Placenta 64 (2018) 1–6

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Chronic histiocytic intervillositis — Clinical, biochemical and radiological findings: An observational study

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ARTICLE INFO

Article history:
Received 3 March 2017
Received in revised form
28 January 2018
Accepted 5 February 2018

Keywords:
Chronic histiocytic intervillositis
Placental ultrasound
Placental pathology
Adverse pregnancy outcomes
Serum biomarkers
Serum alkaline phosphatase

ABSTRACT

Introduction: Chronic histiocytic intervillositis (CHI) of the placenta although rare, has a high recurrence rate, is associated with serious adverse pregnancy outcomes and has no available treatment. This study aims to determine clinical, biochemical and radiological factors associated with CHI, to guide management of subsequent pregnancies.

Methods: This retrospective observational study included consecutive cases with a histopathologic diagnosis of CHI after 18 weeks of gestation, between 2001 and 2014, and no controls. Clinical (maternal, fetal and delivery outcomes), biochemical (first- and second-trimester biomarkers for fetal aneuploidy and serum alkaline phosphatase) and radiological (second- and third-trimester fetal, placental and Doppler ultrasound) factors associated with a histopathological diagnosis of CHI were identified and results presented as percentages. Outcomes of subsequent pregnancies were described.

Results: Of 231 identified cases of 'intervillositis', 33 were confirmed to have CHI, of which only 4/33 (12.1%) had prior uncomplicated term deliveries. During pregnancy, 10/18 (55.5%) had abnormal first-trimester screening, 4/16 (25%) had abnormal second-trimester screening, 6/19 (31.6%) had at least one elevated alkaline phosphatase level, and 15/20 (75%) had at least one abnormal feature on mid-trimester placental ultrasound. In subsequent pregnancies that were closely followed with a combination of biochemical and radiologic tests, there were no cases of fetal loss, and lower incidence of fetal growth restriction and preterm birth.

Discussion: No clinical, biochemical or radiological finding is consistently associated with CHI and adverse outcomes thereof. Whether the incorporation of these tests in individualized care-plans could improve outcomes in subsequent pregnancies needs to be studied further.

1. Introduction

Chronic histiocytic intervillositis (CHI) of the placenta is a rare and poorly understood condition characterized by maternal mononuclear cell infiltration of the intervillous space [1,2]. Although only identified in 4.4% of first-trimester miscarriages with normal karyotype [3,4] and 6/10,000 in second- and third-trimester placentas [5], the condition is of interest to obstetricians because of its association with adverse pregnancy outcomes including high rates of fetal loss at all gestations, severe intrauterine growth restriction (IUGR), prematurity and a recurrence rate as high as 67–100% [1,2,6]. It has been hypothesized that these clinical consequences are secondary to placental insufficiency resulting from immunologically-mediated flow of maternal histiocytes into the intervillous space, the degradation of syncytiotrophoblast cells, accumulation of fibrin deposits within the syncytiotrophoblast lesions and subsequent compromise of maternal-fetal exchange [7].

Currently there is no treatment to reduce recurrence risk or improve pregnancy outcomes [2,8]. Subsequent pregnancies however, might benefit from close and systematic surveillance and prompt attention to early warning signs. Although information on the prevalence of antenatal predictors including prior obstetric

Abbreviations: ALKP, Alkaline Phosphatase; CHI, chronic histiocytic intervillositis; IUFD, intrauterine fetal death; IUGR, Intrauterine growth restriction.

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https://doi.org/10.1016/j.placenta.2018.02.002
0143-4004/

history, prenatal screening bioanalytes and placental ultrasound findings is documented, these are limited to a small number of studies and case reports [6,7,9,10].

The objectives of this study were to determine clinical, biochemical and radiological factors encountered in pregnancies with a histopathologic diagnosis of CHI, with an aim to guiding the management of subsequent pregnancies at risk of adverse pregnancy outcomes.

2. Methods

We conducted a retrospective chart review of consecutive cases with a histopathologic diagnosis of CHI between January 2001 and December 2014, at Mount Sinai Hospital, Toronto, Canada's largest tertiary obstetrical unit with approximately 7000 deliveries annually. Mount Sinai hospital has a large 'placenta clinic' and a liberal policy of conducting histopathological examination on all cases with adverse fetal outcomes, including IUGR, fetal anomalies, preterm birth, meconium-staining of the amniotic fluid, maternal medical disorders, multiple gestation and suspected placental insufficiency syndromes. Cases were identified through a search of the Department of Histopathology's placenta database by using the search term "intervillositis". Since the primary intent of this study was to determine the prevalence of first, second and third-trimester biomarkers and radiologic abnormalities in pregnancies affected with CHI, and since although the association of CHI with miscarriages is well documented, there is no available treatment at these early gestations and therefore no specific form of surveillance that can be suggested to prevent miscarriages, we excluded specimens obtained from dilatation and curettage (D&C) and dilatation and evacuation (D&E) under 18 + 0 weeks of gestation. A perinatal pathologist (SK) reviewed all identified slides, prepared following formaldehyde fixation for 48 h, in a manner described elsewhere [11], to ensure only those with a diagnosis of CHI were included in the study.

The diagnosis of CHI was based on the presence of predominantly histiocytic mononuclear cellular infiltrate in the intervillous space, regardless of the presence of fibrin deposits. The presence of chronic villitis was not an exclusion criterion if the villous inflammation was low grade or focal [12]. Although cytomegalovirus immunostaining was not performed, viral inclusions were not identified in any of the 33 cases. Associated placental pathology was interpreted using standard definitions and grouped into three distinct categories: (1) pathology related to maternal vascular malperfusion, (2) other significant pathology (apart from maternal vascular malperfusion) and (3) normal or non-significant pathology, based on a previously published classification [11,12]. Upon confirmation of the histopathologic diagnosis, placental weights, dimensions, weight percentile and gross morphology were obtained from the existing database.

Maternal demographic and obstetrical data were collected from patient's obstetric charts. Adverse pregnancy outcomes identified were (1) Pregnancy loss including miscarriage (<20 weeks), intrauterine fetal death (>20 weeks) and early neonatal death (within seven days of birth) (2) Preterm birth (live-birth under 37 weeks of gestation) (3) Small for gestational age (SGA) babies (birth weight under the 10th centile for gestational age and sex) [13] that are at increased risk of perinatal morbidity and mortality regardless of evidence of placental dysfunction [14], (4) Preeclampsia defined as gestational hypertension and one of the following; proteinuria, thrombocytopenia, impaired liver function, new development of renal insufficiency, pulmonary edema or new-onset cerebral or visual disturbances [15].

Maternal laboratory results including serum alkaline phosphatase (ALKP) and prenatal screening bioanalytes for fetal aneuploidy that included pregnancy-associated plasma protein A (PAPP-A), unconjugated estriol (uE3), Inhibin-A, beta unit of human chorionic gonadotropin (β-hCG) and alphafetoprotein (AFP) were obtained from laboratory databases. We used reference ranges recommended by the Society of Obstetrics and Gynecology of Canada [16]. Antenatal placental ultrasound images were obtained from radiological archives where available, and reviewed by two independent reviewers (LK and AKM). Emphasis was placed on the mid-trimester placental ultrasound performed at 22 weeks of gestation and the last ultrasound before delivery or fetal death. The following features were noted: placental length and width, cord insertion, echotexture, presence of echogenic cystic lesions, infarcts and uterine artery pulsatility indices) based on criteria developed in earlier studies [17,18].

Data on subsequent pregnancies where available were gathered and outcomes presented as percentages for direct comparison. Statistics are presented as proportions, medians and interquartile ranges (IQR). Statistical analysis was performed using SAS® software v9.4.

This study received approval of the Mount Sinai Hospital Research Ethics Board [14−0337-C] on 07 January 2015.

3. Results

Between January 2001 and December 2014, 261 cases of "intervillositis" were identified. Upon review of the pathology reports, and where indicated the slides, 33 cases were confirmed to have CHI. The broad term "intervillositis" was used in order to cast as wide a net as possible for the initial search. Cases that were excluded were those with villitis of unknown etiology, with a minor component of chronic intervillositis ("spillover" of inflammation into the intervillous space) or cases of acute intervillositis. Characteristics of these 33 pregnancies (29 women) are presented in Table 1. The median values for maternal age and body mass index were 31 (IQR 28.5, 34.5) and 29.8 (IQR 26, 31.7) with no specific ethnic predilection. Only 2/33 (6.1%) had a history of autoimmune disease and 6/33 (18.2%) had a prior history of hypertension. No other medical comorbidities were identified. Six of the affected pregnancies occurred in nulliparous women. Of the rest, only 2/27 (7.4%) had previous uncomplicated term deliveries. The remainder were complicated by serious adverse events such as miscarriages 18/27 (66.7%), IUGR 18/27 (66.7%), preterm birth 15/27 (55.6%), stillbirths 15/27 (55.6%) and neonatal deaths 1/27 (3.7%). The average number of prior miscarriages was 1.93 (range 1−7).

Only 4/33 (12.1%) of the current pregnancies were uncomplicated. Fetal loss rates were high, with two (6.1%) late miscarriages and 11 (35.5%) stillbirths. Of the 25 pregnancies that continued beyond the age of viability (24 weeks of gestation), 23 (92%) were complicated by IUGR; 15 (60%) of which were under the third centile for growth. Of the 20 live births, 16 (80%) were delivered prematurely, 6 (30%) of which were under 34 weeks of gestation, resulting in 12 (60%) admissions to the neonatal intensive care unit. Nine pregnancies (27.3%) were complicated by preeclampsia.

The biochemical and radiological findings are outlined in Table 2. Of the 33 pregnancies, 18 had first-trimester screening and 16 had second-trimester screening for fetal aneuploidy. Abnormal first-trimester screen results were noted in over half the pregnancies, while only a quarter of those screened in the second-trimester had abnormal results. The markers most likely to be abnormal were first-trimester PAPP-A [7/15 (46.7%)] and second-trimester Inhibin-A [3/6 (50%)]. However, in no instance was a second-trimester marker found to be abnormal, with a normal first-trimester screen. Two fetuses had congenital anomalies (congenital bowel obstruction, multiple anomalies) and one had trisomy 18; however no serum screening was performed in all

Table 1
Characteristics of pregnancies.

Characteristic	Unit of measurement	Summary statistic
Maternal age	In years, median [interquartile range]	31.0 [28.5, 34.5]
Ethnicity	Caucasian, n (%)	15/33 (45.5%)
	African, n (%)	14/33 (42.4%)
	Asian, n (%)	4/33 (12.1%)
BMI	In kg/m^2, median [interquartile range]	29.8 [26.0, 31.7]
Smoker	N (%)	2/33 (6.1%)
Pre-existing medical co-morbidities	Hypertension, n (%)	6/33 (18.2%)
	Diabetes, n (%)	0/33 (0)
	Autoimmune disease, n (%)	2/33 (6.1%)
Previous obstetric history	Nulliparous women, n (%)	6/33 (18.2%)
	Prior uncomplicated term pregnancy, n (%)	2/27 (7.4%)
	Prior miscarriage (<20 weeks), n (%)	18/27 (66.7%)
	Prior intrauterine fetal demise (>20 weeks)	4/27 (14.8%)
	Average number of fetal losses, mean (range)	1.93 (1–7)
	Prior fetal growth restriction, n (%)	16/27 (59.3%)
	Prior preterm birth, n (%)	15/27 (55.6%)
	Prior neonatal death, n (%)	1/27 (3.7%)
Current pregnancy	Uncomplicated pregnancy, n (%)	4/33 (12.1%)
	Miscarriage (fetal loss <20 weeks), n (%)	2/33 (6.1%)
	Intrauterine fetal death (fetal loss >20 weeks), n (%)	11/31 (35.5%)
	Small for gestational age (<10th centile), n (%)	23/25 (92%)
	• 5–10th centile, n (%)	• 5/25 (20%)
	• 3–5th centile, n (%)	• 3/25 (12%)
	• <3rd centile, n (%)	• 15/25 (60%)
	Preterm birth (<37 weeks), n (%)	16/20 (80%)
	• Birth <34 weeks, n (%)	• 6/20 (30%)
	Pre-eclampsia, n (%)	9/33 (27.3%)
	NICU admission, n (%)	12/20 (60%)

n, number; %, percentage.

three cases.

Maternal serum ALKP is yet another biochemical marker that has been associated with CHI. Plasma levels of ALKP in pregnancy are normally elevated and reference ranges for the three trimesters of uncomplicated pregnancy have been determined [19,20]. Using the higher of the two suggested reference ranges (88U/L, 126U/L and 229 U/L) for the three trimesters [19], we noted at least one abnormal level in 31% of the pregnancies. Most of these elevated levels were in the third trimester (38.5%) and there were none in the first trimester. Incidentally, in our series, elevated levels of ALKP were not associated with serious fetal morbidity and all six cases resulted in live births.

Radiological assessment at our center included a formal, mid-trimester ultrasound scan to assess placental structure and function, as well as serial ultrasound scans with or without fetal Doppler studies thereafter, as clinically indicated. Mid-trimester placental ultrasound scans were performed in 20 pregnancies, of which 15 (75%) had at least one abnormal feature. The most common abnormalities were those of placental dimensions [8/20 (40%)] and uterine artery Dopplers [7/20 (35%)]. On subsequent ultrasound scans, 18/25 (72%) had abnormal umbilical artery Doppler studies; 11/25 (44%) had abnormalities in placental morphology, either in the form of abnormal echotexture (7/25) or echogenic cystic lesions (7/15); and 10/25 (40%) had oligohydramnios. Of those that had both, mid-trimester and subsequent scans (16 pregnancies), placental abnormalities persisted in 8 (50%) pregnancies while 3 (18.8%) developed new lesions after a normal mid-trimester placental scan. In 5 pregnancies (31.3%), no radiological abnormalities were detected at any point during the pregnancy. On the last ultrasound scan prior to delivery or fetal demise, abnormal placental morphology (abnormal echotexture and/or echogenic cystic lesions) was only identified in 44% of cases.

On histopathologic examination, in addition to the diagnosis of CHI, 8/33 (24%) of the placentas showed evidence of maternal vascular under-perfusion in the form of placental infarction (2/33), decidual arteriopathy (4/33) or accelerated villous maturation (5/33); Other significant pathology included 25/33 cases with features of impaired placental development/differentiation (small for gestational age placentas), two cases of chronic deciduitis, and one case each of fetal vascular malperfusion [12] (intimal fibrin deposition), ascending infection (acute chorioamnionitis), chronic villitis of unknown etiology and delayed villous maturation [12]. Mild perivillous fibrinoid deposition, not considered to be clinically significant was noted in 25/33 cases.

Nine of these patients had subsequent pregnancies with heightened surveillance by Maternal-Fetal Medicine specialists. The outcomes of these pregnancies are described in Table 3 and compared with the index pregnancies in Table 4. Among these pregnancies, there were no miscarriages or IUFDs and lower rates of pregnancy complications such as IUGR (37.5% vs. 92%) and preterm birth (66.7% vs. 80%). As these were not independent samples, and since numbers were small to make meaningful conclusions, no statistical test was applied for hypothesis testing. Placental histopathology was performed on seven of these nine cases, and none showed evidence of CHI. Adding these seven pregnancies to the original cohort of 33 pregnancies, the recurrence rate of CHI in our series was 7.5%.

4. Discussion

Our study not only confirms that CHI is associated with high rates of adverse pregnancy outcomes including fetal loss, IUGR and preterm birth, bur also identifies important clinical, biochemical and radiological findings in pregnancies with a histopathologic diagnosis of CHI. Although none of these findings in isolation were found to consistently accompany a diagnosis of CHI and adverse pregnancy outcomes thereof, they could help clinicians and patients arrive at individualized care plans for the management of subsequent pregnancies, with the aim of improving outcomes.

With regard to prior history, six (18.2%) pregnancies had pre-

Table 2
Biochemical and radiological findings encountered with a histopathologic diagnosis of chronic histiocytic intervillositis.

Biochemical findings		
Placental biochemistry[a]	Abnormal first trimester screen	10/18 (55.6%)
	• PAPP-A (<0.4 MoM)	• 7/15 (46.7%)
	• βhCG (<0.5 MoM; >3.0 MoM)	• 5/14 (35.7%)
	Abnormal second trimester screen	4/16 (25%)
	• μE3 (<0.5 MoM)	• 3/11 (27.3%)
	• Inhibin-A (>2.0 MoM)	• 3/6 (50%)
	• AFP (<0.25 MoM; >2.5 MoM)	• 4/16 (25%)
	Normal first- and abnormal second trimester screen	0/5 (0)
Alkaline Phosphatase >2.5 times normal[b]	At least once during entire pregnancy	6/19 (31.6%)
	• First trimester	• 0/3 (0)
	• Second trimester	• 2/11 (18.2%)
	• Third trimester	• 5/13 (38.5%)
Radiological findings		
Mid-trimester placental ultrasound	At least one abnormal marker	15/20 (75%)
	• Abnormal dimensions	• 8/20 (40%)
	• Length <10cm	• 5/20 (25%)
	• Width >4cm	• 3/20 (15%)
	• Abnormal echotexture	• 5/20 (25%)
	• Echogenic cystic lesion(s)	• 6/20 (30%)
	• Abnormally elevated mean uterine artery pulsatility index for gestational age	• 7/20 (35%)
Subsequent obstetric ultrasound	Abnormal placental morphology	11/25 (44%)
	• Abnormal echotexture	• 7/25 (28%)
	• Echogenic cystic lesion(s)	• 7/25 (28%)
	Other abnormal ultrasound findings	19/25 (76%)
	• Abnormal umbilical artery Doppler studies	• 18/25 (72%)
	• Oligohydramnios	• 10/25 (40%)
	Abnormal placental morphology but normal Dopplers and amniotic fluid	4/25 (16%)
Progression of lesions detected on mid-trimester and subsequent ultrasounds	• Persistence of placental lesions	• 8/16 (50%)
	• Development of new placental lesions	• 3/16 (18.8%)
	• Regression of placental lesions	• 0/16 (0)
	• No placental lesions detected on ultrasound	• 5/16 (31.3%)

Legend: n, number; %, percentage; MoM, multiples of the median; PAPP-A: pregnancy-associated plasma protein A; uE3: unconjugated estriol; β-hCG: free beta until of human chorionic gonadotropin; AFP: alphafetoprotein; AKLP: alkaline phosphatase.
[a] Reference ranges as per SOGC guidelines Gagnon et al. [16].
[b] Reference range for ALKP obtained from Abbassi-Ghanavati et al. [19] and Larsson[20].

Table 3
Outcomes in pregnancies subsequent to an affected pregnancy.

Patient	Maternal	Offspring	Placental evidence of CHI
1	Preterm preeclampsia	Preterm delivery of a severely growth restricted fetus (<3rd centile) at 31 + 3 weeks	None
2	No details; followed at another hospital	Preterm birth of a fetus with an unrelated fetal congenital anomaly (craniosynostosis) at 30 + 3 weeks.	Placental histopathology not performed
3	None	Delivery at 36 + 5 weeks. Birth weight not available	None
4	None	Preterm birth of an average for gestational age fetus (50th centile) at 25 weeks	None
5	Preterm preeclampsia	Preterm birth of an average for gestational age fetus (30th centile) at 33 weeks	None
6	Worsening hypertension	Term delivery of an average for gestational age fetus (50th centile) at 38 weeks	None
7	None	Preterm birth of a severely growth restricted fetus (<3rd centile) at 36 weeks	None
8	None	Term delivery of an average for gestational age fetus (25th centile) at 37 + 6 weeks	None
9	Gestational diabetes	Term delivery of a severely growth restricted fetus (<3rd centile) at 37 weeks.	Placental histopathology not performed

CHI, Chronic histiocytic intervillositis.

existing hypertension, two (6.1%) had an autoimmune condition and 25/27 (92.6%) with an antecedent pregnancy had a history of adverse pregnancy outcomes. Therefore, while medical conditions including autoimmune diseases are not consistently associated with CHI or adverse outcomes – autoimmune conditions being seen in 6–58% of CHI cases [7,8,21], – a prior adverse obstetric history could be considered predictive of adverse outcomes in a current pregnancy [6,8]. First- and second-trimester markers for fetal aneuploidy that are often used as surrogate markers of placental dysfunction [16,22], and are almost universally performed in most countries, could be an ideal screening tool for CHI. However, the correlation between these markers and CHI is modest at most. Similarly, it has been suggested that elevated levels of maternal serum ALKP in CHI are secondary to syncytial cell lesions resulting in increased maternal release of ALKP by injured syncytiotrophoblasts, and that using a cut off of 2.5 times the normal upper limit could be a possible means of identifying those at higher risk of CHI [7]. Elevated maternal serum ALKP has been reported in up to 50% of pregnancies complicated with CHI [19]. As our center has not adopted serial estimation of maternal serum ALKP, just over half of the pregnancies had documentation of at least one level during pregnancy, 31% of which were abnormal, most notably in

Table 4
Comparison of outcomes in pregnancies affected by CHI and subsequent pregnancies.

Pregnancy outcome	Affected pregnancies	Subsequent pregnancies
Uncomplicated pregnancy, n (%)	4/33 (12.1%)	2/9 (22.2%)
Miscarriage (fetal loss <20 weeks), n (%)	2/33 (6.1%)	0/9 (0%)
Intrauterine fetal death (fetal loss >20 weeks), n (%)	11/31 (35.5%)	0/9 (0%)
Small for gestational age (<10th centile), n (%)	23/25 (92%)	3/8 (37.5%)
• 5–10th centile, n (%)	• 5/25 (20%)	• 0/8 (0%)
• 3–5th centile, n (%)	• 3/25 (12%)	• 0/8 (0%)
• <3rd centile, n (%)	• 15/25 (60%)	• 3/8 (37.5%)
Preterm birth (<37 weeks), n (%)	16/20 (80%)	6/9 (66.7%)
• Birth <34 weeks, n (%)	• 6/20 (30%)	• 4/9 (44.9%)
Preeclampsia, n (%)	9/33 (27.3%)	2/8 (25%)

the third trimester. None of the pregnancies with elevated ALKP levels however, had adverse pregnancy outcomes. Therefore, although there maybe come correlation between second- and third-trimester ALKP and CHI, its value as a predictor of CHI and adverse outcomes needs to be further explored. Our study also found limited correlation between abnormal radiologic findings at any stage in pregnancy and CHI. Abnormal mid-trimester uterine artery Doppler findings were noted in 35% of cases, similar to reported rates of 27–45% [6,7].

When compared with results from a literature review looking at obstetric outcomes in 333 pregnancies with CHI [8], our series had a lower incidence of miscarriages [2/33 (6.1%) vs. 103/327 (31%)] and IUFDs [11/31 (35.5%) vs. 115/230 (50%, range 17–77%)], and a higher incidence of IUGR [23/25 (92%, of which 60% were under the third centile) vs. 42% (range 17–83%)] and preterm birth [16/20 (80%)] with as many as 30% delivering less than 34 weeks of gestation. The reason for our low miscarriage rate was that we included only intact placentas and excluded D&C and D&E specimens (under 18 weeks of gestation). The differences in rates of IUFD, IUGR and preterm birth are probably the result of intensive surveillance strategies already adopted by our unit that include serial umbilical artery, middle cerebral artery and venous Doppler studies, and a low threshold for delivery when the venous Dopplers begin to become abnormal, in keeping with current guidelines [14,23]. These strategies allow the prolongation of pregnancies affected by IUGR, the administration of antenatal corticosteroids for fetal lung maturation and prompt delivery regardless of gestational age, if there is evidence of fetal decompensation. Although preeclampsia has been associated with CHI, the unusually high rate (27%) of preeclampsia in our series could merely be a result of higher numbers [6/33 (18.2%)] with pre-existing hypertension (a known risk factor for preeclampsia).

4.1. Strengths and limitations

Our study is one of the larger published series of CHI, and the first to report correlations between CHI, serum markers for fetal aneuploidy and a detailed mid-trimester ultrasound assessment of the placenta in pregnancies affected by CHI. The limitations of the study include its small sample size and retrospective nature. The latter made it difficult to conclusively rule out the use of aspirin, heparin and/or steroids during pregnancy, although it was not our policy to administer any of these medications solely for the purpose of managing CHI. As many of our patients were referred from other centers, and insufficient data was available on prior placental histopathology, we were unable to adequately comment on recurrence risk. However, unlike some studies that quote a 67–100% rate of recurrence of CHI [2,5,6], we noted a much lower recurrence (7.5%), similar to a large, recent series that reported recurrence in 9/50 (18%) of pregnancies [7]. It is however possible that a large number of prior pregnancies in our cohort were affected with CHI unbeknown to us. In addition, there is gestational age bias from excluding D&C and D&E specimens, the rationale for which has been presented earlier. Finally, although it would seem like a combination of clinical, biochemical and radiologic findings could support the development of an algorithm for the management of subsequent pregnancies, the lack of a control group does not allow clinical recommendations to be made.

In conclusion, CHI is associated with serious adverse pregnancy outcomes and a variable recurrence rate. As no treatment is currently available, individualized care plans for fetal surveillance, based on clinical, biochemical and radiologic findings can best guide management in subsequent pregnancies.

Contribution to authorship

LK extracted clinical, biochemical and radiological data and performed the analysis. SK performed all the histopathological examinations and edited all versions of the manuscript. AKM was the second reviewer for placental ultrasound images and edited the final version of the manuscript. RD conceived and designed the study, helped with analysis of data and wrote and revised the manuscript.

Contributors

Lawrence Koby. I declare that I participated in extracting all clinical, biochemical, and radiological data and performing the analysis. I have seen and approved the final version. I have no conflicts of interest.

Sarah Keating. I declare that I participated in performing all the histopathological examinations and editing all versions of the manuscript. I have seen and approved the final version. I have no conflicts of interest.

Ann Kinga Malinowski. I declare that I participated in being the second reviewer for the placental ultrasound images and editing the final version of the manuscript. I have seen and approved the final version. I have no conflicts of interest.

Rohan D'Souza. I declare that I participated in conceiving and designing the study, helping with analysis of data, and writing all versions of the manuscript. I have seen and approved the final version. I have received a speaking honorarium from Ferring, Canada in December 2017.

Josie Chundamala. I declare that I participated in editing and preparing the final version of the manuscript for submission. I have no conflicts of interest.

Disclosure of interests

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Details of ethics approval

This study received approval of the Mount Sinai Hospital Research Ethics Board [14–0337-C] on 07 January 2015.

Acknowledgements

We would like to thank Josie Chundamala, Scientific Grant Editor funded by the Department of Obstetrics and Gynaecology at Mount Sinai Hospital, for assistance editing and preparing this manuscript for submission.

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