.25) and 1 for the control group (range: 0–3). More detailed information is provided in Table 1. Simple and multiple logistic regression analysis showed no statistically significant association between any of the studied possible maternal risk factors, including maternal age, BMI, gestation type, gravidity, and parity (Table 1).

The association between chorangiosis and pregnancy outcomes is reported in Table 2. Among women with placental chorangiosis, five had abortion compared to none within the control group (RR: 21.59, 95% CI: 1.24–376.20, $p = 0.003$). There were four cases of intrauterine fetal death (IUFD) in each group. Comparison of the pregnancy outcomes, combining abortions and IUFD, also showed a statistically significant association (RR: 4.50, 95% CI: 1.53–13.25, $p = 0.004$). The percentage of newborns with APGAR score of 5 or less at 1 minute and 5 minutes was higher in the chorangiosis group, although the 5-minute APGAR score was the only one statistically significant (RR: 3.31, 95% CI: 1.22–9.01, $p = 0.029$).

Table 2 shows no statistical significance between chorangiosis and preterm delivery, cesarean delivery, birth weight, mean placental weight, or mean umbilical cord pH. Sixteen women with placental chorangiosis had a preterm delivery (61.54%) compared to twenty-nine women in the control group (55.77%). Additionally, 71.43% of women with placental chorangiosis had a cesarean section compared to 59.62% in the control group.

Four cases and five controls gave birth to either twins or triplets; consequently, the number of responses related to the pregnancy outcomes for a few variables was increased to a maximum of 88 during the analysis (Table 2). These variables include the APGAR score at 1 and 5 minutes (n = 88), newborn birth weight (n = 88), placental weight (n = 70), and umbilical cord pH (n = 59), based on the availability of related information.

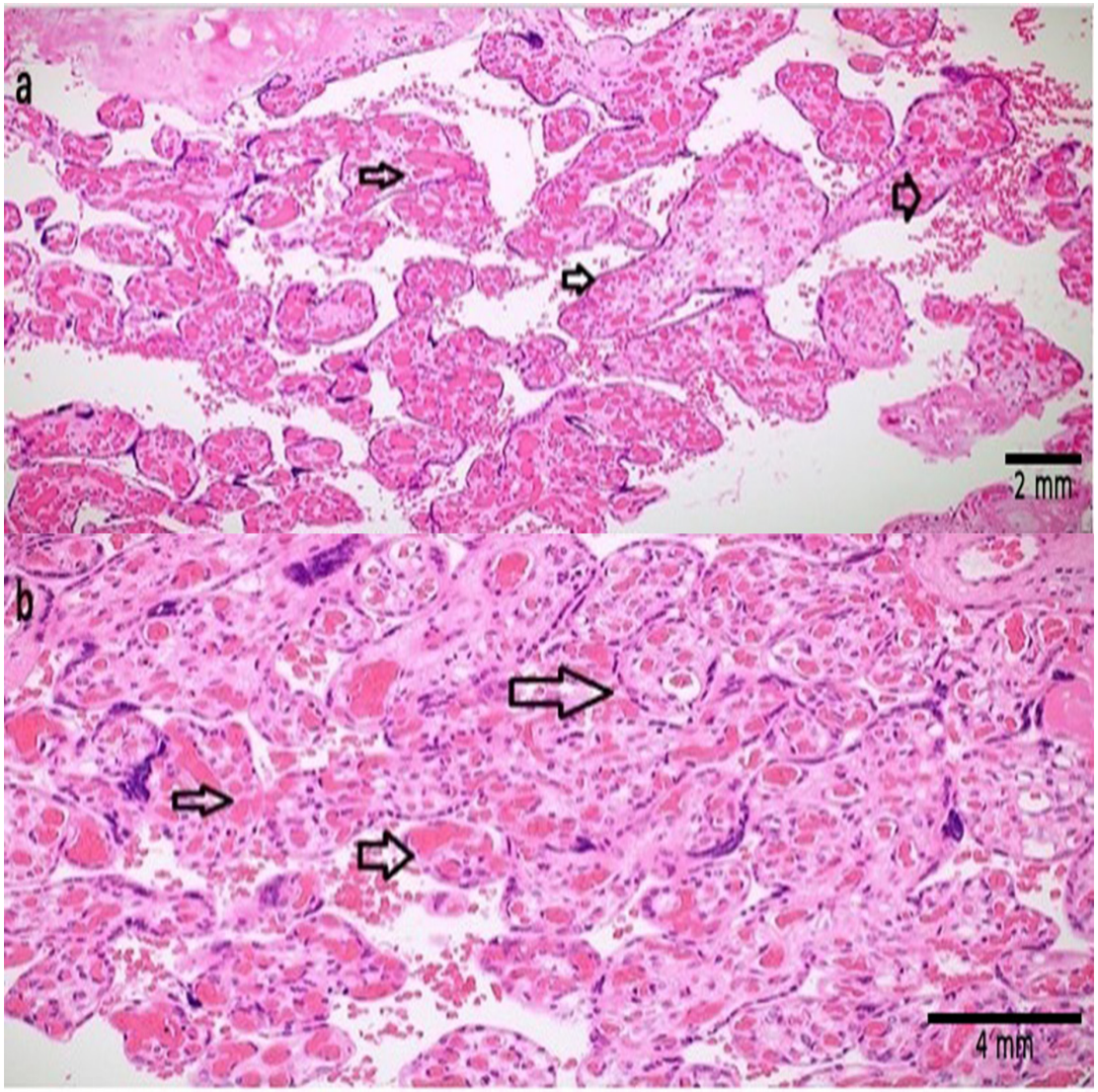

Fig. 1. Placental chorangiosis histopathology. (a) shows a photomicrograph of a placenta with an increased number of capillaries (indicated by arrows) within the chorionic villi (×100). (b) Close-up magnified view. The placental sections were stained with hematoxylin and eosin (H&E) (×200).

4. Discussion

It has been suggested that prolonged placental hypoperfusion or tissue hypoxemia triggers several compensatory changes in the placenta in adaptation to the low oxygen supply, including vascular remodeling, leading to chorangiosis [8]. Suzuki *et al*. [8] conducted a study on forty-seven pregnant women using near-infrared spectroscopy to measure placental tissue oxygen index (TOI) values. Furthermore, they retrospectively compared these values with the detection of placental chorangiosis, which was observed in cases with small-for-gestational-age (SGA) newborns and/or maternal complications. They found significantly elevated TOI values in cases of chorangiosis, indicating high oxygen saturation in the intervillous spaces [8].

Chorangiosis is a disease that is not yet well understood, characterized by overlapping contributing maternal, fetal, and placental factors, and an unclear etiology [2]. Previous studies have reported an association between chorangiosis and several maternal conditions, including maternal age, obesity, smoking, DM, HTN, drug use, and infections [1,6]. In our study, we did not include DM and HTN as these risk factors are well-established in the literature, and we acknowledge this as a limitation to our study. Chorangiosis has also been reported in pregnancies and placentas from women who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing coronavirus disease 19 (COVID-19). In a review by Wong *et al*. [9], the most common finding in placentas showing evidence of SARS-CoV-2 infection after the second half of pregnancy was changes related to maternal vascular malperfusion in the one-third of patients, inflammation in another third, and fetal vascular malperfusion in

Table 1. Relation of maternal risk factors with chorangiosis among cases (n = 26) and controls (n = 52).

Maternal risk factor	Cases n (%) (Total = 26)	Controls n (%) (Total = 52)	Crude OR	Adjusted OR	*p*-value	95% CI of Adjusted OR	
Maternal age							
15 to 24 years	3 (11.54%)	8 (15.38%)	1	1			
25 to 34 years	15 (57.69%)	28 (53.85%)	1.43	1.51	0.610	0.310	7.351
35 to 44 years	8 (30.77%)	16 (30.77%)	1.33	1.26	0.812	0.191	8.266
BMI							
25 or less	3 (11.54%)	11 (21.15%)	1	1			
More than 25	23 (88.46%)	41 (78.85%)	2.06	2.15	0.300	0.506	9.100
Gestation type							
Singleton	22 (84.62%)	47 (90.38%)	1	1			
Multiple gestion	4 (15.38%)	5 (9.62%)	1.71	1.33	0.710	0.298	5.923
Gravidity							
Less than three times	13 (50%)	24 (46.15%)	1	1			
Three or more times	13 (50%)	28 (53.85%)	0.86	0.85	0.846	0.170	4.277
Parity							
None (primigravida)	10 (38.46%)	17 (32.69%)	1	1			
Less than 3	7 (26.92%)	19 (36.54%)	0.63	0.62	0.504	0.152	2.525
3 or more	9 (34.62%)	16 (30.77%)	0.96	1.11	0.912	0.167	7.412

BMI, body mass index; n, number; OR, odds ratio; CI, confidence interval.

almost 10% of the patients. Chorangiosis constituted the most common histopathological change related to fetal vascular malperfusion (33.3%) [9].

The study of Antolini-Tavares *et al*. [10] analyzed 91 placental discs from COVID-19-positive women and 42 from negative cases. Maternal vascular malperfusion was significant in the COVID-19-positive group. Additionally, three placentas exhibited COVID-19-related placentitis. Decidual arteriopathy was associated with infection in first-/mid-trimester, while chorangiosis was observed in cases of asymptomatic infections [10].

In a study by Surekha *et al*. [11] on 212 women, 58% were seropositive for SARS-CoV-2 IgG. Placental histology showed a significant increase in villous hypervascularity, dilated villous capillaries, and syncytiotrophoblasts in the seropositive group, suggesting placental hypoxia. SARS-CoV-2 seropositivity emerged as an independent risk factor for severe chorangiosis, dilated blood vessels, syncytiotrophoblasts, and villus agglutination [11].

In the study of Vafaei *et al*. [1], they compared 308 cases of chorangiosis with 308 controls. Their results showed that chorangiosis cases had significantly higher rates of preeclampsia, DM, cesarean section, oligohydramnios, fetal anomaly, stillbirths, and neonatal intensive care unit (NICU) admissions, while also exhibiting lower rates of the amniotic fluid index, birth weight, cord pH amount, 1st and 5th APGAR scores (p-value < 0.05 for all) [1]. On the other hand, Petersen *et al*. [5] showed no association between placental chorangiosis and several maternal risk factors and obstetrics outcomes, such as hypertensive disorders, DM, or preterm deliveries.

Chorangiosis was previously believed to not occur in normal placentas. However, Akbulut *et al*. [12] reported that 14% of placentas had chorangiosis, and none of the cases were attributed to maternal disorders or fetal complications.

Our study found no statistically significant correlation between chorangiosis and the evaluated maternal factors, such as BMI, gestation type, gravidity, and parity, which is consistent with the findings of Torous *et al*. [13]. Our results showed that one-third of chorangiosis is associated with advanced maternal age. Surprisingly, two-thirds of cases occurred in women younger than the age of 35 years, which is inconsistent with the risk factors cited in the literature. Similar to our study, chorangiosis was found with high frequency in women $\geq$35 years old (40.5%) compared to younger women (26.7%), although these results did not reach statistical significance [13].

On the other hand, the incidence of chorangiosis was lower among women with multiple gestations (twins/triplets) (15.38%) and higher among multiparous women (61.54%), consistent with previous studies [13]. It has been suggested that chronic fetal hypoxia resulting in chorangiosis, coupled with the stress of labor, can lead to abnormal fetal heart rhythms, thus increasing the rates of cesarean section deliveries. In this study, although most women among the cases and controls opted for a cesarean section delivery, the rate was higher among the cases (71.43% *vs.* 59.62%), which is consistent with previous reports. However, there was no statistically significant correlation between chorangiosis and cesarean delivery [13].

Chorangiosis has also been linked to poor fetal outcomes, including major congenital anomalies, congestive

Table 2. Association of pregnancy outcomes with chorangiosis among the study participants.

Pregnancy outcome	Cases n (%) (Total = 26)	Controls n (%) (Total = 52)	Total (%)	*p*-value	RR	95% CI of RR
Abortion in current pregnancy						
No	21 (80.77%)	52 (100%)	73 (93.6%)	0.003	21.59	1.24, 376.20
Yes	5 (19.23%)	0 (0.0%)	5 (6.4%)			
Gestational age at delivery						
Preterm	16 (61.54%)	29 (55.77%)	45 (57.7%)	0.627	1.10	0.75, 1.63
Early/full/late/post-term	10 (38.46%)	23 (44.23%)	33 (43.3%)			
Mode of delivery (excluding abortions, n = 73)						
Cesarean section	15 (71.43%)	31 (59.62%)	46 (63.01%)	0.250	1.20	0.84, 1.70
Vaginal (spontaneous/induced)	6 (28.57%)	21 (40.38%)	27 (36.99%)			
Born alive						
Yes	17 (65.38%)	48 (92.31%)	65 (83.3%)	0.004	4.50	1.53, 13.25
No (abortions and IUFD)	9 (34.62%)	4 (7.69%)	13 (16.7%)			
APGAR score at 1 minute (n = 88)						
0 to 5	12 (38.71%)	12 (21.05%)	24 (27.28%)	0.076	1.84	0.94, 3.59
More than 5	19 (61.29%)	45 (78.95%)	64 (72.72%)			
APGAR score at 5 minutes (n = 88)						
0 to 5	9 (29.03%)	5 (8.77%)	14 (15.90%)	0.029	3.31	1.22, 9.01
More than 5	22 (70.97%)	52 (91.23%)	74 (84.10%)			
Birth weight (n = 88)						
Normal	8 (25.81%)	22 (38.59%)	30 (34.09%)	0.227	1.21	0.90, 1.62
Low to extremely low	23 (74.19%)	35 (61.41%)	58 (65.91%)			
Mean placental weight by gram (SD)	451.16 (188.97)	399.13 (114.16)	420.68 (150.71)	0.193#		
Mean umbilical cord pH (SD)	7.26 (0.15)	7.28 (0.09)	7.27 (0.11)	0.532#		

APGAR, Appearance, Pulse, Grimace, Activity, and Respiration; IUFD, intrauterine fetal death; n, number; SD, standard deviation; RR, relative risk; CI, confidence interval.

p-value is derived from the *t*-test instead of the chi-square test.

heart failure, fetal cardiomegaly, fetal hemolytic anemia, thrombocytopenia, APGAR scores less than 5, irreversible central nervous system injuries, stillbirths, and neonatal deaths. A study by Wu *et al*. [2] analyzed 900 neonates. The neonates were classified into chorangiosis group and control groups (n = 450 each) based on whether their placental pathology showed chorangiosis. The chorangiosis group had a higher rate of cesarean section deliveries, maternal gestational HTN, and incidence of several health issues, including congenital malformation, low APGAR score, and brain injury compared to the control group [2].

Rakha *et al*. [14] conducted a study to evaluate placental pathologies in twenty-one fetuses diagnosed with major congenital heart disease (CHD) through fetal echocardiography. They found that hypoplastic left heart syndrome was the most common lesion and detected significant differences in middle cerebral artery (MCA) systolic/diastolic (S/D) ratio and pulsatility index. Placental histopathologies were demonstrated in 85.7% cases, predominantly involving fetal malperfusion lesions, especially chorangiosis [14].

Miyoshi *et al*. [15] explored the link between placental pathology and fetal heart failure in 168 singletons with a CHD and/or arrhythmia, along with 52 gestational age-matched controls. The study found that chorangiosis, premature and edematous villi, and increased nucleated red blood cells in villous vessels were higher in cases of fetal heart failure cases [15].

Our results show a statistically significant difference in women with placental chorangiosis regarding the risk of abortion, IUFD, and low APGAR score at 5 minutes (RR: 21.59, 95% CI: 1.24–376.20, $p = 0.003$), (RR: 4.50, 95% CI: 1.53–13.25, $p = 0.004$) and (RR: 3.31, 95% CI: 1.22–9.01, $p = 0.029$), respectively. Placental pathology reports of perinatal deaths in New Zealand from 2008 to 2017 were analyzed in the study of de Graaff *et al*. [16]. South Asian women had higher rates of maternal vascular malperfusion among preterm deaths and higher rates of abnormal villous morphology among term deaths, mostly due to increased rates of chorangiosis [16].

Recently, Valdovinos-Bello *et al*. [3] correlated intrahepatic cholestasis of pregnancy (ICP) and placental chorangiosis. Chorangiosis and arteriovenous malformation without intraplacental thrombosis were more prevalent in normal weight rather than obese ICP patients [3].

The relationship of fetal weight and chorangiosis differs in two recent studies [17,18]. Mehreen *et al*. [17] compared two cohorts of placentas from singleton term deliveries. They found that large-for-gestational-age (LGA) pla-

centas had higher birth weight babies, obesity, hypertensive disorders, pre-gestational, and GDM. LGA placentas had a higher prevalence of villous chorangiosis and increased expression of CD15 in villous capillary endothelium [17]. In the study of Dankó *et al*. [18], placental slides, cardiotocograms, and neonatal parameters were analyzed retrospectively in fitty cases of FGR. Reduced baseline variability and lack of accelerations were associated with poor neonatal outcomes. Maternal vascular malperfusion, avascular villi, villous immaturity, and chorangiosis were more common in cases with reduced baseline variability and absent accelerations [18].

Hochberg *et al*. [19] found that women with polycystic ovary syndrome (PCOS) were more likely to develop GDM. The study compared 47 women with PCOS to 1121 ovulatory controls and showed that 38.3% of the former group developed GDM compared to 9.8% of the latter ($p < 0.001$). Placentas from women with PCOS were more likely to exhibit abnormalities such as circumvallate placentas, hypercoiled umbilical cords, villitis of unknown etiology, chorangiosis, and nucleated fetal red blood cells [19].

4.1 Strength and Limitation of the Study

The strength of our study is that it is a case-control study that primarily explored the association between chorangiosis, and fetal outcomes based on the data availability. Our study has several notable limitations. Firstly, we included a small number of cases, although this was due to the lower incidence of chorangiosis and not all placenta were evaluated by histopathology for all of our patients in our center. Secondly, as stated above in the discussion, placental chorangiosis has many evolving risk factors that were not included in our study such as: DM, HTN, PCOS and infections.

4.2 Clinical Implication of the Study

Obstetricians should encourage placental histopathology for all cases with maternal or fetal risk factors to study the role of placental pathologies, including chorangiosis.

4.3 Recommendation for Further Studies

The microscopic examination of the placenta provides essential information about the pathophysiological changes occurring during pregnancy. Thus, larger-scale multicenter studies are recommended to determine further the etiology of chorangiosis, elucidate the mechanism by which it is implicated in poor outcomes, investigate its association with maternal and fetal risk factors, and assess future implication and recurrence risk in subsequent pregnancies.

5. Conclusion

Placental chorangiosis is a rare pathological change in the placenta and may result from several maternal and fetal disorders. When present, it can be an ominous indicator of chronic fetal hypoxia and poor obstetrical outcomes.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

All authors jointly contributed to the conception and design of the study. NA: design of the study, obtaining ethical committee approval, helped in the review of literature, revision of results and data analysis, writing the manuscript. MA: Histopathological work, review of literature and revision of the manuscript. WA: design of the study, reviewing the literature, sharing in the collection of data, revision of results and data analysis, and contributing to writing the manuscript. KA: design of the study, revision of results and data analysis, writing the manuscript. GA helped in the review of literature and revision of the manuscript. MAMA: Data collection. LA: Data collection. ASAH: helped in the review of literature, revision of results and data analysis, writing the manuscript and corresponding author. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Following local regulations, the protocol gained ethical and research approval from t the Institute's Ethical Committee, College of Medicine, King Saud University IRB number: (E-20-4906). We confirm that all methods were performed by the relevant guidelines and regulations according to the Declaration of Helsinki. All Participants had informed consent before we carried out this study.

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Conflict of Interest

The authors declare no conflict of interest.

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