Perinatal outcome of pregnancies complicated by placental chorioangioma: a systematic review and meta-analysis

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ABSTRACT

Objectives: To report perinatal outcome of singleton pregnancies complicated by placental choriangioma diagnosed on prenatal ultrasound.

Methods: Medline, Embase, Cinahl and Clinicaltrials.gov databases were searched. Inclusion criteria were singleton pregnancies complicated by placental chorioangioma with no other associated structural anomalies. Primary outcome was perinatal mortality; secondary outcomes included associated non-structural anomalies detected on prenatal ultrasound (including fetal hydrops, anemia, polyhydramnios or other signs of hyperdynamic circulation), small for gestational age (SGA) at birth, composite perinatal morbidity and preterm birth (PTB). Sub-analyses according to presence of hydrops, size of the tumor and outcome of pregnancies undergoing fetal therapy were also performed. Random effect meta-analyses of proportions were used to analyze the data.

Results: Twenty-eight studies (161 pregnancies) were included. In chorioangioma not undergoing intervention, IUD occurred in 8.2% (95% CI 3.8-14.0), while NND and PND in 3.8% (95% CI 1.0-8.1) and 11.1% (95% CI 5.0-19.4) of cases. SGA at birth was present in 24.0% (95% CI 13.5-36.5), of cases, while PTB <37 weeks complicated 34.1% (95% CI 21.1-48.3) of pregnancies. Finally, composite neonatal morbidity occurred in 12% (95% CI 4.5-22.3) of cases. On ultrasound, signs of fetal hyperdynamic circulation, were present in 21.0% (95% CI 9.6-35.3) of cases, while increased PSV in the MCA in 20.6% (95% CI 10.9-32.3).

Sub-analysis according to the size of chorioangioma, showed a progressive increase in the occurrence of most of the outcomes explored with increasing size of the tumor. Furthermore, the prevalence of adverse perinatal outcome was high in pregnancies complicated by chorioangioma presenting with fetal hydrops. There was no randomized controlled trial comparing intervention vs expectant management in pregnancies complicated by chorioangioma with signs of fetal compromise (hydrops, hyperdynamic circulation). Overall, perinatal mortality occurred in 31.2% (95% CI 18.1-46.6) of fetuses undergoing in utero therapy and 57.3% (95% CI 39.2-74.4) had resolution of hydrops or hyperdynamic circulation, after treatment.

Conclusion: Placental chorioangioma is associated with adverse perinatal outcome. The size of the mass and presence of fetal hydrops are likely to be the main determinants of perinatal outcome in these pregnancies.

INTRODUCTION

Chorioangioma is the most common non-trophoblastic vascular tumor of the placenta, with an estimated incidence of 1%[1,2]. Although its precise etiology has not been completely elucidated, it is thought to be the result of an abnormal proliferation of vessels in various stages of differentiation in fibrous stroma arising from chorionic tissue. [1-2]

Prenatal diagnosis of placental chorioangioma relies in the visualization of a hypoechogenic rounded, well-circumscribed placental mass of homogeneous or heterogeneous structure located on the fetal surface of the placenta. Application of color Doppler allows the visualization of the feeding vessel entering in the placental mass and of the peri-tumoral diffuse vascularization. In the most severe cases, signs of high-output cardiac failure, including cardiomegaly, polyhydramnios, increased velocity in the middle cerebral artery (MCA) and fetal hydrops can co-exist with the tumor[1,3,4] (Figure 1). Size of the mass, presence of hydrops and gestational age at occurrence of cardiac failure have been reported to be the main determinants of perinatal outcome in pregnancies complicated by chorioangioma. [5,6]

Most chorioangiomas are small asymptomatic lesions that are only found postnatally after careful slicing of the placenta.[5] Conversely, large tumors have been associated with a multitude of adverse perinatal outcome, including growth restriction, preterm birth (PTB), intra-uterine death (IUD) and abnormal neurodevelopmental outcome.[6]

The literature on the association between placental chorioangioma and adverse perinatal outcomes is likely to be biased due to the small sample size of published studies, the inclusion of cases mainly affected by fetal hydrops, and therefore at high risk of adverse outcome, and the heterogeneity in gestational age at diagnosis, tumor size and the observed outcomes.[1,3,6-8] Fetal therapy, including alcohol embolization, interstitial or fetoscopic coagulation of the tumor feeding vessels, has been anecdotally reported in the recent literature, but its actual role in modifying the natural history of these complicated pregnancies is yet to be defined. [9-10]

The aim of this systematic review was to quantify the adverse outcome in pregnancies complicated by placental chorioangioma.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to a priori designed protocol recommended for systematic reviews and meta-analysis.[11-13] Medline, Embase, Cinahl and Clinicaltrials.gov databases were searched electronically in January 2019, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "chorioangioma" or "placental "or "tumors" and "outcome". The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA and MOOSE guidelines were followed.[14-16] The study was registered with the PROSPERO database (CRD42019121891).

Study selection, data collection and data items

Inclusion criteria were singleton pregnancies complicated by isolated placental chorioangioma diagnosed on prenatal ultrasound, defined as chorioangioma with no apparently associated fetal structural anomalies at the time of diagnosis.

The primary outcome was mortality, including:

- Intra-uterine death (IUD)
- Neonatal death (NND)
- Perinatal death (PND)

The secondary outcomes were:

- Associated non-structural anomalies on prenatal ultrasound including fetal hydrops, anemia, polyhydramnios, signs of hyperdynamic circulation and small for gestational age (SGA) fetus.
- Small for gestational age (SGA) at birth, defined as birthweight $<10^{th}$ percentile for the gestational age.
- A composite score of neonatal morbidity including the occurrence of either, respiratory, neurological, infectious, abnormal acid-bases status, necrotizing enterocolitis and admission to neonatal intensive care unit.
- Preterm birth (including overall, spontaneous and iatrogenic deliveries) <37, 32 and 28 weeks of gestation.
- Maternal medical complications co-existing with the chorioangioma, including pre-eclampsia and diabetes
- Need for fetal intervention, including fetoscopic or interstial laser or alcohol ablation of the tumor feeding vessel.

- Outcome of fetuses undergoing in utero therapy, including the occurrence of fetal hydrops, hyperdynamic circulation, IUD, NND, PND, resolution or persistence of hydrops or hyperdynamic circulation after the procedure and PTB

All these outcomes were explored in pregnancies complicated by chorioangioma not undergoing and in those undergoing fetal therapy. The rationale for this choice was based upon the fact that fetal therapy does not represent the standard of care in pregnancies with chorioangioma. Therefore, pooling together treated and untreated cases would have led to an inclusion bias in view of the fact that fetuses undergoing in utero intervention are theoretically at higher risk of adverse outcome and tend to present with most severe signs of hemodynamics compromise, such as hydrops, compared to those not undergoing fetal therapy. Furthermore, we planned to perform sub-group analyses according to the size of the tumor (≥ 2, 4, 6, 8 and 10 cm) and the presence of hydrops on prenatal ultrasound.

Only studies reporting the incidence of these outcomes in singleton pregnancies with chorioangioma were considered eligible for analysis. The rational was based upon the assumption that the multiple pregnancies are at higher risk of perinatal mortality and morbidity compared to singleton.

Studies reporting non-isolated cases of chorioangioma were excluded. Autopsy-based studies without information on prenatal imaging were also excluded on the basis that fetuses undergoing termination of pregnancy are more likely to show associated major structural and chromosomal anomalies. Likewise, studies including only cases detected postnatally were also excluded because they report higher rates of adverse outcomes and do not reflect the natural history of the anomaly. Finally, studies published before 2000 were also excluded, because we felt that advances in prenatal imaging techniques and improvements in the diagnosis and definition of this anomaly make them less relevant.

Only full-text articles were considered eligible for inclusion. Case reports, conference abstracts, and case series with <3 cases, irrespective of whether the anomaly was isolated or not, were also excluded from the main analyses to avoid publication bias. However, for the assessment of the outcomes in those pregnancies undergoing in utero therapy, we opted to include case reports. The reason for this choice is based upon the fact that placental chorioangioma is a rare anomaly, with only few cases undergoing prenatal intervention reported in the published literature. Therefore, in order to have an overall estimation on the occurrence of the various explored outcomes in pregnancies undergoing prenatal intervention, we decided to include case reports.

Two authors (DB, CI) reviewed all abstracts independently. Agreement regarding potential relevance or inconsistencies was reached by consensus or resolved by discussion with a third reviewer (FDA). Full text copies of those papers were obtained, and the same reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies. According to NOS, each study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest.[17] Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.[17]
For case reports on fetal therapy, quality assessment of the included studies was assessed using the methodological quality and synthesis of case series and case reports described by Murad *et al.*[18] According to this tool, each study is judged on four broad perspectives: the selection of the study groups, the ascertainment and the causality of the outcome observed and the reporting of the case. A study can be awarded a maximum of one star for each numbered item within the Selection and Reporting categories, two stars for Ascertainment and four stars for Comparability.

Statistical analysis

We used meta-analyses of proportions to combine data and reported pooled proportion (PP). Funnel plots (displaying the outcome rate from individual studies versus their precision (1 per SE) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was <10. In this case, the power of the tests is too low to distinguish chance from real asymmetry.

Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I2 values ≥50% indicate a substantial level of heterogeneity. A random effect model was used to compute the pooled data analysis. All proportion meta-analyses were carried out by using StatsDirect version 2.7.9 (StatsDirect, Ltd, Altrincham, Cheshire, United Kingdom).

RESULTS

General characteristics

322 articles were identified, 68 were assessed with respect to their eligibility for inclusion (Table S1) and 28 studies were included in the systematic review (Table 1, Figure 2, Supplementary Table 1).[1-4,6-7,9-10,19-39] These 28 studies included 161 singleton pregnancies affected by isolated placental chorioangioma, defined as the presence of chorioangioma with no associated anomalies at the time of diagnosis; out of these, 11 studies were cases series[1-4,6-7,19-24], while 17 case report on cases undergoing in utero treatment of the chorioangioma (Table 1).[9-10,25-39]

The results of the quality assessment of the included studies using NOS are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size and different protocols for antenatal monitoring and management of fetuses affected by chorioangioma.

Quality assessment of the included case reports performed using the methodological quality of case reports and case series as reported by Murad et al. is reported in Table 2.[18] Despite being case reports, the included studies reported an overall good score for the selection and ascertainment of the outcome of interest and an accurate description of fetal procedure, perinatal outcome and management protocol adopted.

Synthesis of the results

Chorioangiomas not undergoing in utero treatment

Nine studies (106 pregnancies) explored the incidence of mortality in pregnancies complicated by chorioangioma. Overall, IUD occurred in 8.2% (95% CI 3.8-14.0) of cases, while NND and PND in 3.8% (95% CI 1.0-8.1) and 11.1% (95% CI 5.0-19.4), respectively (Table 3, Figure 3). When assessing the gestational age at death, IUD occurred in 7.5% (95% CI 3.2-13.4) before and in 2.8% (95% CI 0.6-6-7) from 34 weeks of gestation.

SGA at birth was present in 24.0% (95% CI 13.5-36.5) of cases. PTB <37 weeks occurred in 34.1% (95% CI 21.1-48.3) of cases, while the corresponding figures for delivery <32 and <28 weeks of gestation were 11.9% (95% CI 5.2-20.8) and 3.0% (95% CI 0.6-7.2), respectively. When exploring the type of PTB, 18.6% (95% CI 11.1-27.6) were spontaneous, while in 11.4% (95% CI 5.5-19.5) the delivery was required for fetal indications (Figure 3). Finally, composite neonatal morbidity occurred in 120% (95% CI 4.5-22.3) of the included cases (Figure 3).

Eight studies (98 pregnancies) reported detailed information on prenatal ultrasound characteristics of pregnancies complicated by chorioangioma. The diagnosis of SGA fetus on prenatal ultrasound was made in 21.4% (95% CI 11.4-33.5) of pregnancies complicated by placental chorioangioma, while hydrops was present in 14.5% (95% CI 6.5-24.9) of cases. Signs of fetal hyperdynamic circulation, including either cardiomegaly or increased peak systolic velocity (PSV) in the middle cerebral artery (MCA) in the absence of fetal hydrops, occurred in 21.0% (95% CI 9.6-35.3) of cases, while polyhydramnios was reported in 37.8% (95% CI 24.9-51.5) (Supplementary Table 2). Information on Doppler was reported only by a small proportion of the included studies; Raised PI in the umbilical artery was present in 3.8% (95% CI 0.3-11.2) of these pregnancies, while increased PSV in the MCA in 20.6% (95% CI 10.9-32.3). Finally, abnormal flow patter in the ductus venosus and umbilical vein occurred in 12.4% (95% CI 4.0-24.2) and 17.5% (95% CI 4.2-37.2), respectively (Supplementary Table 2). Among the included cases, maternal medical complications occurred in 23.4% (95% CI 12.9-36.0) of cases, mainly consisting in pre-eclampsia (Table S4).

Sub-group analysis: size of the mass, hydrops and in utero therapy

Table 4 reports the occurrence of the different outcome stratified according to the size of the chorioangioma. There was a progressive increase in the occurrence of most of the outcomes explored with increasing size of the tumour. Fetal hydrops complicated 15.2% (95% CI 6.3-27.0), 16.2% (95% CI 7.1-28.2). 20.3% (95% CI 10.3-32.7), 27.8% (95% CI 11.3-48.2) and 51.6% (95% CI 20.9-81.5) of chorioangiomas ≥2, 4, 6, 8 and 10 cm, respectively. Likewise, PND occurred in 10.4% (95% CI 3.9-19.5) of pregnancies with chorioangioma ≥2 cm, 11.2% (95% CI 4.6-20.3) in those ≥4 cm, 13.9% (95% CI 6.0-24.3) in those ≥6 cm, 20.6% (95% CI 7.0-39.0) in those ≥8 cm and 27.9% (6.9-56.2). Finally, PTB complicated 32.4% (95% CI 19.5-46.9), 31.5% (95% CI 18.1-46.7), 42.5% (95% CI 27.5-58.2), 46.9% (95% CI 25.0-69.4) and 58.9% (95% CI 31.8-83.3) pregnancies with chorioangiomas ≥2, 4, 6, 8 and 10 cm, respectively.

The prevalence of adverse perinatal outcome was high in pregnancies complicated by chorioangioma presenting with fetal hydrops. The prevalence of PND was 40.5% (95% CI 20.6-62.3), while that of SGA and PTB were 32,9% (95% CI 11.4-59.2) and 68.0% (95% CI 43.5-88.2), respectively. Finally, 42.5% (95% CI 15.6-62.1) of pregnancies complicated by fetal hydrops underwent in utero therapy.

Finally, we explored the outcome of pregnancies complicated by placental chorioangioma which underwent fetal therapy. There was no randomized controlled trial comparing intervention vs

expectant management in pregnancies complicated by chorioangioma with signs of fetal compromise (hydrops, hyperdynamic circulation). Furthermore, there was no trial comparing the different techniques for treating chorioangioma in utero. Overall, 22 studies including 30 fetuses reported the outcome of pregnancies complicated by chorioangioma undergoing in utero treatment. The large majority of cases having in utero treatment underwent intervention before 25 weeks of gestation; 41.3 (95% CI 26.9-55.5) showed signs of fetal hydrops before the procedure, while 72.1% showed signs of hyperdynamic circulation, including cardiomegaly or increased PSV in the MCA. The size of the mass was 2-4 cm in 3.3% (1/30), 5-7 cm in 33.3% (10/30), 8-10 cm in 53.3% (16/30) and >11 cm in 10% (3/30) of cases. The gestational age was 20-22 weeks in 16.7% (5/30), 23-25 in 53.3% (16/30), 25-27 in 43.3% (13/30) and >28 in 10% (3/30) of cases undergoing intervention. Information on individual cases undergoing in utero therapy is reported in Supplementary Table 3.

Overall, perinatal mortality occurred in 31.2% (95% CI 18.1-46.6) of fetuses undergoing in utero therapy, while IUD and NND occurred in 23.6% (95% CI 12.0-37.6) and 17.5% (95% CI 7.6-30.5), respectively. 57.3% (95% CI 39.2-74.4) of the fetuses had resolution of hydrops or hyperdynamic circulation, while persistence of haemodynamic compromise occurred in 30.6% (95% CI 13.8-50.6). Finally, 52.5% (95% CI 37.0-67.7) of the pregnancies delivered preterm (Table 5).

DISCUSSION

Summary of the main findings

The findings from this systematic review show that placental chorioangioma is associated with adverse perinatal outcome and that the risk of adverse outcome increases with increasing size of the tumour. Furthermore, the prevalence of adverse perinatal outcome is also higher in fetuses presenting with hydrops. Finally, there is still scarce evidence on the role of in utero therapy in modifying the outcome of pregnancies complicated by chorioangioma. The lack of randomized trials, the multitude of treatments offered, and the paucity of published cases did not allow us to extrapolate an objective evidence on which chorioangiomas should undergo in utero therapy. Most of the cases undergoing treatment were affected by hydrops or severe haemodynamic compromise and were far from viability, thus suggesting a potential beneficial effect of therapy in this sub-set of fetuses.

Strengths and limitations

Thorough literature search aimed at identifying all studies including fetal tumors, the multitude of outcomes explored, exclusion of cases affected by co-existing anomalies, stratification of the analysis according to tumor size and presence of the hydrops and ascertainment of the role of fetal therapy in affecting the outcome of pregnancies complicated by chorioangioma represent the main strengths of the present systematic review. The small number of included studies, their retrospective non-randomized design, differences among the included populations in the prenatal management and time at follow-up of fetuses with a prenatal diagnosis of placental chorioangioma are the main limitations of the present systematic review.

Most of the placental chorioangiomas are not routinely detected at the second trimester scan and are incidentally diagnosed after birth, while some are identified only when complicated, such as polyhydramnios, growth restriction or hydrops. In this scenario, the figures reported in the present systematic review may represent an overestimation of the actual burden of adverse outcomes associated with this condition. Assessment of the role of in utero therapy in pregnancies complicated by chorioangioma was also problematic; the large majority of the included studies were case reports, and this might have led to an overestimation of the adverse outcome in the cases undergoing in utero therapy. Furthermore, in view of the very small number of cases included, it was not possible to stratify the analysis according to the type of procedure and gestational age at intervention, making the interpretation of these results quite challenging. Finally, information on placental location and proximity of the tumor to the umbilical cord, which are fundamental in choosing the optima surgical approach, were not reported for many of the included cases.

Implications for clinical practice and future research studies

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommends that, during the routine anomaly scan, placental location, its relationship with the internal cervical os and its appearance should be described in order to identify abnormal findings including hemorrhage, multiple cysts and placental masses such as chorioangioma.[40]

The importance of prenatal diagnosis of chorioangioma relies on its potential association with adverse perinatal outcome. Most chorioangiomas are small and of no significant importance. Conversely, large masses can lead to high output cardiac failure, hydrops, PTB and or fetal demise.[1,3,6,8] More importantly, a persistent state of hyperdynamic circulation may not only lead to death but also predispose to abnormal neurodevelopment in childhood.[6]

In the present systematic review, there was a progressive increase in the incidence of hydrops, PND, PTB and morbidity with increasing tumor size, thus confirming that the tumor size is among the main determinants of adverse perinatal outcome in pregnancies complicated by chorioangioma. These findings suggest that pregnancies presenting with large placental masses should undergo intensive fetal monitoring in order to identify early signs of fetal compromise, although the frequency of follow-up is yet to be established. Fetal assessment every 1-2 weeks has been proposed as a reasonable option in these cases although the quality of this evidence is low being based on expert opinion rather than large and appropriately designed trials.

Previous reports suggest that the occurrence of fetal hydrops represents one of strongest risk factors for adverse perinatal outcome in pregnancies complicated by chorioangioma.[1-2,6,8] In the present systematic review, there was a high incidence of adverse perinatal outcome in fetuses presenting with hydrops. PND occurred in 54% of cases, while SGA and PTB in 32.9% and 68.0%, respectively. This data demonstrates that the highest risk of mortality and morbidity in pregnancies complicated by chorioangioma occurs when associated with fetal hydrops.

If complications develop late in pregnancy, planned delivery is a reasonable option. However, most complications occur early in gestation making iatrogenic preterm delivery unacceptable due to the high risk of mortality and morbidity secondary to prematurity. Furthermore, in cases presenting with hydrops, iatrogenic preterm delivery represents an additional risk factor for an already compromised fetus, likely leading to perinatal death. In such circumstances, especially in those cases far from viability, in utero therapy has been proposed as an alternative approach to prevent

fetal demise from the anemia or hemodynamic complications of chorioangiomas.[46] Several in utero techniques for treating chorioangioma have been reported in the last decade, mostly involving the use of fetoscopic or interstitial approaches.[1-2,8,33,41,42]

Unfortunately, in the present review, it was not possible to stratify the analysis according to the type of fetal procedure performed. Furthermore, all cases undergoing in utero therapy presented with signs of hemodynamic compromise at early gestational age. Therefore, the figures reported in the present review may present an overestimation of the incidence of adverse outcome following fetal therapy. However, in cases where fetal therapy is considered, less invasive approaches, such as interstitial coagulation or embolization of the feeding vessels, should be preferred to more invasive approaches in order to reduce the risk of PTB.

Conclusion

Placental chorioangioma is associated with adverse perinatal outcome. The size of the mass and presence of fetal hydrops are the main determinants of perinatal outcome in pregnancies complicated by chorioangioma. Further large studies are needed in order to elucidate the role of fetal therapy in improving the outcome of those pregnancies, determine the long-term consequence on the cardiovascular and neurodevelopmental performance of these fetuses with sustained hemodynamic compromise induced by the tumor.

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Figure legend

Figure 1a-d. a-c: Ultrasound pictures of the chorioangioma, with the feeding vessel displayed on color Doppler. D: Cardiomegaly in a fetus with chorioangioma.

Figure 2. Systematic review flowchart.

Figure 3a-c: Pooled proportions for the rates of IUD, PTB and composite morbidity in pregnancies complicated by chorioangioma.

Author	Year	Country	Study period	Study design	GA at diagnosis	Prenatal imaging	US follow-up	Outcomes observed	Cases (n)
Case series									
Sirotkina[19]	2016	Sweden/Norway	1996-2012	Retrospective	NS	US	NS	Mortality, PTB, SGA	10
Lim[1]	2015	United States	2005-2012	Retrospective	24.14 (20.1-28.9)	US, MRI	NS	US appearance, mortality, PTB, SGA, fetal intervention	15
Iacovella[6]	2014	United Kingdom	2000-2011	Retrospective	28.0(4.0)	US	Every 2 weeks	US appearance, mortality, PTB, SGA, fetal intervention	23
Wu[20]	2015	China	2003-2015	Retrospective	31 (2-35)	US	Every 2 weeks	US appearance, mortality, PTB, SGA	22
Liu[7]	2013	China	1999-2011	Retrospective	26.9 (5.0)	US	Every 2 weeks	US appearance, mortality, PTB, SGA	14
Wou[8]	2011	Canada	2003-2007	Retrospective				US appearance, mortality, PTB, SGA	23
Sepulveda[9]	2009	Chile		Retrospective	26-28	US	NS	Fetal therapy	3
Sepulveda[3]	2003	Chile	1997-2001	Prospective	26(20-36)	US	NS	US appearance, mortality, PTB, SGA, fetal therapy	11
Zalel[21]	2002	Israel	1992-2000	Retrospective	23(18-29)	US	NS	US appearance, mortality, PTB, SGA	7
Jauniaux[22]	2000	United Kingdom		Retrospective	22.9(4.6)	US	NS	US appearance, mortality, PTB, SGA, fetal therapy	9
Pilu[23]	2000	United States	1989-1998	Retrospective	26.7(5.7)	US	NS	US appearance, mortality, PTB, SGA	7
Case reports on fetal therapy									
Papaioannou[24]	2017	Greece	2017	Case report	24	US	Yes	Fetal therapy	1
Voon[25]	2017	Malaysia	2017	Case report	20	US	NS	Fetal therapy	1
Chen[26]	2016	China	2016	Case report	21	US	NS	Fetal therapy	1
Hosseinzadeh[27]	2015	United States	2015	Case report	16	US	NS	Fetal therapy	1
Jhun[28]	2014	United States	2014	Case report	29	US	Yes	Fetal therapy	1
Boll[29]	2014	Switzerland	2014	Case report	22	US	Yes	Fetal therapy	1
Basic[30]	2012	Saudi Arabia	2012	Case report	22	US	Every week	Fetal therapy	1
Ercan[31]	2012	Turkey	2012	Case report	25	US	NS	Fetal therapy	1
Jon[32]	2012	United States	2012	Case report	25	US	Yes	Fetal therapy	1
Gajewska[9]	2010	Belgium	2010	Case report	18	US, MRI	Yes	Fetal therapy	1
Mendez-Figueroa[33]	2009	United States	2009	Case report	25	US	NS	Fetal therapy	1
Bermudez[34]	2007	United States	2007	Case report	24	US	NS	Fetal therapy	1
Quarello[35]	2005	France	2005	Case report	23	US	Every week	Fetal therapy	1
Deren[36]	2005	Turkey	2005	Case report	16	US	NS	Fetal therapy	1
Lau[37]	2005	Hong Kong	2005	Case report	24	US	Yes	Fetal therapy	1
Lau[4]	2003	Hong Kong	2003	Case report	24	US	NS	Fetal therapy	1
Wanapirak[38]	2002	Thailand	2002	Case report	27	US	Yes	Fetal therapy	1

Table 1. General characteristics of the included studies

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) for cohort studies; a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.
For case reports on fetal therapy, quality assessment of the included studies was assessed using the methodological quality and synthesis of case series and case reports described by Murad *et al*. According to this tool, each study is judged on four broad perspectives: the selection of the study groups, the ascertainment and the causality of the outcome observed and the reporting of the case. A study can be awarded a maximum of one star for each numbered item within the Selection and Reporting categories, two stars for Ascertainment and four stars for Comparability.

		Case series		
Author	**Year**	**Selection**	**Comparability**	**Outcome**
Sirotkina[19]	2016	★★	★	★★★
Lim[1]	2015	★★	★	★★
Iacovella[6]	2015	★★	★	★★
Wu[20]	2013	★★	★	★★
Liu[4]	2011	★★	★	★★
Wou[7]	2014	★★	★	★★
Sepulveda[2]	2009	★★	★	★
Sepulveda[3]	2003	★★	★★	★★
Zalel[21]	2002	★★	★	★★
Prapas[23]	2000	★★	★	★

		Case reports			
Author	**Year**	**Selection**	**Ascertainment**	**Causality**	**Reporting**
Papaioannou[24]	2017	★	★★	★★★	★
Voon[25]	2017	★	★★	★★	★
Cheng[26]	2016	★	★	★★	★
Hosseinzadeh[27]	2015	★	★	★★	★
Jhun[28]	2014	★	★★	★★	★
Bolla[29]	2014	★	★★	★	★
Babic[30]	2012	★	★★	★★★	★
Ercan[31]	2012	★	★★	★★	★
Jones[32]	2012	★	★★	★★★	★
Gajewska[10]	2010	★	★★	★★★	★
Mendez-Figueroa[33]	2009	★	★★	★★	★
Bermudez[34]	2007	★	★	★★	★
Quarello[35]	2005	★	★	★★	★
Deren[36]	2005	★	★★	★★★	★
Lau[37]	2005	★	★★	★	★
Lau[9]	2003	★	★★	★★★	★
Wanapirak[38]	2002	★	★★	★★★	★

Table 3. Pooled proportions of adverse perinatal outcomes in pregnancies with chorioangioma not undergoing in utero intervention.

Outcome	Studies	Fetuses (n/N)	Pooled proportions (95% CI)	I^2 (%)
IUD	9	8/106	8.19 (3.8-14.0)	10.9
• **<34 weeks**	9	7/106	7.47 (3.2-13.4)	7.1
• **≥34 weeks**	9	1/106	2.79 (0.6-6.7)	0
NND	9	3/106	3.78 (1.0-8.1)	0
PND	9	11/129	11.14 (5.0-19.4)	31.5
SGA	8	23/96	24.01 (13.5-36.5)	45.3
PTB (overall)	8	31/96	34.05 (21.1-48.3)	50.9
PTB <32 weeks	8	11/96	11.85 (5.2-20.8)	31.4
PTB <28 weeks	8	2/96	2.96 (0.6-7.2)	0
Spontaneous PTB	6	14/81	18.62 (11.1-27.6)	0
Iatrogenic PTB	6	8/81	11.41 (5.5-19.0)	0
Composite morbidity	4	5/48	11.97 (4.5-22.3)	0

*: Includes cases with fetal intervention and cases from which it was not possible to extrapolate whether fetal intervention was performed.

PTB: preterm birth; IUD: intra-uterine death; NND: neonatal death; PND: perinatal death; SGA: small for gestational age

Table 4. Pooled proportions of the adverse perinatal outcomes in pregnancies with chorioangioma according to the tumor size.

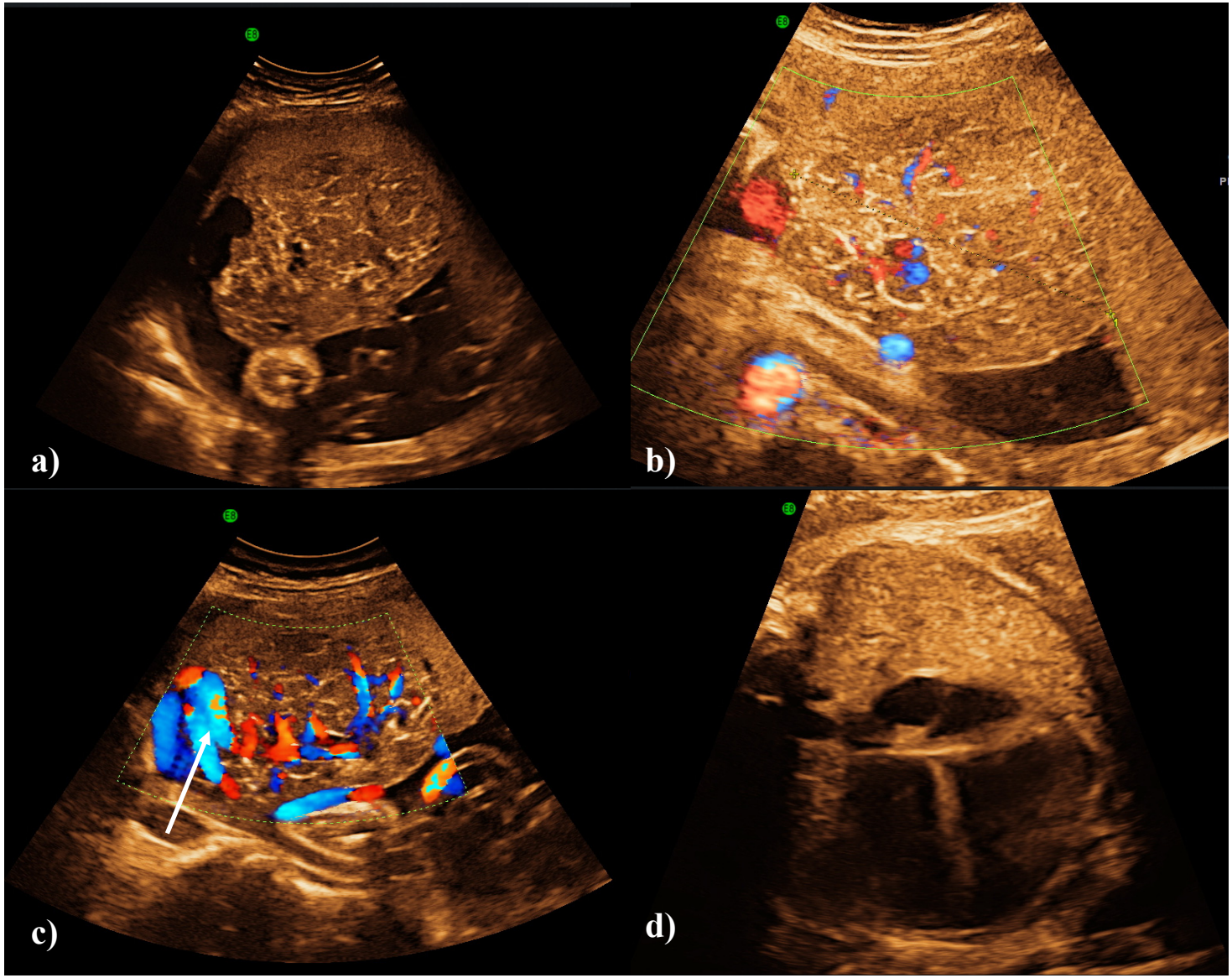
Outcome	Studies	Fetuses (n/N)	Pooled proportions (95% CI)	I^2 (%)
	Chorioangioma ≥2 cm			
Hydrops	8	13/93	15.16 (6.3-27.0)	51.7
SGA	7	12/78	17.50 (10.1-26.5)	0
PND	8	9/93	10.37 (3.9-19.5)	38.6
PTB	8	28/93	32.39 (19.5-46.9)	53.0
Composite morbidity	3	2/34	7.87 (1.4-18.8)	0
Fetal therapy	7	7/79	8.37 (1.8-19.1)	51.6
	Chorioangioma ≥4 cm			
Hydrops	8	13/85	16.24 (7.1-28.2)	46.0
SGA	7	12/70	19.48 (11.3-29.3)	0
PND	8	9/85	11.22 (4.6-20.3)	28.7
PTB	8	25/85	31.47 (18.1-46.7)	54
Composite morbidity	3	2/33	8.01 (1.4-19.2)	0
Fetal therapy	7	7/71	9.12 (2.0-20.7)	50.5
	Chorioangioma ≥6 cm			
Hydrops	8	12/61	20.34 (10.3-32.7)	22.5
SGA	7	7/47	17.49 (8.4-29.1)	0
PND	8	8/61	13.87 (6.0-24.3)	14.7
PTB	8	24/61	42.50 (27.5-58.2)	37.7
Composite morbidity	3	2/31	8.35 81.5-20.1)	0
Fetal therapy	7	8/53	15.00 (5.9-27.4)	23.8
	Chorioangioma ≥8 cm			
Hydrops	7	8/30	27.78 (11.3-48.2)	30.3
SGA	6	1/21	8.34 5 (8.6-22.49	0
PND	7	6/30	20.63 (7.0-39.0)	24.8
PTB	7	14/30	46.86 (25.0-69.4)	40.0
Composite morbidity	2	1/16	8.69 (0.4-26.2)	0
Fetal therapy	6	4/28	14.82 (2.3-35.5)	41.6
	Chorioangioma ≥10cm			
Hydrops	7	6/13	51.56 (20.9-81.5)	42.2
SGA	6	1711	14.79 (17.6-37.3)	0
PND	7	3/13	27.88 (6.9-56.2)	28.5
PTB	7	8/13	58.89 (31.8-83.3)	20.7
Composite morbidity*	-	-	-	-
Fetal therapy	6	2/11	21.84 (4.5_47.4)	6.6

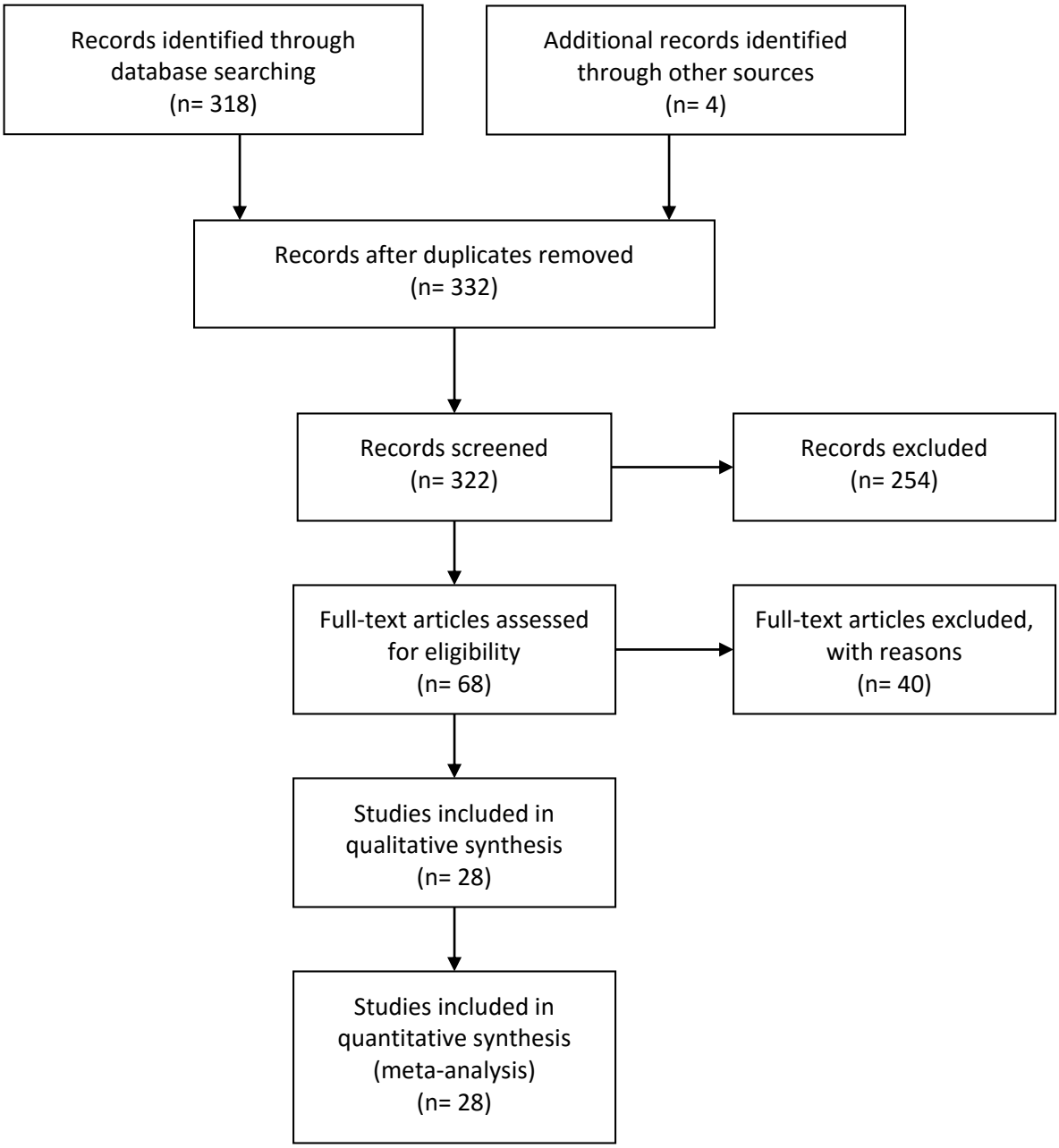
PTB: preterm birth; IUD: intra-uterine death; NND: neonatal death; PND: perinatal death; SGA: small for gestational age.
*: Less than two studies were included

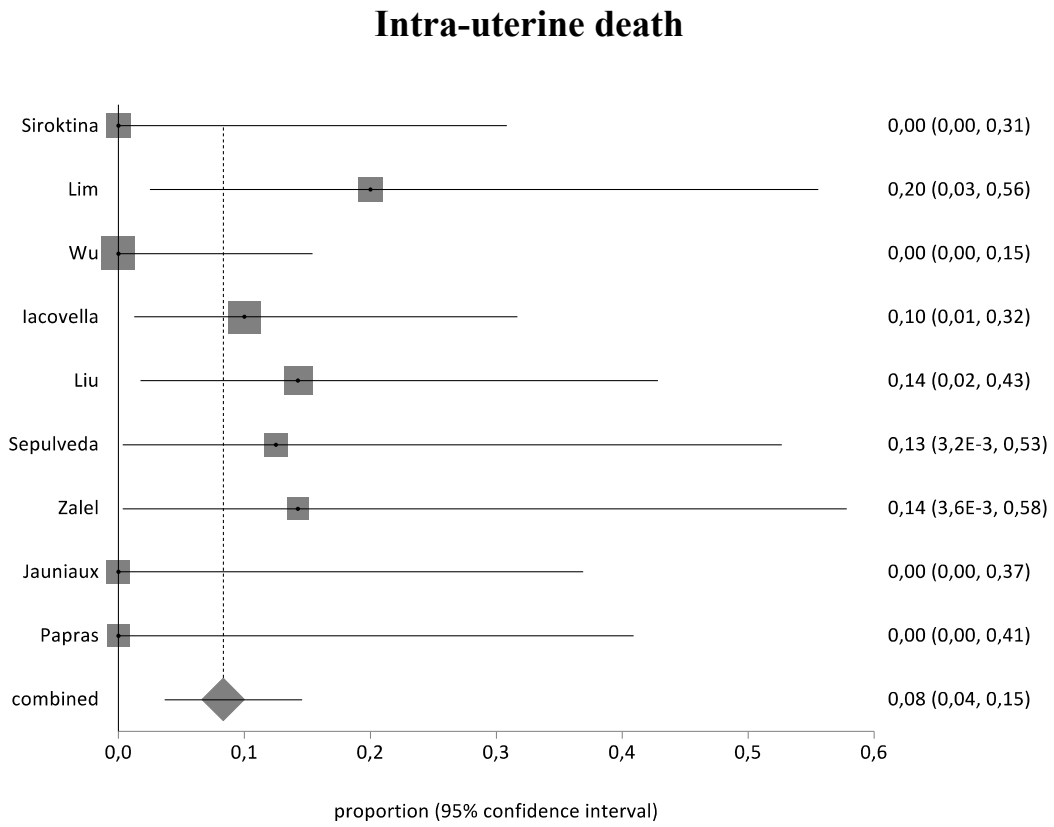
Table 5. Pooled proportions of the adverse perinatal outcomes in the pregnancies complicated by placental chorioangioma and undergoing in utero therapy.

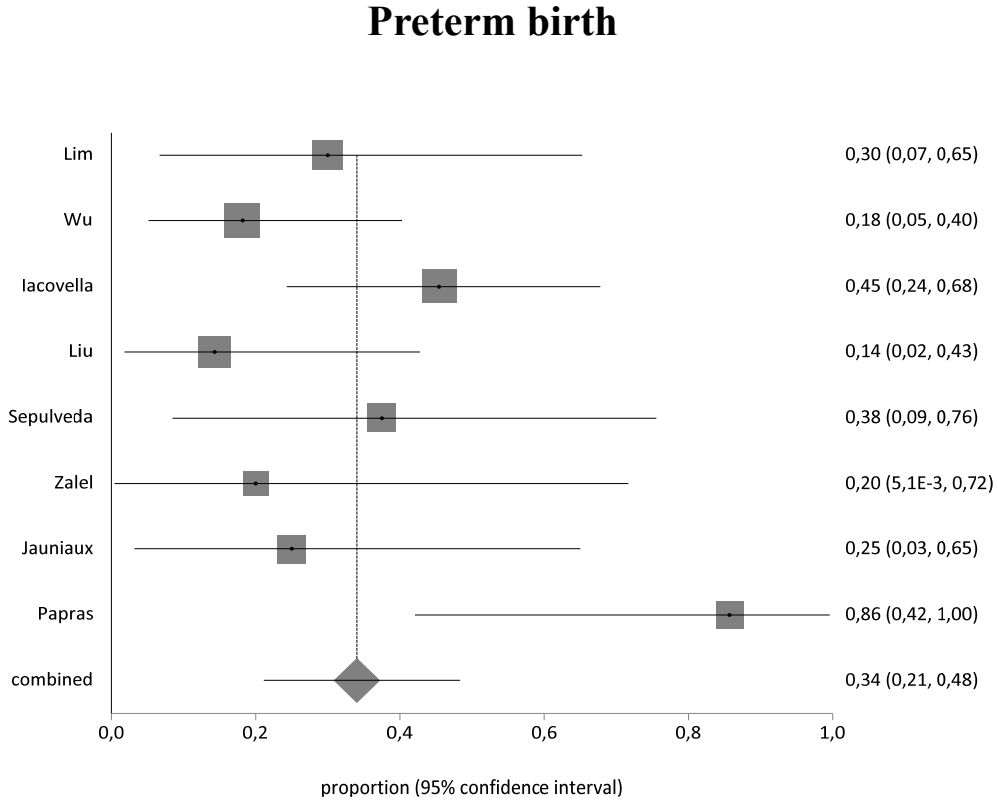
Outcome	Studies	Fetuses (n/N)	Pooled proportions (95% CI)	I^2 (%)
Hydrops	22	12/30	41.29 (26.9-55.5)	0
Hyperdynamic circulation	22	23/30	72.09 (57.5-84.6)	0
IUD	22	5/30	23.57 (12.0-37.6)	0
NND	22	3/30	17.54 (7.6-30.5)	0
PND	22	8/30	31.24 (18.1-46.1)	0
Resolution of hydrops or hyperdynamic state	17	15/30	57.28 (39.2-74.4)	10.5
Persistence of hydrops or hyperdynamic state	13	5/30	30.58 (13.8-50.6)	8.7
PTB	21	15/30	52.46 (37.0-67.7)	0

PTB: preterm birth; IUD: intra-uterine death; NND: neonatal death; PND: perinatal death.









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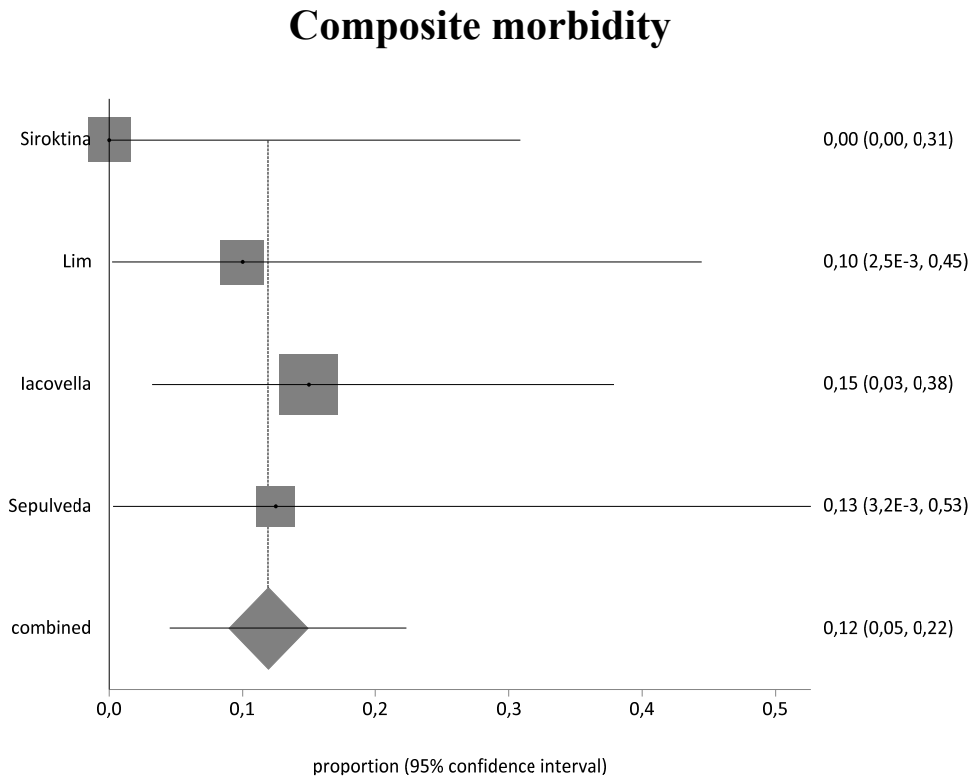

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