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REVIEW ARTICLE

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Maternal and fetal outcomes of intraplacental choriocarcinoma complicated by fetomaternal hemorrhage: a systematic review
A risk in pregnancy that is difficult to diagnose

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ABSTRACT

Introduction: Intraplacental choriocarcinoma is a gestational trophoblastic neoplasia located within the placenta. Due to the usual silent presentation, more than half of the cases are diagnosed incidentally. It has been demonstrated that this pathology is linked to feto-maternal hemorrhage (FMH), stillbirth, and intrauterine growth restriction. The aim of our review was to establish if there are recurrent signs that might lead to an early diagnosis and better management in cases complicated by FMH.

Materials and methods: We performed a systematic review of the literature from 2000 up to March 2023. The adopted research strategy included the following terms: (gestational choriocarcinoma obstetrics outcome) AND (intraplacental choriocarcinoma) AND (gestational choriocarcinoma). The MEDLINE (PubMed), Google Scholar, and Scopus databases were searched.

Results: The research strategy identified 19 cases of FMH coexisting with intraplacental choriocarcinoma (IC), as described in 17 studies. The perinatal mortality rate was 36.8%. In eight cases, histological diagnosis of IC was made post-delivery. Metastatic lesions were found in 75% (6/8) of described cases. One case of maternal death has been described. Chemotherapy was necessary in seven cases. Sporadical prenatal ultrasound signs were described.

Discussion: The diagnosis of IC is usually delayed, mostly due to aspecific symptoms and signs. Histological analysis of the placenta, when not routinely performed, should be performed when warning symptoms are encountered. The maternal prognosis was good, with a mortality rate of 5.5%. A fertility-sparing approach is always possible even in the presence of metastasis. Chemotherapy seems to be useful in cases of maternal and neonatal metastasis.

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Introduction

Gestational trophoblastic neoplasia is a rare tumor that arises from cells of conception, either from a molar pregnancy or a normal euploid pregnancy [1]. Intraplacental choriocarcinoma (IC) is a gestational trophoblastic neoplasia located within the placenta and represents 2% of all gestational trophoblastic tumors. It has an estimated overall incidence of one case per 50,000 pregnancies [2,3].

Clinically, IC can be silent or paucisymptomatic, with vaginal bleeding being the most common symptom [4]. The metastatic form is less common with possible maternal, neonatal, and/or childhood diseases. The most frequent metastatic sites are the lungs, brain, uterus, and the vagina [5].

Due to the usual silent presentation of IC, more than half of the cases are diagnosed incidentally [6]. Placental histological examination is not routinely performed in most centers; therefore, histological examination is usually delayed after the occurrence of major complications.

Benson et al. [7] described the first case of massive feto-maternal hemorrhage (FMH) as a complication of IC in 1962. Thereafter, other reports documented an association between IC and FMH. Moreover, IC is

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associated to stillbirth and fetal growth restriction [8,9]. In these scenarios, a post-partum placental histopathological examination is required, which might lead to the diagnosis. Alternatively, when the maternal and newborn's outcomes are optimal, the most common symptoms that lead to a diagnosis are persistent vaginal bleeding, with dilatation and curettage being performed [2]. Rarely, the patient shows metastasis-related symptoms such as persistent coughing or neurological alterations [10].

Most frequently, IC cases are associated with elevated serum human chorionic gonadotropin levels, which can be used for the diagnosis and monitoring of the disease [5].

When IC is confirmed, a thorough examination of the patient and newborn is warranted, and the mother should be referred urgently to a referral center for further evaluation and to determine the subsequent therapy according to the established guidelines [5].

Usually, the prognosis for IC is good, with a cure rate approaching 100% for both the mother and the newborn. However, when associated with FMH, fetal and neonatal distress are frequent with the need for advanced therapy and prolonged stay in the NICU [11].

The aim of our review was to establish whether there are recurrent clinical signs and symptoms or ultrasound signs that might lead to an early diagnosis of IC in case of FMH, and thus for a better management.

Materials and methods

This systematic review was approved by Institutional Review Board of the Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy (RC 08/2020).

The MEDLINE (PubMed), Google Scholar, and Scopus databases were searched from 2000 up to May 2023. Only articles published in English or French languages were included. The research strategy adopted included different combinations of the following MESH terms: (gestational choriocarcinoma obstetric outcome) AND (intraplacental choriocarcinoma) AND (gestational choriocarcinoma) with the aim to identify only women in whom IC was complicated by FMH. The following variables were considered: women's age, gestational age at delivery, type of delivery, ante and post-partum maternal, fetal and newborn's symptoms and outcome, newborn weight, and the need for chemotherapy.

Cases of IC without documented FMH or histological diagnosis of IC, were excluded.

Identified studies were examined for year, citation, title, authors, abstract, and full texts. Duplicates were identified through manual screening performed by two researchers and then removed (G.S., R.G.). PRISMA guidelines were followed [12]. A PRISMA flow diagram of the selection process is presented in Table 1. The systematic review was not submitted to PROSPERO [13] as only a limited number of case reports have been reported in the literature. For eligibility process, three authors independently screened the titles (G.S., R.M.G., and G.O.) and abstracts of all non-duplicated papers and excluded those not pertinent to the topic. The same three authors independently reviewed the full text of eligible papers and identified those that responded to inclusion criteria and that were subsequently included in the review. Discrepancies were resolved through consensus. Due to the rarity of this pathology, the included studies were all case reports. Therefore, we present the data in a descriptive manner. The inclusion of only case reports represents a risk of bias. We used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports (Table 2) to assess the methodological quality of the included studies. This check list evaluates the demographic characteristics, clinical history and conditions, management and post-intervention clinical conditions of the women (Supplementary Table S1).

Results

The research strategy identified 19 cases of IC coexisting with FMH described in 17 studies. Table 3 summarizes the characteristics of these cases [8,10,14–27].

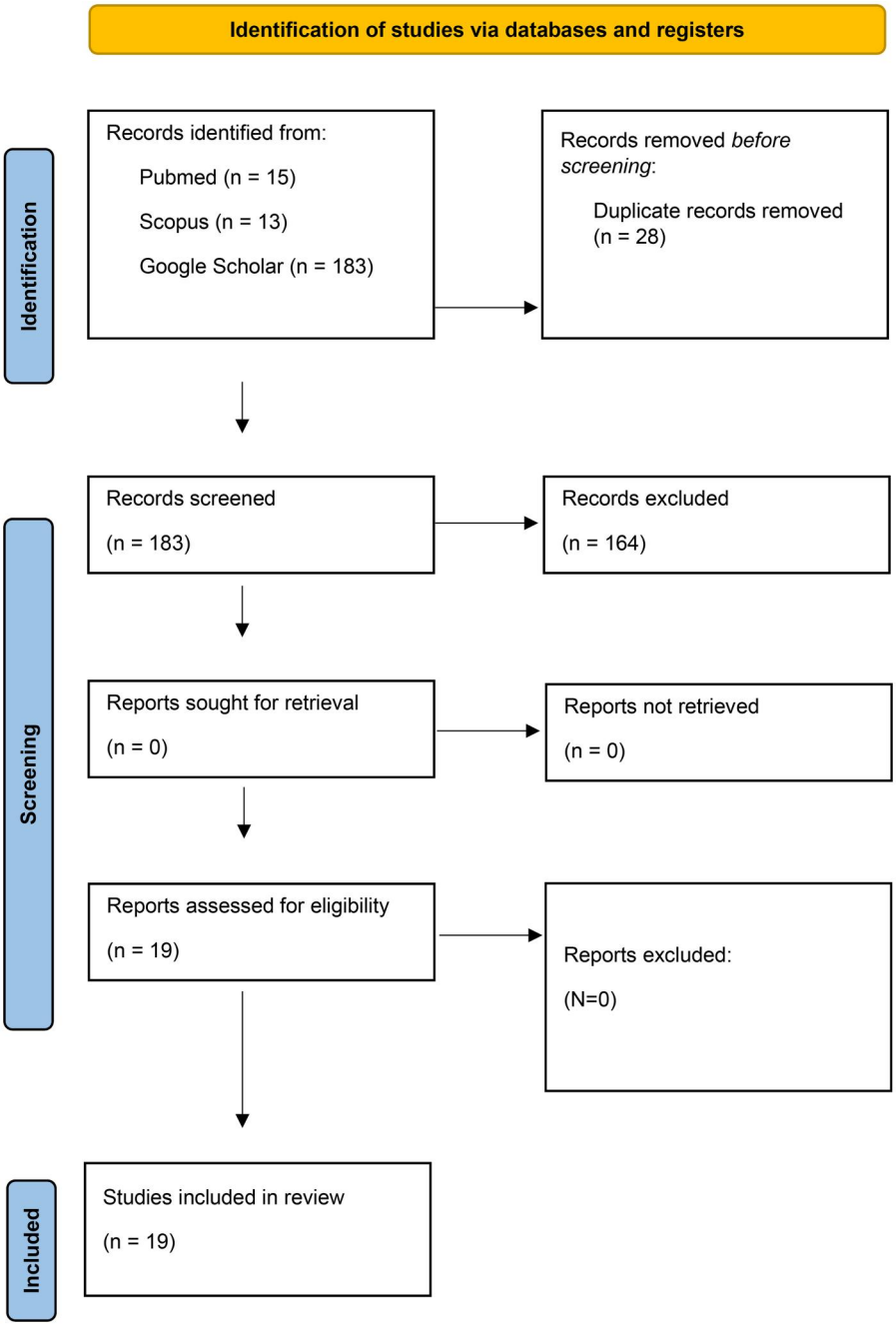
The mean women's age was 31.1 ± 5.9 years (range 21–47). Most pregnancies were uneventful, with term delivery. Method of conception was not specified in the studies.

One case of maternal death was reported (5.5%). When described, the main reason for seeking medical assistance was reduced fetal movements, with subsequent emergency cesarean section performed for pathological fetal heart rate at cardiotocography (14/19 of reported cases, 73.7%). The second most frequent symptom was persistent vaginal bleeding weeks after delivery.

The mean gestational age at delivery was 38 ± 2 weeks (range 31–41) with mean birthweight of 2747 ± 531 g (range 1878–3275 g). The sex of the fetuses at birth was male in seven cases, female in five cases, while in remaining seven cases it was not reported.

Fetal growth restriction was described in four cases (21%), while intrauterine fetal death in three cases (15.7%), all delivered vaginally. Additional four cases of neonatal deaths were described after failed resuscitation maneuvers (21%). Thus, the overall perinatal mortality rate was 36.8% (7/19).

Table 1. PRISMA flow diagram of study selection.



At birth, most newborns experienced distress, with anemia being the most common sign (15/20, 75%). Blood transfusion was reported in 12 of the 19 cases (63.16%). Infant metastases were found only in one case [25].

Regarding the ultrasound signs of FMH in case of IC, no definitive signs were reported. Beside the fetal growth restriction in three fetuses, the following ultrasound signs have been described: fetal cardiomegaly and ascites ($n = 1$), oligoamnios ($n = 1$), and signs of anemia at Doppler velocimetry performed due to a pathological fetal heart rate at cardiotocography ($n = 1$).

Tumor size was described in 11 studies, with mean diameter of 16.7 ± 6 mm. No correlation was detected between tumor size and maternal or perinatal outcomes or fetal anemia grade. However, in a case of the larger mass (30 mm), there was a more severe fetal anemia (Hb 2.1 g/dL).

In eight cases (42%), histological confirmation of IC was obtained a few days post-delivery, with placental examination required shortly after delivery due to

Table 2. Joanna Briggs Institute Critical Appraisal Checklist for case reports.

	Title	Reference	D1	D2	D3	D4	D5	D6	D7	D8
1	Fetomaternal hemorrhage: a clue to intraplacental choriocarcinoma and neonatal malignancy	Simões et al. [14]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
2	Fetomaternal hemorrhage caused by an intraplacental choriocarcinoma	Jeong et al. [15]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
3	Hémorragie fœtomaternelle sur choriocarcinome placentaire	Touboul et al. [16]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
4	Intraplacental choriocarcinoma with fetomaternal hemorrhage: a case study and literature review	Takahashi et al. [17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Intraplacental choriocarcinoma and fetomaternal haemorrhage and maternal disseminated intravascular coagulopathy in a term pregnancy: a case report	Hookins and Vatsayan [18]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
6	Intraplacental choriocarcinoma coexisting with fetomaternal hemorrhage: case report, chemotherapy management, and literature review	She et al. [11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Fetomaternal hemorrhage caused by intraplacental choriocarcinoma: a case report and review of literature in Japan	Koike et al. [19]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
8	Massive feto-maternal hemorrhage: an	Lam et al. [20]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
9	early presentation of women with gestational choriocarcinoma		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Massive fetomaternal hemorrhage caused by an intraplacental choriocarcinoma: a case report	Henningsen et al. [21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	Prenatal findings in a case of massive fetomaternal hemorrhage associated with intraplacental choriocarcinoma	Aso et al. [8]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	Term pregnancy with choriocarcinoma presenting as severe fetal anemia and postpartum hemorrhage	Peng et al. [22]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
13	Intraplacental choriocarcinoma with fetomaternal transfusion	Takai et al. [23]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
14	Intraplacental choriocarcinoma:	Jiao et al. [24]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
15	systematic review and management guidance									
16	Infantile choriocarcinoma with idiopathic massive fetomaternal hemorrhage	Chou et al. [25]	No	No	Yes	Unclear	Yes	Yes	Yes	Yes
17	Intraplacental choriocarcinoma associated with pregnancy continuum: a diagnostic dilemma	Datta et al. [10]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
18	Intraplacental choriocarcinoma as an unexpected cause of intrauterine death at term	Nagel et al. [26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19	Intraplacental choriocarcinoma in twin pregnancy causing fetomaternal haemorrhage and single twin demise: case report	Schepisi et al. [27]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes

neonatal complications. In three cases, the timing of the histological diagnosis was not described. In the other eight cases, histological diagnosis of IC was performed up to 3 months post-delivery, with specimen obtained mainly by dilatation and curettage. In these women, metastatic lesions were found in six of the eight cases described (75%), although there was no clear association between delayed diagnosis and the probability of metastasis. Chemotherapy was necessary in 7/19 cases (36.8%). If no other therapy was necessary, patients were monitored by oncological centers using serial blood tests until B-HCG was undetectable. In none of the women, hysterectomy was performed.

Discussion

Synthesis of the findings

The true incidence of IC in case of FMH remains unknown because histopathological placental examination is not routinely performed in all complicated pregnancies with FMH or fetal distress. However, we

Table 3. Characteristics of the cases with IC and FMH included in the review.

Description of the case																					
Mother											Fetus										
Source of data	Age	Gravida/ para	Presentation	Size of tumor	Site of diagnosis	Time of diagnosis after delivery	HCG at diagnosis (IU/L)	Metastasis	Treatment	Outcome	Gestational age	Delivery	Symptoms	CTG	EFW (g)	Gender	Apgar score (1/5 min)	K–B test	Metastasis	Treatment	Outcome	HGB (g/dL)
Takai et al. [23]	35	G2P0	Asymptomatic	20 mm	Placental examination	1–3 days	NA	–	HCG monitoring	Alive	37	Emergency CS	Fetal distress, IUGR (known), neonatal anemia Hb 3.0	Pathological	1878	Male	6/7	Positive for FMH	–	Blood transfusion	Discharged	3
Lam et al. [20]	27	G1	Chest pain 3 weeks after VD	NA	NA	3 weeks	1,200,000	Lung	Chemotherapy	Alive	39	VD	Neonatal anemia Hb 5.8, heart failure	Normal	3160	NA	9/NA	Positive for FMH	–	Blood transfusion	Discharged	5.8
	30	G2P1	Asymptomatic, heavy bleeding 7 weeks after VD	10 mm	D&C, retrospective placental examination	7 weeks	986	Uterus	Chemotherapy	Alive	35	VD	Intrauterine death	–	3000	NA	–	Positive for FMH	–	–	Died	–
Chou et al. [25]	NA	NA	NA	Grossly normal	NA	NA	NA	–	HCG monitoring	Alive	40	Emergency CS	Fetal distress, neonatal anemia	Pathological	3020	Male	5/9	NA	Liver	Blood transfusion; hepatic segmentectomy	Died after rupture of hepatic tumor	5.9
Koike et al. [19]	31	G1	Asymptomatic	NA	Placental examination	1–3 days	NA	–	HCG monitoring	Alive	39	Emergency CS	Fetal distress, IUGR, neonatal anemia Hb 5.1	Pathological	2272	Female	5/6	Positive for FMH	–	Blood transfusion	Discharged	Negative
Nagel et al. [26]	30	G2P0 previous hydatiform mole	Vaginal bleeding 3 months after delivery	Grossly normal	Retrospective placental examination	3 months	11.311 (three months postpartum)	–	Chemotherapy	Alive	40	VD	Intrauterine death	–	3275	Male	–	Positive for FMH	–	–	Died	
Takahashi et al. [17]	30	G1	Reduced fetal movements	20 mm	Placental examination	1–3 days	NA		HCG monitoring	Alive	38 + 2	Emergency CS	Fetal distress, IUGR, neonatal anemia Hb 5.1	Pathological	2272	Female	5/6	NA	–	Blood transfusion	Discharged	5.1
Henningsen et al. [21]	47	P7	Reduced fetal movements	30 mm	Retrospective placental examination	1–3 days	510 (17 days postpartum)	–	HCG monitoring	Alive	35 + 6	Emergency CS	Fetal distress, neonatal anemia Hb 2.1	Pathological	2800	Female	0/7	NA	–	Blood transfusion	Discharged	2.1
Aso et al. [8]	27	G2P1	Reduced fetal movements	15 mm	Placental examination	1–3 days	90,600	–	Chemotherapy	Alive	37	Emergency CS	Fetal distress, neonatal anemia Hb 3.6, hypovolemic shock	Pathological	2450	Male	7/7	NA	–	Blood transfusion	Died	3.6
Datta et al. [10]	23	G2P1	Reduced fetal movements, persistent vaginal bleeding 4 weeks post-partum, headache + chest pain 2 months later	NA	Retrospective placental examination	2 months	766,433	Lung	Chemotherapy	Alive	36	CS	Fetal distress, neonatal anemia Hb 5.0	Pathological	2925	NA	8/10	Positive for FMH	–	NA	Discharged	5
Touboul et al. [16]	34	G1	Asymptomatic	13 mm	Placental examination	1–3 days	NA	–	HCG monitoring	Alive	41	Operative vaginal delivery	Asymptomatic, neonatal anemia Hb 7.6	Non reassuring	3820	NA	8	Positive for FMH	–	NA	Discharged	NA
Jeong et al. [15]	27	G1	Reduced fetal movements	NA	Placental examination	4 days	195 (18 days post-partum)	–	HCG monitoring	Alive	31 + 4	Emergency CS	Fetal cardiomegaly and ascites, fetal distress	–	2020	NA	3/5	NA	–	Blood transfusion, mechanical ventilation	Died	NA
	34	G3P2		NA	D&C	2 weeks	538,312	Uterus; lung	Chemotherapy	Alive	37	Emergency CS		Pathological	2650	Male	2/3	NA	–	Blood transfusion	Discharged	3.7

(*continued*)

Table 3. Continued.

	Description of the case																			
	Mother									Fetus										
Source of data	Age	Gravida/ para	Presentation	Size of tumor	Site of diagnosis	Time of diagnosis after delivery	HCG at diagnosis (IU/L)	Metastasis	Treatment	Outcome	Gestational age	Delivery	Symptoms	CTG	EFW (g)	Gender	Apgar score (1/5 min)	K–B test	Metastasis	Treatment	Outcome	HGB (g/dL)
Peng et al. [22]			Reduced fetal movements, Vaginal bleeding 2 weeks post CS										Oligoamnios, fetal distress, neonatal anemia Hb 3.7									
Jiao et al. [24]	32	G5P4	Asymptomatic	20 mm	Placental examination	NA	NA	–	HCG monitoring	Alive	40	VD	Intrauterine death	–	NA	NA	–	Positive for FMH	–	–	Died	
	32	G1P0	Asymptomatic	<10 mm	Placental examination	NA	NA	–	HCG monitoring	Alive	40	Emergency CS	Fetal distress, neonatal anemia	Pathological	NA	Female	NA	NA	–	Blood transfusion	Discharged	NA
She et al. [11]	21	G1	Reduced fetal movements	20 mm	Placental examination	6 days	31,280 (6 days postpartum) 42,269 (95 days postpartum)	Uterus, lung	–	Died	35	Emergency CS	Fetal anemia diagnosed with US, neonatal anemia Hb 2.6	Pathological	2170	Male	8/8	Positive for FMH	–	Blood transfusion	Discharged	30.4
Hookins and Vatsayan [18]	31	G1	Reduced fetal movements, DIC after CS, vagina bleeding 3 weeks after CS	11 mm	D&C	3 weeks	1,000,000 (3 weeks postpartum)	Uterus, right adnexa	Chemotherapy	Alive	38 + 1	Emergency CS	Fetal distress, neonatal anemia Hb 4.7	Pathological	3050	Male	8/7	Positive for FMH	–	NA	Discharged	NA
Simões et al. [14]	35	G2P1	Vaginal bleeding after VD	NA	D&C	2 months	66.780	Lung	NA	Alive	39	VD	Neonatal distress, anemia Hb 3.6	Non reassuring	3200	Female	7/9	Not performed	–	Blood transfusion, antibiotic therapy	Discharged	Negative
Schepisi et al. [27]	34	G1P0, D/D twin pregnancy	Preterm labor, twin A fetal distress	15 mm	Placental examination	1–3 days	18 (1 month post-partum)	–	HCG monitoring	Alive	35	Emergency CS	Twin A: fetal distress, neonatal death, neonatal anemia Hb 2.1	Pathological	NA	NA	NA	NA	–	–	Died	NA
													Twin B: SGA, no complication at birth	–	NA	NA	NA	NA	–	–	Discharged	NA

found a high rate of perinatal mortality, that is 36.8%. Unfortunately, as emerges from our review, prenatal ultrasound diagnosis does not help in early diagnosis, as there are no conclusive ultrasound signs except in the final stages of severe anemia and fetal distress, which lead to fetal heart rate alterations. In 16% of fetuses, a fetal growth restriction was described, rising the hypothesis regarding a possible association between these conditions. One case of maternal death was described. In the remaining cases, IC is silent or correlated with nonspecific symptoms, such as vaginal bleeding. Due to this aspect of the disease, diagnosis is commonly delayed up to months after delivery [4] often requiring chemotherapy, but no cases of hysterectomy have been described.

Clinical and research implications

Our review highlights that when IC is associated with FMH, perinatal mortality and distress are frequent. Most cases end with emergency cesarean section (68.42%), with fetal distress occurring in otherwise uneventful, low-risk pregnancies. FMH occurs when the malignant growth of trophoblastic tissue from the IC invades the uterine muscle and maternal vascular spaces, leading to leakage of large fetal hemorrhage into the maternal circulation and consequent fetal anemia. The event is mostly sudden and unpredictable. This explains the high perinatal mortality rate (36.8%) despite an advanced gestational age at delivery (mean 38 + 2 weeks).

Even if no correlation is detectable between tumor size and anemia grade in the fetus, the largest mass found in our review was associated with a more severe fetal anemia grade. Indeed, a major infiltration of the myometrial wall by a larger lesion may lead to a higher blood loss or sequestration.

The maternal prognosis in IC associated with FMH was better than the perinatal prognosis, although one maternal death was reported (5.5%) [10]. There is no clear association in the literature between diagnostic delay and the presence, site, and number of metastases, but our review shows that in 75% of cases in which there was a diagnostic delay of up to 3 months after delivery, distant metastases were present. Thus, there is a justified assumption that a diagnostic delay (as for many other types of neoplasia) increases the risk of metastases and worsens patient's prognosis.

A fertility-sparing approach is always possible even in the presence of metastasis. Surveillance of serum B-hCG levels is generally sufficient in cases without metastasis, and most tumors spontaneously regress. Chemotherapy seems to be useful in cases of maternal metastasis, with a good prognosis for patients. Treatment based on the FIGO score is indicated as single-agent chemotherapy (methotrexate) in low-risk tumors (FIGO score 0–6) and multi-agent chemotherapy (EMA-CO) in high-risk tumors (FIGO score >6) [5].

In the case of neonatal metastasis, the therapy is based on chemotherapy, with a positive outcome for the newborn, although the event is rare; therefore, more studies should be conducted to confirm these data.

We were not able to identify specific prenatal ultrasound signs in case of IC associated with FMH that might influence the management. As a matter of fact, even if the placental lesion is identified, it enters into the differential diagnosis with other placental masses such as placental chorioangioma, placental teratoma, degenerated myoma, blood clot, or epithelioid trophoblastic tumor [28]. However, we suggest to perform an accurate placental ultrasound examination in all cases of fetal growth restriction or other signs of fetal impairment in order to identify possible placental mass.

Although choriocarcinoma represents a malignant neoplasm of the placenta, its impact on the fetus has some similarities with other benign placental lesions (e.g. multifocal chorangiomatosis, multiple chorangioma syndrome) with adverse outcomes. Fetal anemia induced by benign placental lesions is usually caused by blood sequestration within the lesion. In the case of choriocarcinoma, anemia is mostly caused by infiltration of the uterine wall and maternal vascular space, which induces FMH. Furthermore, choriocarcinoma has the capacity to metastasize, negatively impacting maternal outcome.

In conclusion, choriocarcinoma combines the worst characteristics of benign placental pathologies and the worst behavior of placental neoplasms.

While ultrasound diagnosis has many limitations, histological diagnosis is simpler, with typical lesions [29,30] appearing macroscopically as a heterogeneous, echogenic, vascular masses with necrosis and hemorrhage.

Differential diagnosis has to be made between other placental conditions that may have similar clinical behavior, such as multifocal chorangiomatosis [31], multiple chorangioma syndrome [32] and, lastly, chorangiocarcinoma, an underestimated histological entity with a better prognosis than choriocarcinoma but often not adequately identified [33,34].

Strengths and limitations

To our knowledge, this is the first systematic review on IC and FMH. Despite the scarceness of cases, which

represents the major limitation, we report the largest number of IC with FMH. Moreover, the strength of our study is represented by the long period of time overviewed in the literature. All the studies selected during the eligibility phase have been further evaluated by manual comparison of populations, study settings and authors to avoid overlapping cases.

The limitation of our study is represented by the fact that we included only case reports in the review, which represents a major source of risk of bias. However, this is due to the rarity of this pathology and the low rate of early diagnosis. Other limitations are represented by the lack of standardized criteria for antenatal surveillance and management during the FMH.

Conclusions

Intraplacental gestational choriocarcinoma associated with feto-maternal hemorrhage is a rare condition with high perinatal mortality rate due mainly to severe anemia. The diagnosis of IC is usually delayed, mainly due to the lack of specific symptoms and signs of IC complicated pregnancies.

Histological analysis of the placenta, when not routinely performed, should be performed when warning clinical symptoms or ultrasound signs are encountered. Sudden fetal distress, fetal or neonatal anemia, perinatal death, and unusual post-partum vaginal bleeding might be signs of IC associated with FMH and should be further investigated using placental histological analysis. Even if ultrasound diagnosis is not possible, a prenatal suspicious of a placental lesion can be done through a more stringent ultrasound checks in all cases of demonstrated fetal impairment.

Author contributions

Conceptualization, G.S. and M.B.; methodology, G.S., R.G., and M.B.; software, R.G.; validation, G.S., M.B., M.G., and T.S; formal analysis, G.S., M.B., and S.C.; investigation, G.S., G.O., M.B., and R.G.; data curation, R.G., S.B., and G.S.; writing – original draft preparation, G.S., R.G., and S.C.; writing – review and editing, G.S. and R.G.; visualization, T.S., G.O., M.G., and S.B.; supervision, T.S. and M.G.; project administration, G.S. and M.B. All authors have read and agreed to the published version of the manuscript.

Ethical approval

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved on 15/04/2020 by the Institutional Review Board of IRCCS Burlo Garofolo (RC 08/2020).

Disclosure statement

The authors declare no conflicts of interest.

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Data availability statement

The authors confirm that data supporting the findings of this study are available within the article.

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