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Villous Capillary Malformation and Intermediate Trophoblast Invasiveness: Histopathologic Findings From Fetomaternal Hemorrhage with Gestational Choriocarcinoma

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To editor:

Fetomaternal hemorrhage (FMH) refers to the fetal blood transfection into the maternal circulation, usually involving a bleeding volume exceeding 30 ml. This phenomenon can promptly trigger a sinusoidal fetal heart rate pattern, posing a significant risk of life-threatening fetal anemia and even mortality[1,2] Upon suspicion of FMH, immediate intervention is essential to prevent neonatal death, often leading to the insufficient recognition of placental examination in many published reports. However, an increasing number of FMH case reports have underscored the potential subsequent risk of choriocarcinoma.[3,4]

The incidence of choriocarcinoma (CC) ranges from 1 in 20,000 to 1 in 40,000 pregnancies,[5] with approximately half of these cases arising within 1 year after a seemingly normal pregnancy.[6] Despite the absence of a clear definition for the early forms of gestational CC, the consensus in previous literature suggests that early gestational CC typically manifests as late postpartum bleeding with metastasis. Around 40% of early gestational CC cases have been reported to co-occur with intrapartum FMH. However, to date, no research has elucidated the underlying reasons for the high correlation between FMH and early metastatic CC. Therefore, our study was conducted to investigate this association and reveal the presence of atypical intermediate trophoblasts (ITs) in the placenta of the presented case. The patient has given her consent to publish her clinical information and figures in this journal.

Case presentation

The 30-year-old female, gravida 2 para 2, presented at 40 2/7 weeks gestation due to prolonged and intense uterine contraction pain. The pregnancy had been uneventful until this point. During the 13-hour labor, electronic fetal heart monitoring consistently revealed severe variable decelerations with absent fetal heart rate variability and decreased fetal movements (Fig. 1). Approximately 3 hours after the artificial rupture of the fetal membranes, the patient proceeded to a vaginal delivery, giving birth to an extremely pale male infant weighing 3,120 grams. The infant exhibited peripheral oxygen saturation levels ranging from 45% to 60% and received Apgar scores of 8 at 1 minute, 8 at 5 minutes, and 8 at 10 minutes. The fetal hemoglobin in maternal circulation was detected to account for 7.9% tested by Hb electrophoresis, providing primary evidence of fetal blood transfection. Analysis of umbilical arterial blood at birth indicated metabolic acidosis (pH = 7.150), extremely severe anemia (hemoglobin concentration = 47 g/L), and hypoxemia (blood gas tensions = 4.00 kPa). Following intensive care, the infant demonstrated improvement and was discharged home on day 16 after birth (Fig. 1).

Unfortunately, 5 days later, the patient was readmitted to the hospital, complaining of significant vaginal bleeding for the past 2 days. A physical examination in the emergency department revealed 20 ml of bright red blood accumulated at the posterior vaginal fornix. Upon clearing the blood, more than 100 ml of bright red blood rapidly flowed out of the uterine cavity. Pelvic examinations indicated a normal, large, and mobile uterus. Intravenous oxytocin infusion was promptly administered; however, the bleeding persisted. About 6 hours after admission, the estimated blood loss reached 1,090 ml.

Emergency procedures, including ultrasound-guided uterine curettage and bilateral uterine arterial embolization were immediately performed (Fig. 1). Subsequently, serum human chorionic gonadotropin tests were conducted, revealing levels of 209,555.05 IU/L before uterine curettage and 118,339.83 IU/L after the procedure. The human chorionic gonadotropin level subsequently declined to 73,155.73 IU/L following uterine artery embolization. On the second day, a biopsy pathological examination confirmed the diagnosis of choriocarcinoma. Further systemic

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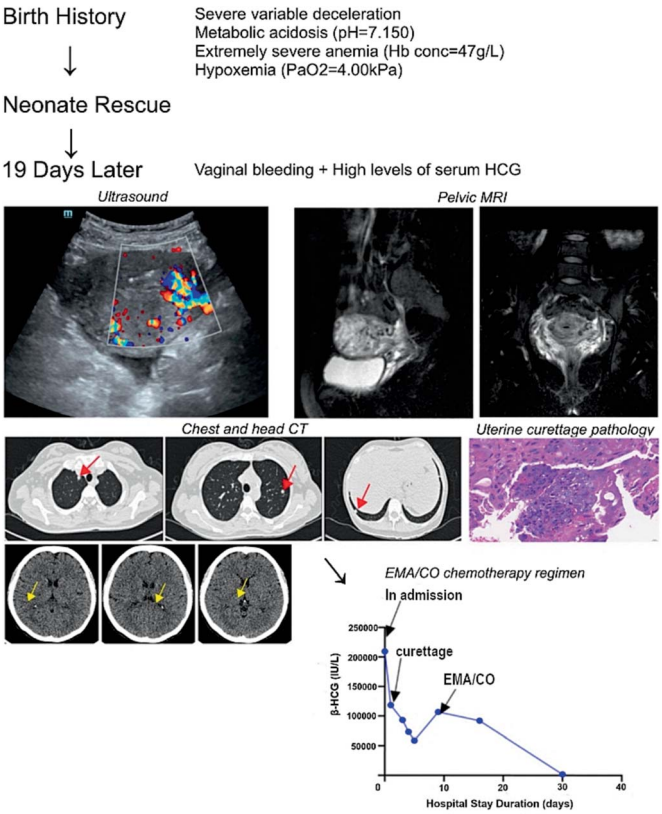

Figure 1. The review of the disease course. Red arrows indicate multiple high-density pulmonary nodules in the bilateral upper lobe and right lower lobe. Yellow arrows indicate spotted high-density signals at the pineal region and posterior horns of the bilateral lateral ventricle. The black arrows indicate crucial treatment time-points. β-HCG: Beta subunits of human chorionic gonadotropin.

inspections were administered: pelvic magnetic resonance imaging revealed uneven thickening of the uterine wall; chest computed tomography identified multiple pulmonary nodules with high density in the bilateral upper lobe and right lower lobe (Fig. 1, red arrow); head computed tomography observed spotted high-density signals at the pineal region and posterior horns of the bilateral lateral ventricle (Fig. 1, yellow arrow).

Pathological findings

We conducted a thorough examination of the placenta, revealing two primary pathological characteristics: typical fetal vascular malperfusion (FVM) and infiltrating behaviors of nuclear atypical ITs, as shown in figures, where they referred to as corresponding placentas. Hematoxylin and eosin (H&E) staining demonstrated extensive vascular ectasia, delayed villous maturation, and segmental hypovascular villi in the placental villi vessels, classified as "FVM." These findings align with nonspecific pathological features observed in the hypoxic placenta, as per the criteria outlined in the "Amsterdam Placental Workshop Group Consensus Statement" (Fig. 2A).[7] The stem villous vessels in this case exhibited a considerable proportion of nucleated erythrocytes, and the average red blood cell density in the lumen and terminal vessel was significantly decreased compared to the normal control (Fig. 2A). Sparse α-smooth muscle actin staining confirmed a remarkable reduction in perivascular smooth muscle. Additionally, occasional discontinuities in the endothelial lining under CD34 staining further supported increased fragility and leakiness of villous capillaries.[8,9] So far, these features represent the first reported instances of vasculopathy lesions in the placenta associated with FMH and CC.

Significantly, we observed the infiltration of atypical ITs into the walls of some villi vessels (Fig. 2A). In this rare case, these nuclear atypical trophoblasts were scattered inside the stem and terminal villi (Fig. 2A), with some undergoing division and even invading and damaging the walls of villi vessels (Fig. 3). Meanwhile, these cells exhibited a remarkable increase in the expression of HLA-G, indicative of immune-; escaping features. At the implantation site, intermediate cells presented an aberrant multinucleate phenotype with the loss of Mel-CAM, hPL, and EGFR. The ITs surrounding vascular lumens exhibited high expression of vimentin, suggesting a tendency toward epithelial-mesenchymal transition and increased invasiveness. The aforementioned ITs could be differentiated by CK7, distinguishing them from decidual cells (Fig. 3 & See Supplemental File 1, http://links.lww.com/MFM/A47).

Discussion

The transition from precancer stages to the development of invasive tumoral processes typically takes several years.[10] Choriocarcinoma, recognized as one of the most highly malignant tumors, exhibits a median onset duration of 13 months from the antecedent pregnancy to diagnosis.[11] In the case we encountered, the manifestation occurred significantly earlier than most gestational choriocarcinomas. A national retrospective study in the UK suggested that approximately 14.9% of gestational choriocarcinomas exhibit initial symptoms within 1 month after delivery. For some very early forms, intraplacental (in-situ) neoplasms have been documented in the placentas.[12]

In our case, although carcinoma in situ was not confirmed, the presence of atypical tumor cells was evident. The atypical ITs primarily localized in the chorion laeve and exhibited an invasive tendency toward villous arteries in terminal and stem villi. These cells had pale cytoplasm and a single uniform appearance, similar to decidual cells.[11] We propose that placentae transform a highly invasive, tumor-like organ that invades the uterus and its vasculature to obtain oxygen and nutrients for the fetus while exchanging waste products. Although primary cancer or precancer lesions in placentae are rare, the immune-inhibitory environment at the maternal-fetal interface could be conducive to tumor-like cell growth. The placenta and decidua are expelled soon after delivery, preventing some tumor and malignant cells in situ from further spreading and growing, making them undetected by clinicians. Hematoxylin and eosin staining may not easily distinguish between IT and decidual cells, but cytokeratin, inhibin-α, and hPL can provide clear distinctions.[11,13]

In this case, the atypical villous ITs positively expressed inhibin α, HLA-G, and Vimentin, exhibited unequal nuclear division, and showed loss of EGFR expression. These ITs are suspected culprits in the malignant transformation into some forms of gestational trophoblastic disease, given their proliferative and invasive properties.[14] The upregulation of vimentin

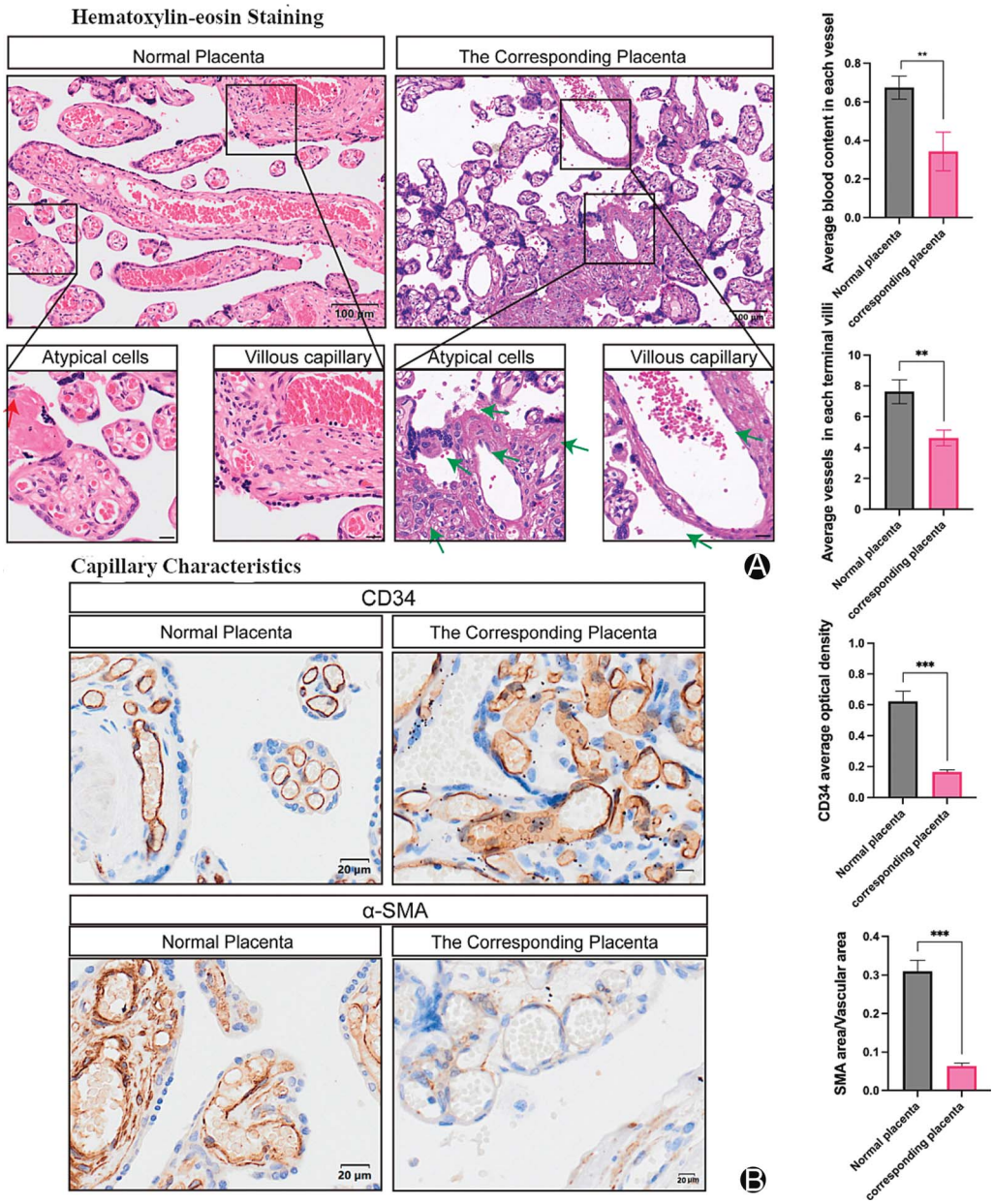

Figure 2. The fetomaternal hemorrhage placenta characteristics: fetal vascular malperfusion. A Representative HE staining images of a normal placenta and the corresponding placenta from the FMH case collected at delivery. The FMH placenta is characterized by decreased vascular density and pronounced vessel dilation. Nucleated red blood cells are visible within the placental vessels of the FMH sample. Green arrows indicate these atypical cells. B The FMH placenta shows a discontinuous endothelial lining and a lack of perivascular smooth muscle compared to the normal placenta. Statistical analysis was based on multiple photographs of placental bed, measured by Fiji Image J (Open-source Version 2.7.0, National Institutes of Health, USA), and data present as mean ± SEM; $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$ versus normal group. FMH: Fetomaternal hemorrhage; SEM: Standard error of the mean.

in epithelial cells may contribute to the migratory and invasive phenotype of metastatic cells.[15] The loss of EGFR may suggest increased invasiveness accompanied by limited replicative potential, as each cell has its finite energy budget.[16] Implantation site ITs could form placental site nodules. Chorionic-type ITs are the origin of some epithelioid trophoblastic tumors and placental site nodules.[17] However, no previous reports have demonstrated a correlation between ITs and FMH or gestational CC.

Although there may be phenotypic changes in ITs, it is challenging to identify specific preliminary ultrasound signals before they form sufficiently sized masses. Indeed, discerning sizable placental lesions poses a significant diagnostic challenge, requiring meticulous differentiation from various other placental masses like chorioangioma syndrome, degenerated myoma, hematoma, etc.[18] The early detection and diagnosis of placental tumors during pregnancy emerge as pivotal focal points for prenatal diagnostic advancements in the foreseeable future.

The increased vascular disruption in the placenta is one of the widely recognized conjectures behind FMH, despite most pathological studies being limited to case reports. Considering the aggressive property of ITs and their endothelium-denuded

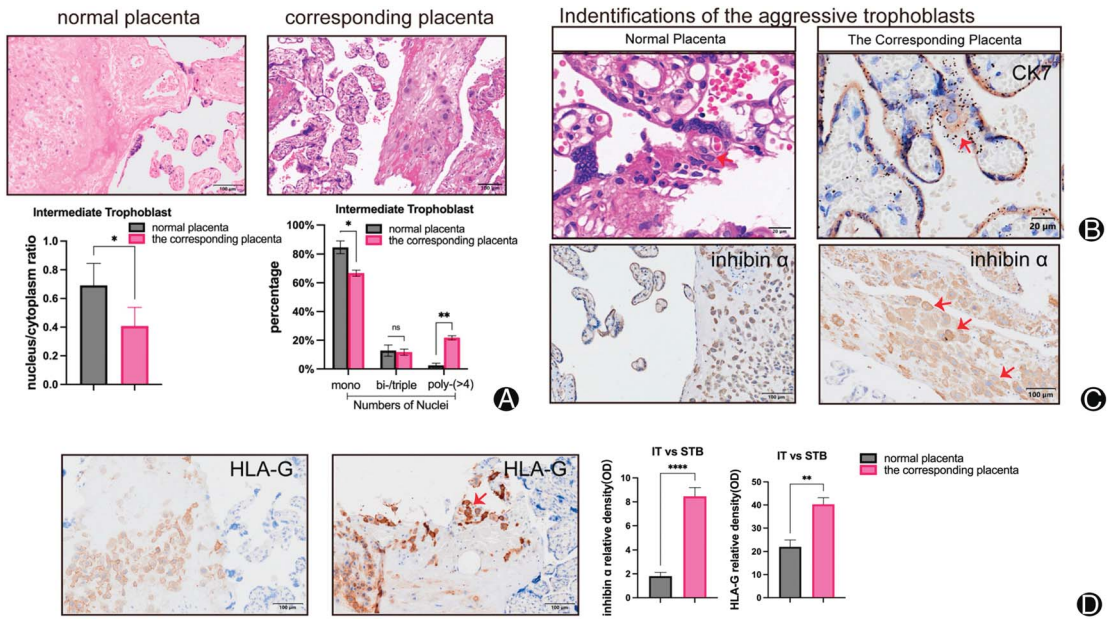

Figure 3. Identification of perivascular trophoblast cells with invasive and destructive tendencies. A Representative H&E staining images show atypical intermediate trophoblasts with unequal nuclear division and polykaryon formation in the FMH-complicated placenta, confirmed by the analysis of nuclear-to-cytosolic ratio and the number of nuclei. B-D Intermediate trophoblasts from decidual cells by immunohistochemical staining for cytokeratin, inhibin-α, and HLA-G. Syncytiotrophoblast densities were used as loading controls for relative expression calculations. Red arrows indicate ITs. Staining intensity quantification utilized Fiji Image J (Open-source Version 2.7.0, National Institutes of Health, USA), with syncytiotrophoblast intensity as the control. Intensities presented as mean ± SEM; ns, not significant. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$ versus the normal group. FMH: Fetomaternal hemorrhage; ITs: Intermediate trophoblasts; H&E: Hematoxylin and eosin; SEM: Standard error of the mean; STB: Syncytiotrophoblast.

characteristics, we suppose that part of perinatal FMH may originate from the precancerous transformation of ITs and involve the breakage of villous capillaries. This intriguing correlation has also been posited by previous researchers. Literature reports suggest that about 38% of patients with intraplacental CC have encountered FMH.[3] This hypothesis may necessitate further validation through additional clinical cases to substantiate its veracity.

Conclusion

Fetal maternal transfusion syndrome may highlight precancerous lesions and villous vascular malformations in the placenta when excluding pregnancy complications. When extensive vascular injury inside the placenta is suspected, the placenta should be consecutively sectioned for a strict examination of placental pathology. The anomaly of ITs is a potential culprit in penetrating the villous vascular bed and undergoing malignant transformation into post-term CC. The timing of the malignant transformation of ITs is a topic worthy of in-depth studies.

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Author Contributions

Huishu Liu conceptualized and designed the study, offering critical insights into the research framework. Zi Lv executed experimental procedures, conducted comprehensive data analysis, and provided insightful interpretation. Xiuyu Pan monitored patient progress during childbirth and postpartum, ensuring timely interventions and precise sample collection. Congmin Gu conducted pathological analyses with meticulous attention, ensuring the accuracy and reliability of results. Fen Liu led choriocarcinoma screening and chemotherapy efforts. Zi Lv and Huishu Liu collaboratively drafted the manuscript, with Zi Lv leading the writing and Huishu Liu offering revisions.

Conflicts of Interest

None.

Data Availability

All data generated or analyzed during this study are included in this published article.

References

[1] Henningsen AK, Maroun LL, Havsteen H, et al. Massive fetomaternal hemorrhage caused by an intraplacental choriocarcinoma: a case report. Case Rep Med 2010;767218. doi: 10.1155/2010/767218.

[2] Rubod C, Deruelle P, Le Goueff F, et al. Long-term prognosis for infants after massive fetomaternal hemorrhage. Obstet Gynecol 2007;110 (2 Pt 1):256–260. doi: 10.1097/01.AOG.0000271212.66040.70.

[3] Simões M, Vale G, Lacerda C, et al. Fetomaternal hemorrhage: a clue to intraplacental choriocarcinoma and neonatal malignancy. J Matern Fetal Neonatal Med 2022;35(25):6615–6617. doi: 10.1080/14767058.2021.1918665.

[4] Ryu N, Ogawa M, Matsui H, et al. The clinical characteristics and early detection of postpartum choriocarcinoma. Int J Gynecol Cancer 2015; 25(5):926–930. doi: 10.1097/IGC.0000000000000184.

[5] Jiao L, Ghorani E, Sebire NJ, et al. Intraplacental choriocarcinoma: systematic review and management guidance. Gynecol Oncol 2016; 141(3):624–631. doi: 10.1016/j.ygyno.2016.03.026.
[6] Li J, Yang J, Liu P, et al. Clinical characteristics and prognosis of 272 postterm choriocarcinoma patients at Peking union medical college hospital: a retrospective cohort study. BMC Cancer 2016;16:347. doi: 10.1186/s12885-016-2383-1.
[7] Khong TY, Mooney EE, Ariel I, et al. Sampling and definitions of placental lesions: Amsterdam placental workshop group consensus statement. Arch Pathol Lab Med 2016;140(7):698–713. doi: 10. 5858/arpa.2015-0225-CC.
[8] Kong M, Liu L, Yi F, et al. Prevalence of infarct and villous clumps, and the expression of α-smooth muscle actin in the placental basal plate in severe preeclampsia. Mol Med Rep 2013;8(4):1067–1073. doi: 10.3892/mmr.2013.1651.
[9] Stanek J, Abdaljaleel M. CD34 immunostain increases the sensitivity of placental diagnosis of fetal vascular malperfusion in stillbirth. Placenta 2019;77:30–38. doi: 10.1016/j.placenta.2019.02.001.
[10] Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: a systematic review. PloS One 2020;15(11):e0241955. doi: 10.1371/ journal.pone.0241955.
[11] Shih IM, Kurman RJ. The pathology of intermediate trophoblastic tumors and tumor-like lesions. Int J Gynecol Pathol 2001;20(1):31–47. doi: 10.1097/00004347-200101000-00004.
[12] Horn LC, Einenkel J, Vogel M. Histopathology of gestational trophoblastic disease. An update Pathologe 2009;30(4):313–323. doi: 10.1007/s00292-009-1147-y.
[13] Mao TL, Kurman RJ, Huang CC, et al. Immunohistochemistry of choriocarcinoma: an aid in differential diagnosis and in elucidating pathogenesis. Am J Surg Pathol 2007;31(11):1726–1732. doi: 10. 1097/PAS.0b013e318058a529.
[14] Buza N, Hui P. Immunohistochemistry in gynecologic pathology: an example-based practical update. Arch Pathol Lab Med 2017;141(8): 1052–1071. doi: 10.5858/arpa.2016-0541-RA.
[15] Winter M, Meignan S, Völkel P, et al. Vimentin promotes the aggressiveness of triple negative breast Cancer cells surviving chemotherapeutic treatment. Cell 2021;10(6):1504. doi: 10.3390/cells10061504.
[16] Fock V, Plessl K, Fuchs R, et al. Trophoblast subtype-specific EGFR/ ERBB4 expression correlates with cell cycle progression and hyperplasia in complete hydatidiform moles. Hum Reprod 2015;30(4):789–799. doi: 10.1093/humrep/dev027.
[17] Buza N. Gestational trophoblastic disease: contemporary diagnostic approach. Surg Pathol Clin 2022;15(2):197–218. doi: 10.1016/j.path.2022.02.002.
[18] Stabile G, Gentile RM, Carlucci S, et al. Maternal and fetal outcomes of intraplacental choriocarcinoma complicated by fetomaternal hemorrhage: a systematic review. J Matern Fetal Neonatal Med 2023;36(2):2285238. doi: 10.1080/14767058.2023.2285238.

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Erratum

Erratum to Clinical Management Guidelines for Intrahepatic Cholestasis of Pregnancy. Volume 6, Issue 1, Janurary 2024

In reference to Clinical question 5 in the original article publication, the authors suggest removing specific sections from the first and third paragraphs, as well as Recommendation 5-2, to avoid ambiguity.

The first and third paragraphs of Clinical question 5 have been revised as follows:

The levels of TBA in pregnant women with ICP are closely related to adverse perinatal outcomes. Several studies have indicated that the risks of stillbirth, preterm birth, neonatal asphyxia, Acute Respiratory Distress Syndrome, and fetal cardiac dysfunction are significantly higher in pregnant women with TBA levels ≥40 μmol/L.[19,22,29,36] Based on the latest research findings,[23,24,33] this guide recommends the definition of severe ICP as: 1) maternal serum TBA levels ≥40-99 μmol/L; 2) elevated serum bilirubin; 3) other accompanying conditions, such as multiple pregnancies, preeclampsia, recurrent ICP, and previous perinatal death due to ICP.

Outcomes for perinates in early-onset ICP are worse, so it is recommended to manage as severe ICP.[37] However, there is currently no universal standard for the diagnosis of early-onset ICP owing to varying gestational weeks in various studies involving early-onset ICP.[38-42]

The Recommendation 5-2 has been revised as follows:

Diagnostic criteria for severe ICP: 1) Maternal serum TBA level ≥ 40-99 μmol/L; 2) Bilirubin >Normal value; 3) Accompanied by other circumstances, such as multiple pregnancies, pre-eclampsia, recurrent ICP, previous perinatal death due to ICP, etc. (Strongly recommended, Moderate level of evidence).

The authors would like to apologize for any inconvenience caused.

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