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Placental lesions in stillbirth following the Amsterdam consensus: A systematic review and meta-analysis

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ABSTRACT

Placental disorders remain one of the main causes of stillbirth. However, the lack of standardised nomenclature has significantly limited the clinical utility of placental histology. Following the Amsterdam consensus classification, which now allows proper comparisons of placenta histology across the world, we conducted the first systematic review and meta-analysis (Prospero CRD42023410469) to assess the commonest stillbirth-associated placental lesions worldwide. Eighteen studies with 3082 placentas were included. Maternal vascular malperfusion and fetal vascular malperfusion were the most prevalent placental lesions in stillbirth, and significantly more frequent in stillbirths than livebirths [OR 3.0 (95 % CI 2.0–4.5), $p < 0.001$ and OR 5.12 (95 % CI 3.09–8.47), $p < 0.001$, respectively]. However, when adjusting for gestational age, only maternal vascular malperfusion remained significant at term. Better understanding of the pathophysiology underlying placental lesions is needed to inform timely risk assessment and therapeutic interventions capable of reducing placental-related stillbirths.

1. Introduction

Stillbirths account for approximately two million births worldwide annually [1,2]. In the UK, the stillbirth rate remains high at 4.1 per 1000 total births i.e.1:250 pregnancies and seems to be decreasing more slowly than in many other high-income countries [3]. Understanding what causes stillbirth is crucial to providing better targeted interventions able to improve perinatal outcomes [4]. Furthermore, given the two-fold increased risk of recurrence of stillbirth improved identification and management of antecedents' risks minimise recurrence risks in future pregnancies [5–7].

According to the *Mothers and Babies: reducing risk through audits UK* (MBRRACE-UK) reports [8], placental dysfunction accounts for more than 30 % of stillbirths, even though some seminal studies suggest it might be responsible for up to 60 % [8–11]. However, despite providing potentially causative insight into stillbirth etiology, examining the placenta remains underrated as part of autopsy examinations, a problem to which previous work has alluded [9,12].

Prior to the establishment of the Amsterdam Consensus, the value of placental histology in the stillbirth work-up was limited as explained by Ptacek et al. (2014) [9]. They concluded that due to a lack of standardisation when reporting histopathological placental findings, it was difficult to gather consistent data and extrapolate findings into clinical practice thus highlighting the need for uniform nomenclature. In 2016, this need was finally met with the creation of the Amsterdam criteria, a classification system which enables most lesions to be classed under four categories: Maternal Vascular Malperfusion (MVM), Fetal Vascular Malperfusion (FVM), Villitis of Unknown Etiology (VUE) and Acute chorioamnionitis (ACA).

MVM corresponds to the pathophysiology of the maternal vascular tree and is commonly referred to as 'placental insufficiency' as it is associated with abnormal blood supply to the feto-placental unit due to insufficient circulation to the placental bed [13,14]. FVM relates to obstruction within the fetal blood flow of the villous parenchyma of the fetal side, subsequently leading to ischemia and thrombosis [15,16]. ACA is the neutrophil response to pathogens in the amniotic fluid. Neutrophil migration into the chorion and amnion is referred to as maternal inflammatory response (MIR) and similarly neutrophil migration into the chorionic plate and umbilical cord is stated as the fetal inflammatory response (FIR), [17]. VUE, as the name suggests, includes cases where etiology is not known [15]. VUE is classified either as low or high grade. The determining factor is the number of contiguous villi presenting with inflammation per section, over 10 villi is considered

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Abbreviations

ACA	Acute chorioamnionitis
DVM	delayed villitis maturation
FIR	fetal inflammatory response
FVM	fetal vascular malperfusion
MIR	maternal inflammatory response
MVM	maternal vascular malperfusion
OR	odds ratio
VUE	villitis of unknown etiology

high grade VUE. High grade VUE is further divided into patchy (<30 %) or diffuse (>30 %) whilst low grade VUE is divided into focal or multifocal [14,15].

With the increasing use of the Amsterdam Criteria as the gold standard for reporting placentas, the rates of unexplained stillbirths have reduced, and placental causes of stillbirth risen [8,9,15].

In our study, we aimed to systematically assess all the available evidence to determine the frequency of placental lesions associated with stillbirths using the Amsterdam criteria to further support the understanding of the pathophysiology that underlies stillbirth.

2. Methods

2.1. Systematic review and meta-analysis

2.1.1. Registration and guidelines

The systematic review was registered in Prospero (CRD42023410469) following the guidelines from Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) checklist [18,19].

2.1.2. Search strategy

A comprehensive search was conducted in MEDLINE via Ovid, Scopus, Web of Science and Cochrane. Searches allowed for relevant Medical Subject Headings (MeSH) and keywords (''Stillbirth''; ''Placenta''; ''Placental Lesions''; ''Histopathology''). Searches were restricted to human studies and publication date from the inception of the Amsterdam criteria in May 2016 to August 2023 [Appendix A]. A grey literature hand search involving the search of papers' references, conference proceedings and published abstract was further conducted.

2.1.3. Selection of studies and data extraction

The only studies eligible for inclusion were those which reported stillbirth-related placental lesions using the Amsterdam criteria [15].

No exclusion was made based on age, obstetric complications, or medical history. However, multiple pregnancies or feticides were excluded.

Studies were also excluded if they were systematic reviews, no translation to English, Spanish and/or French was available or if their full text and/or individual data was missing despite attempts made to contact their corresponding authors.

Studies were selected by two reviewers (VB and ML) who were each blinded to each other's decision. Any discrepancy was resolved by a third independent party (BFN).

Extracted data were transferred into Review Manager Software (Revman 5.8) for further analysis. To ensure accuracy, the features of the vascular lesions and staging and grading of the inflammatory lesions were discussed with an expert perinatal pathologist (MC).

2.1.4. Study quality assessment and risk of bias

Studies were subjected to quality assessment following the modified Newcastle-Ottawa Scale (NOS) criteria [20]. The observational studies were deemed of poor quality if the study lacked a control.

2.1.5. Data synthesis and meta-analysis

Data from all included studies were synthesised via qualitative analysis following synthesis without meta-analysis (SWiM) guidelines [21]. Placental features were selected for inclusion in the meta-analysis if they were reported by two or more studies.

The data was treated as dichotomous i.e. stillbirth or livebirth groups to calculate the Mantel-Haenszel odds ratios (ORs). The analysis was pre-set to "Random Effects" anticipating relatively high heterogeneity amongst the studies. Further subgroup analysis was performed to address confounders.

3. Results

3.1. Systematic review

3.1.1. Selection of studies and data extraction

The search in Medline, SCOPUS, Web of Science and Cochrane produced 528 articles, which was reduced to 473 after duplicates were removed. A further 359 were excluded after screening the titles/abstracts and a further 96 after screening the full-text screening. Studies that did not adhere strictly to the Amsterdam criteria were excluded (n = 44). Amongst these, we removed 29 studies relating to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS)-Placentitis, a lesion which is not included in the Amsterdam criteria as it preceded the pandemic. A total of 18 studies were included in the systematic review (Fig. 1).

3.1.2. Study characteristics

Eighteen studies with a total of 3082 placentas were included in the review. Most of them (67.7 %) were from high-income countries with a minority from low-middle income (22.2 %) and upper middle-income countries (11.1 %) [Appendix A, Table A:1]. All the studies were observational including 11 cohort studies, five case control studies and two case reports, and mostly, retrospective (66.7 %).

The gestational age to define stillbirth varied among the studies, the commonest being 20 weeks. However, close to a quarter of studies (22.22 %) did not specify the gestational threshold at which stillbirth was defined [22–25], [Appendix A, Table A:1].

3.1.3. Quality assessment

The risk of bias was not uniform among the studies [Appendix A, Table A:2]. Overall, 66.7 % were deemed poor quality and 33.3 % considered good quality. The main difference was noticed in the comparability domain with 12 studies deemed high risk for lacking a control of livebirth placentas. Furthermore, only 22.2 % (4/18) studies stated that the pathologist was blinded to clinical information, with the exception to gestational age [24,26,27]. For patient selection and outcome reporting, the risk of bias was considered low for all studies.

3.1.4. Frequency of placental lesions

MVM and FVM were the most prevalent placental lesions seen in stillbirth (57.1 %). However, it is worth noticing that FVM lesions could not be graded in high and low grade as per Redline and Ravishankar [16] as this information was not available in the primary studies. The next most prevalent lesions were inflammatory lesions, Maternal inflammatory response (MIR, 31.8 %) and Fetal inflammatory response (FIR. 31.3 %), followed by high grade VUE (20.5 %) and delayed villous maturation -DVM- (17.1 %), [Appendix A, Table A:3].

3.1.5. Meta analysis

Meta analysis results highlighted that MVM and FVM were more frequently observed in stillbirth placentas than livebirth placentas: MVM [OR 3.00 (95 % CI 2.00–4.50), $p < 0.001$] and FVM [OR 5.12 (95 % CI 3.09–8.47), $p < 0.001$], [Fig. 2].

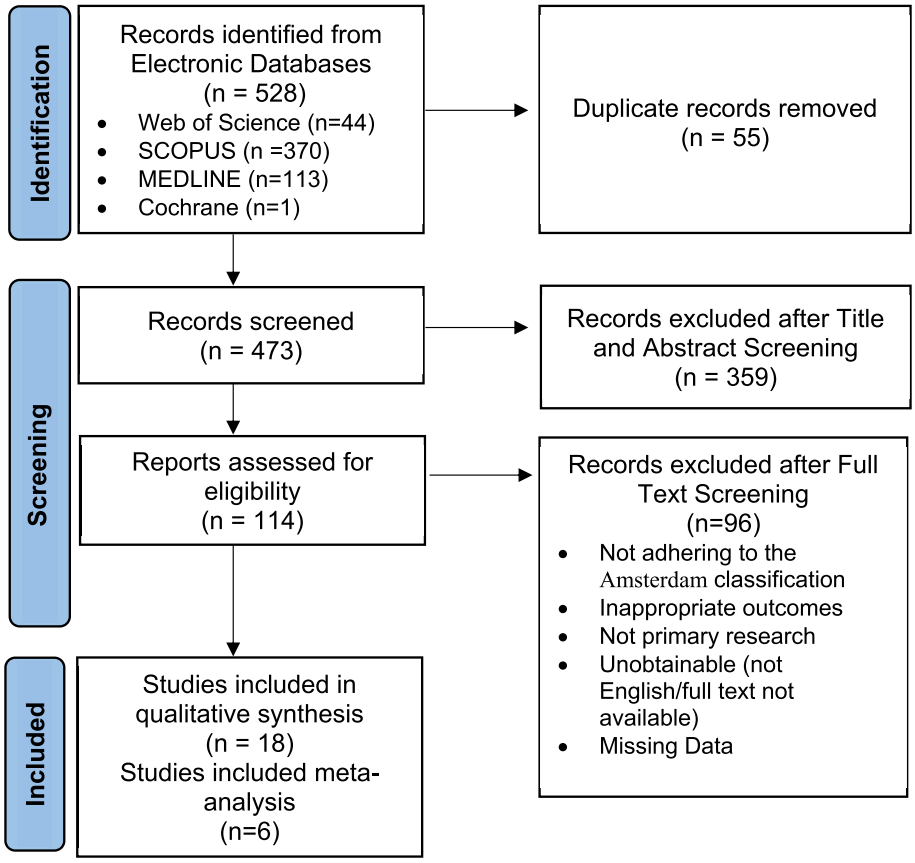

Fig. 1. PRISMA flow chart for selection of studies included in the systematic review.

Initially, all stages of inflammatory lesions were analysed together regardless of staging and grading. There was an association between MIR and stillbirths [OR 1.88 (95 % CI 1.24–2.85), p = 0.003) [Fig. 3 (a)]. However, no significant association was seen between FIR and stillbirths [OR 1.22 (95 % CI 0.66–2.29); p = 0.53], [Fig. 3(b)].

Inflammatory lesions were subsequently analysed based on severity (stage/grading). MIR stage 1 was not significantly associated with either stillbirths or livebirths [OR 1.35 (95 % CI 0.69–2.61), p = 0.38]. However, MIR Stage 2 and Stage 3 were significantly associated with stillbirth placentas [OR 2.05 (95 % CI 1.55–2.72), p < 0.001 and OR 5.67 (95 % CI 2.06–15.61), p < 0.01 respectively), [Fig. 3(a)].

FIR Stage 1 and Stage 2 were not significantly associated with stillbirth and/or livebirth [OR 0.72 (95 % CI 0.28–1.86), p = 0.50 and OR 1.21 (95 % CI 0.39–3.77), p = 0.74 respectively). However, the higher staged FIR (Stage 3) was significantly associated with stillbirth placentas [OR 2.95 (95 % CI 1.53–5.67), p = 0.001] [Fig. 3 (b)].

The studies included in the meta-analysis primarily reported high grade VUE which was strongly associated with stillbirths [OR 4.47 (95 % CI 1.79–11.16), p = 0.001], [Fig. 4 (a)]. Similarly, DVM was more strongly associated with stillbirths than livebirths [OR 2.64 (95 % CI 1.96–3.57), p < 0.001], [Fig. 4 (b)].

3.1.6. *Subgroup analyses for vascular lesions*

Subgroup analyses were further conducted to adjust for factors which are likely to have impacted on placental lesions including gestational age, maternal obesity, hypertensive disorders and socio-economic factors using the gross national income country classification as proxy.

3.1.6.1. Gestational age. Only two thirds of the studies included in the original meta-analysis specified the gestational age of the cases and were therefore suitable for this subgroup analysis. However, due to inconsistencies among primary studies, PTB defined as any birth< 37 weeks could not be subcategorised and matched into early and late PTB.

At term but not preterm, MVM was still significantly more frequent in stillbirth than in livebirth placentas [OR 3.10 (95%CI 2.37–4.05), p < 0.001, Appendix A, Figure A:1, Table A:4].

3.1.6.2. Maternal obesity. Two studies in the meta-analysis investigated the effect of maternal obesity on stillbirth (BMI >30 kg/m^2), [24,26]. When adjusting for obesity, MVM but not FVM remained significantly higher in stillbirths (p = 0.04), [Appendix A, Figure A:2].

3.1.6.3. Hypertensive disorders. Only one study in the meta-analysis reported placental lesions from women affected by preeclampsia (PET) or gestational hypertension (GH), [28]. This study was subsequently excluded from the subgroup analysis and the analysis re-ran. No major differences were observed (MVM p < 0.001; FVM p < 0.001), [Appendix A, Figure A:3].

3.1.6.4. Gross national income. Only one study included in the meta-analysis was from a low-middle-income country. The quantitative analysis remained unchanged when the analysis was conducted exclusively with high-income country data (MVM p < 0.001; FVM p < 0.001), [Appendix A, Figure A:4].

4. Discussion

This is the first systematic review and meta-analysis of stillbirth placental lesions since the Amsterdam consensus was established in 2016. We showed that maternal vascular malperfusion and fetal vascular malperfusion were the most prevalent placental lesions in stillbirth, and more frequently identified in stillbirths than in livebirths (p < 0.001). However, when adjusting for gestational age, only maternal vascular malperfusion remained significant at term which underscores

a)

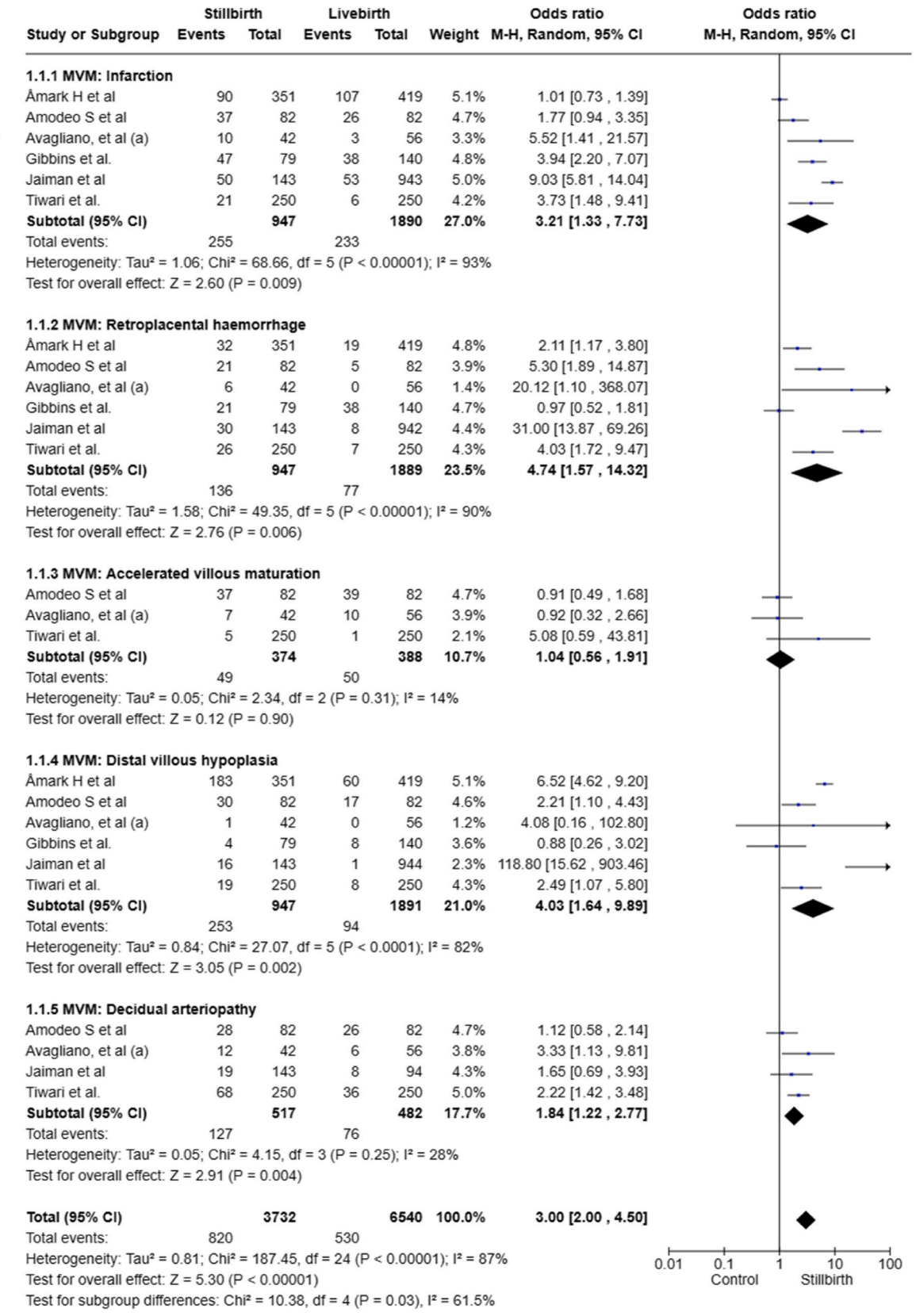

Fig. 2. Forest plot showing odds ratio at a 95 % confidence interval for features of vascular lesions, (a) maternal vascular malperfusion and (b) fetal vascular malperfusion in stillbirth and livebirth pregnancies.

b)

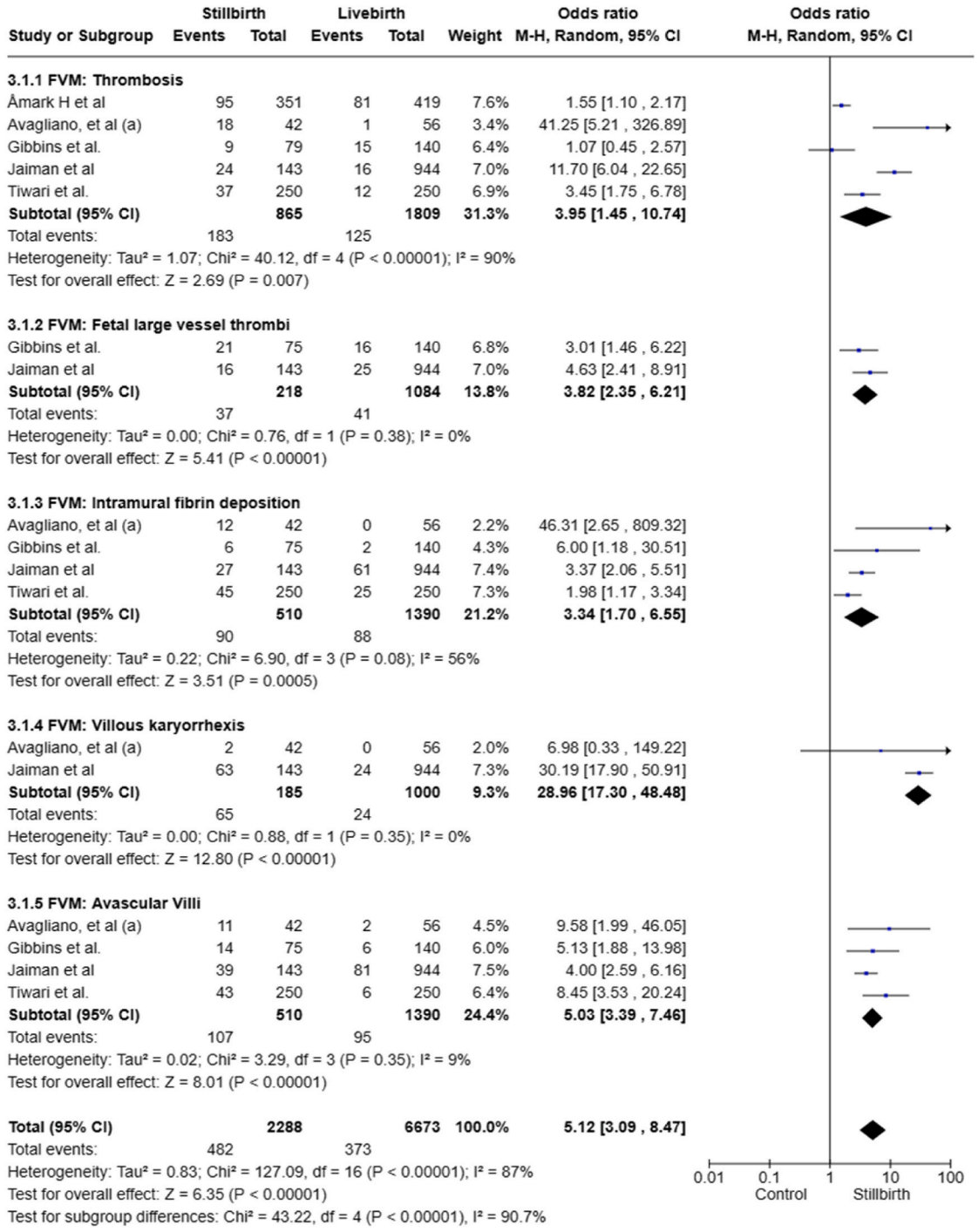

Fig. 2. (*continued*).

the importance of having adequate gestational age-matched controls. These findings are crucial as placental histopathology provides key information about the cause of fetal death and subsequently reduces the number of unexplained stillbirth cases [29]. Identifying MVM in particular is of great importance as there is a higher risk of recurrence of adverse perinatal outcomes in future pregnancies [30].

In healthy pregnancies, the uteroplacental spiral arteries are remodelled to allow a larger volume of blood flow to the placenta [31]. However, in the case of MVM, the placenta fails to transform as the differentiation signals are not adequate for trophoblast invasion, thus resulting in abnormal perfusion (Fig. 1.3) [13]. Consequently, this leads to reduced villous growth and accelerated villous maturation - findings often seen in adverse obstetric outcomes such as preeclampsia, intrauterine fetal growth restrictions and stillbirth [31,32]. Accurate early risk assessment for abnormal placentation leading to MVM lesions is therefore essential as it might inform therapeutic interventions such as aspirin and more regular surveillance capable of improving placentation and perinatal outcomes [33,34].

The systematic review also revealed that all placental lesions were more frequently observed in stillbirths than livebirths, apart from the fetal inflammatory response. However, when investigating this category in more detail, it became apparent that higher staged, necrotizing inflammatory lesions were significantly associated with stillbirth, whereas the less severe were equally distributed in both livebirth and stillbirths.

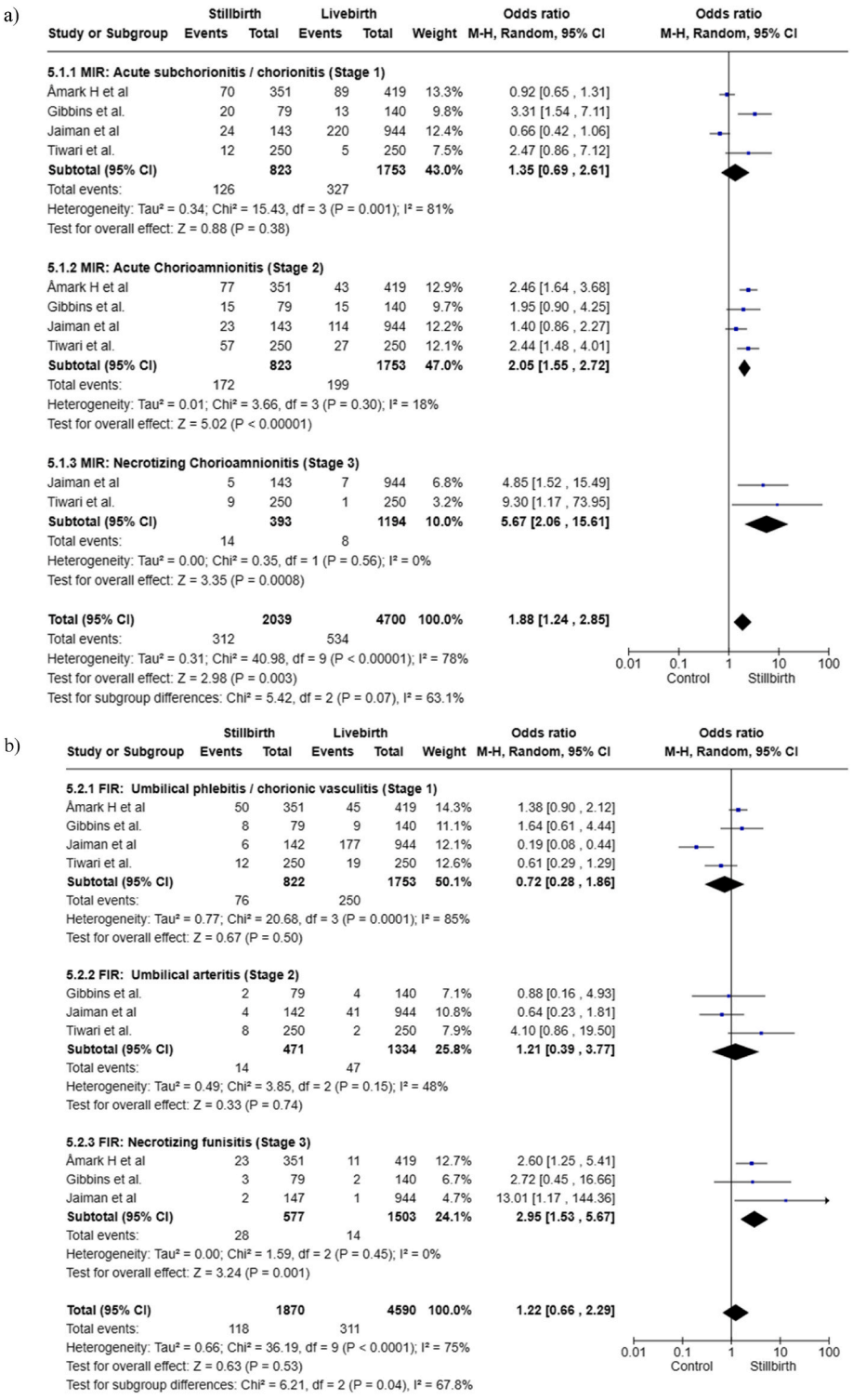

Fig. 3. Forest plot showing odds ratio at a 95 % confidence interval for features of inflammation (a) maternal inflammatory response -MIR- (b) fetal inflammatory response -FIR- and (c) high grade villitis of unknown etiology (VUE), (d) delayed villous maturation (DVM) in stillbirth and livebirth pregnancies.

Inflammatory lesions are thought to be a continuum, with increasing stages and severity of the maternal inflammatory response associated with increasing perinatal mortality, culminating in stillbirth [35].

No major changes were noted after adjusting results for gross national income, hypertensive disorders and obesity. MVM remained significantly associated with stillbirth despite all subgroup analysis.

In our systematic review, we noted that only 4 out of 18 studies included were from low- and middle-income countries and only 1 out of 6 in the meta-analysis despite the highest rate of stillbirths worldwide occurring in these regions(98 %), [36]. This can lead to findings being primarily extrapolated from high-income countries which might not be applicable worldwide as observational data strongly suggests that the primary cause of stillbirth varies between these regions [37]. Such finding emphasises the need to support primary study and research capacity building in low- and middle-income countries to improve care and reduce stillbirths worldwide [37].

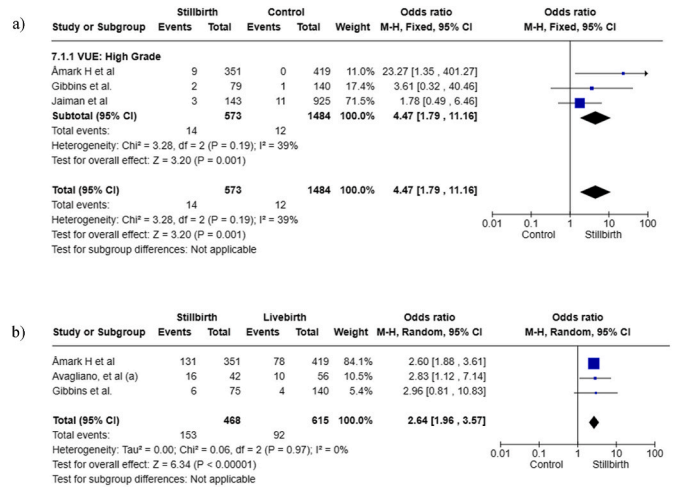

Fig. 4. Forest plot showing odds ratio at a 95 % confidence interval for features of (a) high grade villitis of unknown etiology (VUE) and (b) delayed villous maturation (DVM) in stillbirth and livebirth pregnancies.

4.1. Strengths and limitations

The strength of the systematic review lies in its rigorous methodology including a peer-reviewed protocol registered in Prospero and strict adherence to the PRISMA and MOOSE guidelines. The screening and data extraction processes were conducted by two independent reviewers, which ensured accuracy was maintained throughout. Furthermore, all studies were quality assessed.

Our study, however, did not come without limitations. As the main inclusion criteria was the adherence to the Amsterdam criteria, new entities such as SARS-Placentitis which have not yet been added to the classification were excluded from the analysis [38–42]. This highlights the need for guidelines to constantly update their content.

Not all studies stated whether the placental lesions were causative and/or contributory, Therefore, it cannot be assumed that placental lesions were the sole cause of stillbirth in all the cases.

The systematic review also included studies with different stillbirth definitions. This lack of standardisation in the gestational age's threshold could hinder the findings as some features of MVM are known to be more prevalent in early PTB [43]. To address this limitation, gestational age subgroup analysis was performed. Furthermore, FVM lesions could not be classed as high or low grade but rather presented as a whole because this information was not available in the primary studies which is likely to have affected data interpretation and clinical relevance.

5. Conclusion

Understanding the etiology behind stillbirths is essential to tailor antenatal treatment and consequently improve stillbirth rates. Our study reveals that the most prevalent placental injury in stillbirth is MVM which might be amenable to improved antenatal risk stratification ± mitigating interventions such as enhanced surveillance and aspirin administration.

CRediT authorship contribution statement

Brenda F. Narice: Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Victoria Byrne:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Mariam Labib:** Writing – review & editing, Data curation. **Marta C. Cohen:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization. **Dilly O. Anumba:** Writing – review & editing, Resources, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. (Systematic Review)

Search strategy: example in Scopus

(stillbirth OR stillborn) AND (placenta* OR placental AND lesion) AND (histopathology) AND PUBYEAR>2014 AND PUBYEAR <2024 AND (limit-to-exactkeyword, "Human")

Table A:1
Comparison of study characteristics

Study reference	Type of Study	Retrospective/ prospective	Control	Definition of Stillbirth	GNI	Number of SB Placentas Examined	Inclusion Criteria	Exclusion Criteria
Amark et al., 2021	Case Control	Prospective	Yes	Not defined	HIC	351	Singleton stillbirths at term. Normal BMI (18.5–24.9/m2) and obese women (BMI >30 kg/ m^2) between 2002 and 2018	Fetuses with major malformations. Pregnancies complicated with pre-gestational or gestational diabetes
Amodeo et al., 2022	Case Control	Prospective	Yes	23 + 6 weeks	HIC	82	Stillbirths with UtA recorded singleton pregnancies and placenta histology performed	Multiple pregnancy, diagnosed fetal congenital or genetic abnormalities or TORCH infections
Avagliano et al., 2020	Cohort	Retrospective	Yes	22 weeks	HIC	42	Singleton pregnancies in which maternal BMI was available.	Fetal malformations, abnormal karyotypes, and/or intrapartum stillbirths
Avagliano et al., 2022	Cohort	Retrospective	No	22 weeks	HIC	180	Singleton pregnancies >22 weeks	Multiple pregnancies, fetal malformations, abnormal karyotype and/or intrapartum IUFD

(*continued on next page*)

Table A:1 (*continued*)

Study reference	Type of Study	Retrospective/ prospective	Control	Definition of Stillbirth	GNI	Number of SB Placentas Examined	Inclusion Criteria	Exclusion Criteria
Belhomme et al., 2018	Cohort	Retrospective	No	14 weeks	HIC	49	All women IUFD >14 weeks	Not stated
Darouich and Masmoudi, 2022	Cohort	Retrospective	No	14 weeks	LMIC	147	Fetal death >14 weeks, singleton pregnancy and placenta availability	Multiple pregnancies and fetuses without placentas available for examination
Manocha et al., 2019	Cohort	Retrospective	No	22 weeks	LMIC	100	IUFD >22 weeks	Not stated
McClure et al., 2022	Cohort	Prospective	No	20 weeks	LMIC	611	Women aged 15+ with a known stillbirth >20, weighing 1 kg or more	Birthweight<1 kg, fetuses without examined placentas and gestational age not known
Mtshali et al., 2022	Cohort	Retrospective	No	28 weeks	UMC	122	Stillbirths >28 weeks at a major South African academic hospital between January 2016–July 2018	Not stated
Siassakos et al., 2022	Case Control	Retrospective	No	Not defined	HIC	19	Not stated	Not stated
Taweevisit and Thorner, 2022	Cohort	Retrospective	No	20 weeks	UMC	208	Singleton intrauterine deaths >20 weeks	Lethal malformations, chromosomal aberrations, and without placenta examination
Tiwari et al., 2022	Case Control	Prospective	Yes	28 weeks	LMIC	250	Women aged 18–40, delivered singleton stillbirth (>28weeks) and age-matched livebirth controls	Women induced prematurely, termination of pregnancy associated with congenital anomaly and placenta not available
Gibbins et al., 2016	Case Control	Prospective	Yes	20 weeks	HIC	518	Women with a stillbirth. Control is representative sample of livebirths	Plural birth, placental examination not conducted/ consented or inadequate
Lannaman et al., 2017	Cohort	Retrospective	No	20 weeks	HIC	40	IUFD	Multifetal gestation, pre-gestational diabetes, prenatal diagnoses of fetal anomalies, chromosomal abnormalities
Obermair et al., 2020	Case Report	Retrospective	No	Not defined	HIC	1	Not applicable	Not applicable
Workalemahu et al., 2022	Cohort	Retrospective	No	20 weeks	HIC	387	Singleton stillborn deliveries	Fetal structural malformations and other abnormalities
Jaiman et al., 2020	Cohort	Retrospective	Yes	20 weeks	HIC	143	Fetal death >20 weeks Controls were healthy pregnant women, singleton, term neonate with Apgar score >7 and normal birthweight	Fetal deaths with congenital anomalies and multiple gestations. Excluded from the control were pregnant women presenting with maternal diseases or pregnancy complications
Cersonsky et al., 2023b)	Case Report	Retrospective	No	Not defined	HIC	2	Not applicable	Not applicable

GNI: gross national income, HIC: high income country, LMIC: low middle income country UMC: upper middle country, IUFD: intrauterine fetal death.

Table A:2Quality assessment of the included studies using the Newcastle Ottawa Scale [20].

Study Reference	Selection Criteria	Comparability	Outcome Domain	Overall
Amark et al.,2021	3	1	2	Good
Amodeo et al.,2022	4	2	2	Good
Avagliano et al., 2020	3	1	2	Good
Avagliano et al., 2022	2	0	1	Poor
Belhomme et al., 2018	2	0	1	Poor
Darouich and Masmoudi 2022	2	0	1	Poor
Manocha et al., 2019	2	0	1	Poor
McClure et al., 2022	2	0	1	Poor
Mtshali et al., 2021	2	0	1	Poor
Siassakos et al., 2022	2	0	1	Poor
Taweevisit and Thorner 2022	2	0	1	Poor
Tiwari et al., 2022	4	1	1	Good
Gibbins et al., 2016	4	2	2	Good
Lannaman et al., 2017	1	0	1	Poor
Obermair et al., 2020	1	0	1	Poor
Workalemahu et al.,2022	4	0	2	Good
Jaiman et al.,2020	4	1	2	Good
Cersonsky et al., 2023	2	0	1	Poor

Poor quality if total 0–2 and/or comparability = 0, fair quality if total 3–5, good quality if total>5.

Table A:3Percentage of placental lesions observed in stillbirths from studies that expressed placental lesions with and/or without control (n = 18)

Placental Lesions	n/total of placentas assessed	%
MVM	1279/2241	57.1
FVM	1138/1992	57.1
DVM	143/834	17.1
MIR	652/2050	31.8
FIR	492/1570	31.3
VUE (high grade)	384/1870	20.5

n = number of placentas observed with the placental lesion (%), DVM: delayed villous maturation, MVM: maternal vascular malperfusion, FVM: fetal vascular malperfusion, MIR: maternal inflammatory response, FIR: fetal inflammatory response, VUE: villitis of unknown etiology.

Table A:4Placental lesions observed in stillbirth and livebirth placentas organised by gestational age

Placental lesions	Preterm (<37 weeks)			Term		
	Stillbirth (n = 60)	Livebirth (n = 3)	p-value	Stillbirth (n = 27)	Livebirth (n = 33)	p-value
MVM	34 (56.7 %)	2 (66.7 %)	0.73	12 (44.4 %)	1 (3 %)	**<0.001**
FVM	19 (31.7 %)	0 (0 %)	0.24	11 (40.7 %)	6 (18.2 %)	0.05
DVM	9 (15 %)	1 (33.3 %)	0.39	4 (14.8 %)	5 (15.2 %)	0.97
Inflammatory	11 (18.3 %)	0 (0 %)	0.41	9 (33.3 %)	13 (39.4 %)	0.63
VUE (high grade)	0 (0 %)	0 (0 %)	N/A	1 (3.7 %)	6 (18.2 %)	0.08
SARS-Placentitis	1 (1.7 %)	0 (0 %)	0.82	0 (0 %)	0 (0 %)	N/A
No significant findings	4 (6.7 %)	0 (0 %)	0.64	0 (0 %)	9 (27.4 %)	**0.003**

Data represents the number of placentas with the observed lesions (%),Significant p-value<0.05, MVM: maternal vascular malperfusion, FVM: fetal vascular malperfusion, DVM: delayed villous maturation, VUE: villitis of unknown etiology.

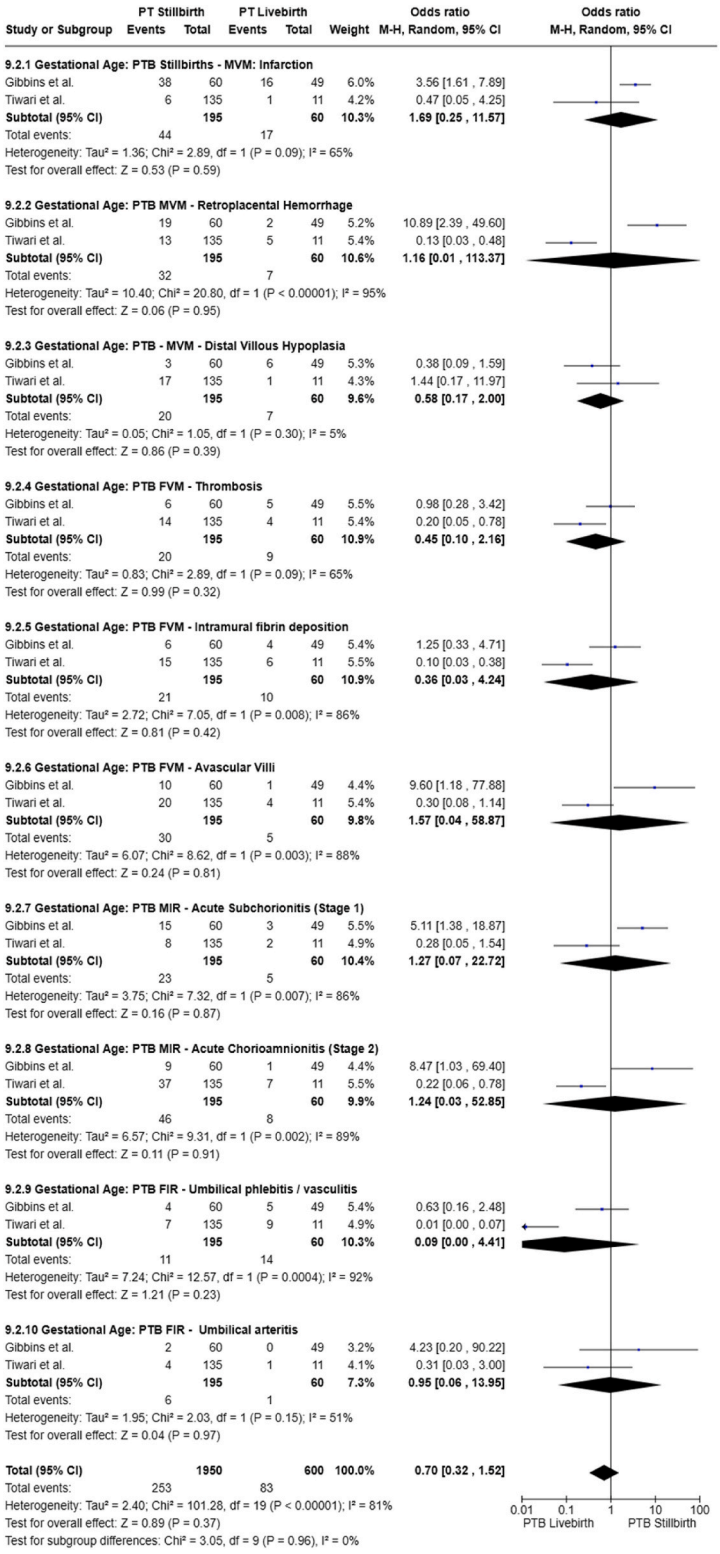

Fig. A:1. Forest plot showing odds ratio at a 95 % confidence interval for placental lesions pooled by preterm birth in stillbirth and livebirth placentasFVM: fetal vascular malperfusion, MVM: maternal vascular malperfusion, PTB: preterm birth

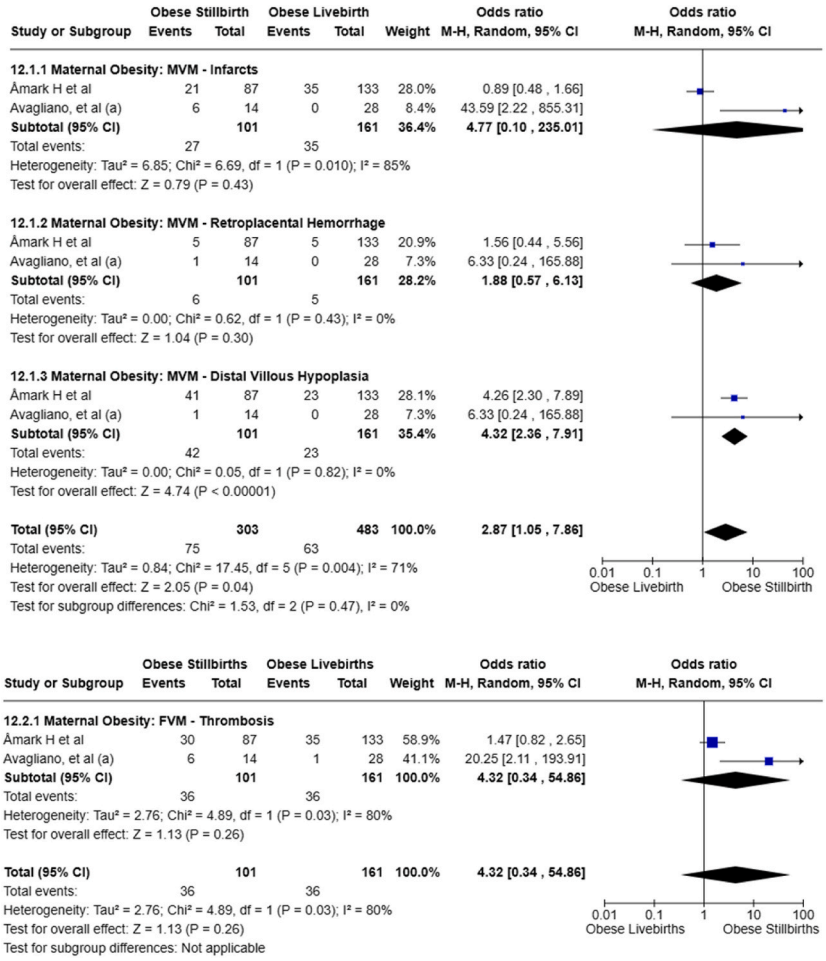

Fig. A:2. Forest plot showing odds ratio at a 95 % confidence interval for placental lesions pooled by maternal obesity, comparing obese livebirth placentas and obese stillbirth placentas. FVM: fetal vascular malperfusion, MVM: maternal vascular malperfusion

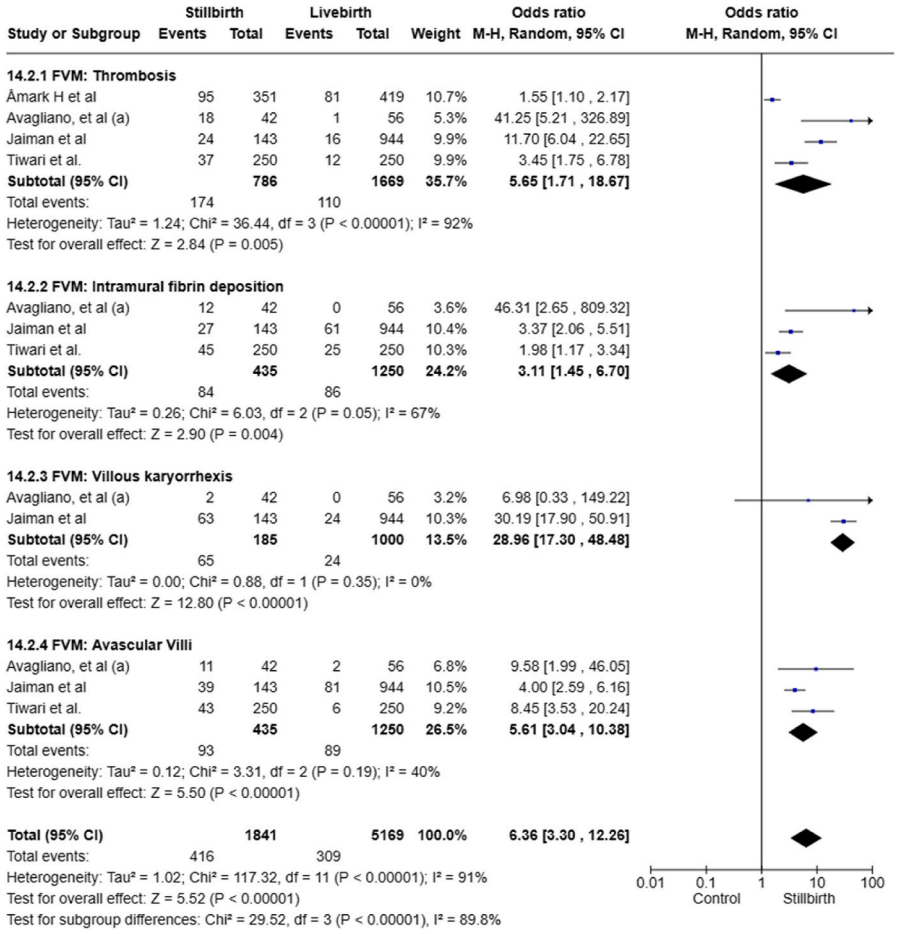

Fig. A:3. Forest plot showing odds ratio at a 95 % confidence interval for placental lesions excluding preeclamptic/ gestational hypertensive affected women. VM: fetal vascular malperfusion, MVM: maternal vascular malperfusion

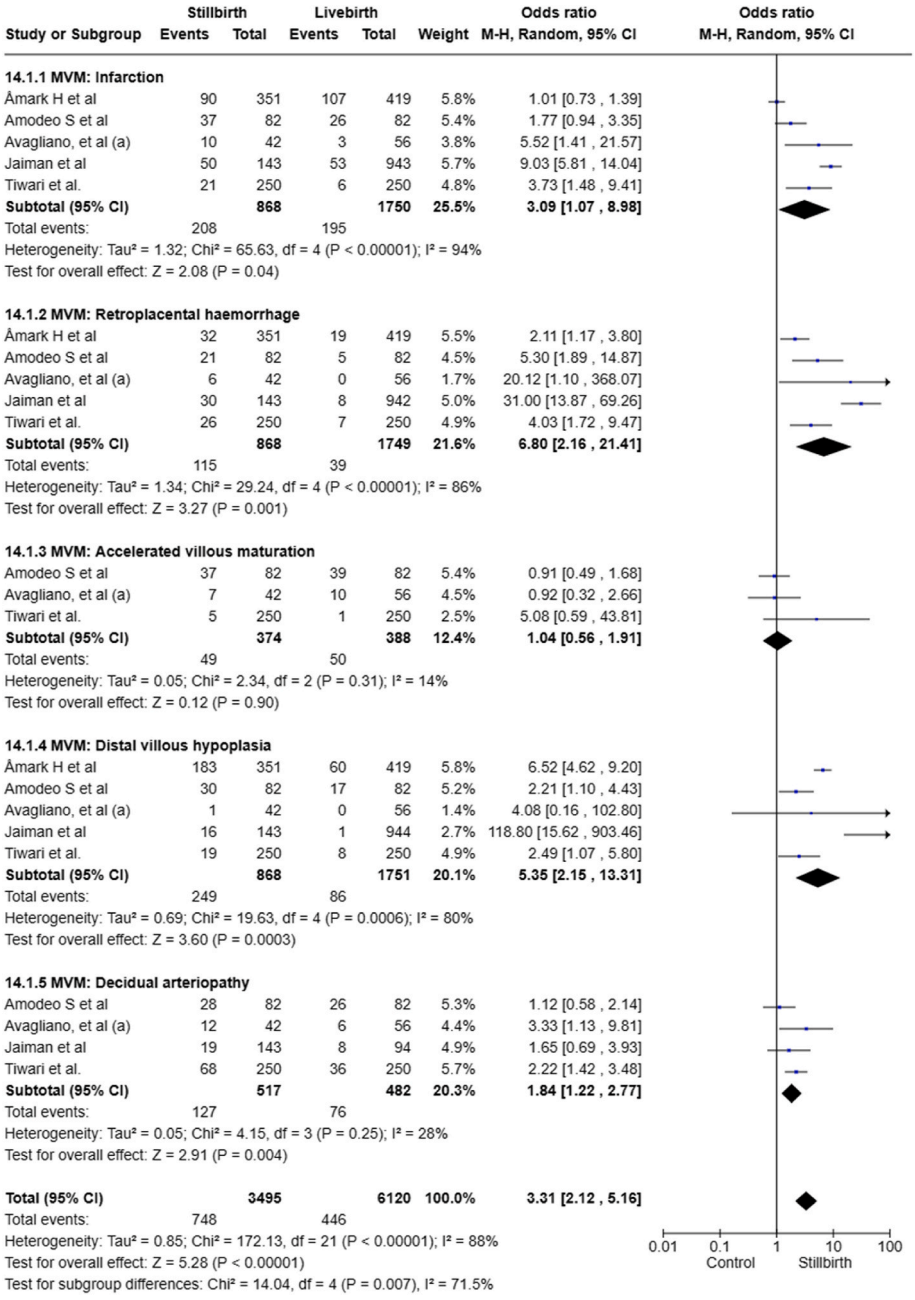

Fig. A:3. (*continued*).

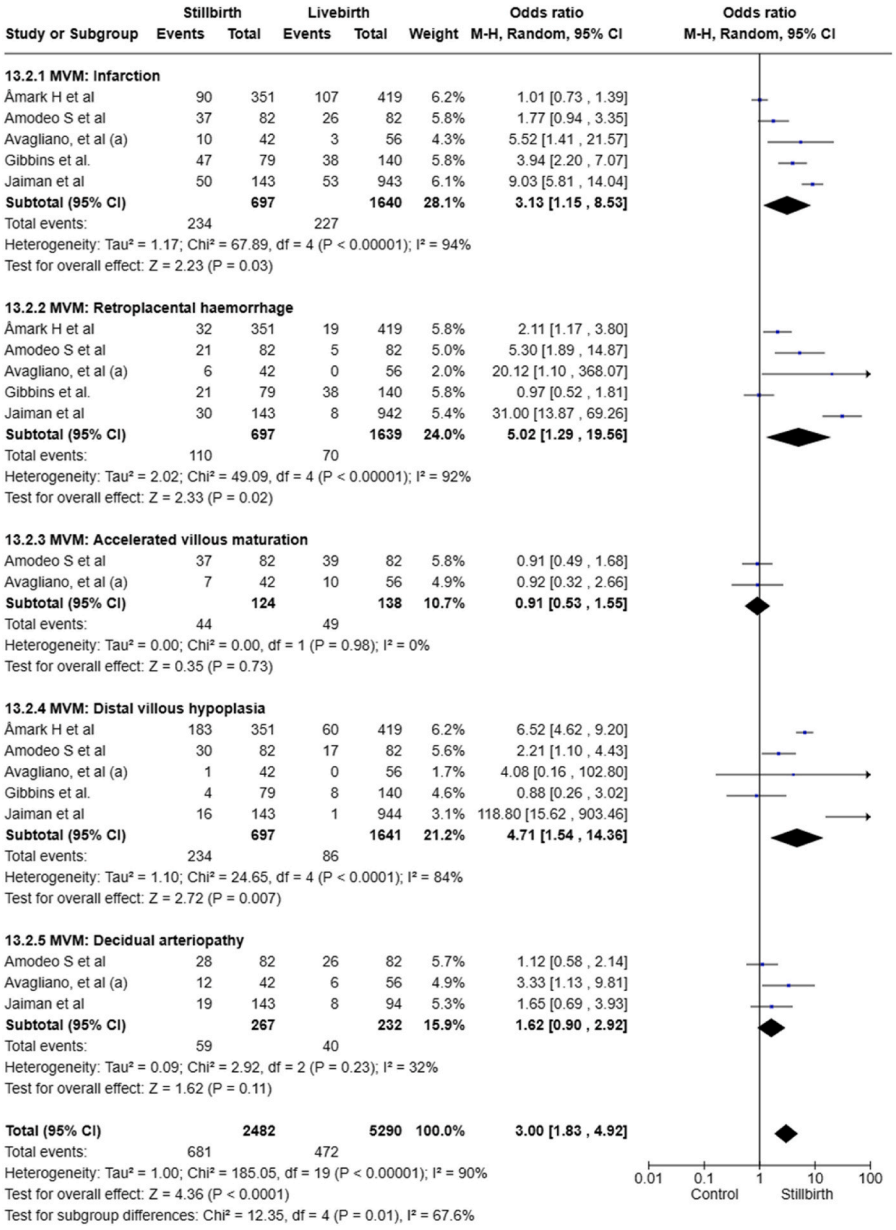

Fig. A:4. Forest plot showing odds ratio at a 95 % confidence interval for placental lesions from HICs only. MVM: fetal vascular malperfusion, MVM: maternal vascular malperfusion

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