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Perinatal and long-term outcomes of fetal intracranial hemorrhage: systematic review and meta-analysis

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Contribution

What are the novel findings of this work?

Fetuses with prenatal diagnosis of intracranial hemorrhage are at high risk of perinatal mortality and adverse neurodevelopmental outcome. Perinatal Death occurred in 14.6% of these fetuses, 27.6% required shunt placement after birth and 32.0% had cerebral palsy. A normal postnatal outcome was reported only in half of the included cases.

What are the clinical implications of this work?

Fetuses with intracranial hemorrhage have increased risk of perinatal mortality and morbidity although the small number of included fetuses, the heterogeneity in reporting and defining outcomes prevent us from drawing robust conclusion. Due to its rarity, multicentre prospective registries should be promoted to collect high quality data.

ABSTRACT

Objective: Fetal intracranial hemorrhage is associated with increased risk of perinatal mortality and morbidity. Healthcare professionals often find it challenging to counsel parents due to its rarity and diverse presentation. The aim of this systematic review and meta-analysis was to investigate the perinatal outcomes of fetuses with intracranial hemorrhage.

Methods: Medline, Embase, Clinicaltrials.gov and Cochrane Library databases were searched. Inclusion criteria were studies reporting the outcomes of fetuses diagnosed with intracranial hemorrhage. The primary outcome was perinatal death (PND) defined as the sum of intra-uterine (IUD) and neonatal death (NND). The secondary outcomes were stillbirth, NND, termination of pregnancy, need for surgery/shunting at birth, cerebral palsy, defined according to the European Cerebral Palsy Network and classified as diplegia, hemiplegia, quadriplegia, dyskinetic, or mixed, neurodevelopmental delay, and intact survival. All these outcomes were explored in the overall population of fetuses with intracranial hemorrhage. A subgroup analysis according to the location of the hemorrhage (intra-axial and extra-axial) was also planned. Meta-analyses of proportions were used to combine data and reported pooled proportion and their 95% confidence intervals (CI).

Results: Sixteen studies (193 fetuses) were included in the analysis. PND occurred in 14.6% (95% CI 7.3-24.0), of fetuses with intracranial hemorrhage. Of those liveborn, 27.6% (95% CI 12.5-45.9) required shunt placement after birth and 32.0% (95% CI 22.2-42.6) had cerebral palsy. 16.7% of children had signs of mild neurodevelopmental delay, while 31.1% (95% CI 19-44.7) experienced severe adverse neurodevelopmental outcome. A normal outcome was reported in 53.6% of the fetuses.

Subgroup analysis according to the location of the intracranial hemorrhage showed that PND occurred in 13.3% (95% CI 5.7-23.4) of fetuses with intra-axial and in 26.7% (95% CI 5.3-56.8) with extra-axial bleeding. In fetuses with intra-axial hemorrhage 24.7% (95% CI 11-41.2) required shunt placement after birth and 27.1% (95% CI 17.1-38.4) experienced cerebral palsy. Mild and severe neurodevelopmental delay were observed in 15% (95% CI 6.9-25.6) and 32.3% (95% CI 19.7-46.3) of cases, respectively, while 51.9% (95% CI 36-67.4) experienced a normal neurodevelopmental outcome. Robust evidence on the incidence of mortality and postnatal outcome in fetuses with extra-axial hemorrhage could not be extrapolated due to the small number of cases.

Conclusions: Fetuses with a prenatal diagnosis of intracranial hemorrhage are at high risk of perinatal morality and impaired neurodevelopmental outcome. Postnatal shunt placement was performed in 28% and cerebral palsy was diagnosed in approximately one third of these infants.

BACKGROUND

Intracranial hemorrhage (ICH) is a common event in premature infants and an important cause of neonatal morbidity and mortality[1-3] . This event may also occur in utero: its true incidence is difficult to estimate because of lack of ascertainment and as different terms are used in the literature to define the same entity[4], ranging from 1 in 10,000 [5] and 1 per 1000 pregnancies[6]. Prenatal diagnosis by either ultrasound and/or magnetic resonance imaging has been increasing over the recent years.[5-9] Maternal risk factors for fetal ICH include maternal alloimmune antiplatelet antibodies causing Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT)[10]; other conditions such as platelet or coagulation disorders[11], maternal seizures, severe maternal trauma, genetic conditions (e.g. COL4A1 mutations)[12], congenital infections, and drugs (in particular cocaine). Fetal predisposing conditions include congenital coagulopathy with factor V and factor X deficiency, hemorrhage into a congenital tumour, twin–twin transfusion syndrome, demise of a co-twin, and fetomaternal hemorrhage. In many cases however, the exact cause remains unknown.[4] Recognition of fetal ICH is important because of the potentially poor outcome of the pregnancy and consequently for management, for the medico-legal issues related to time of occurrence, (i.e. where late TOP is not allowed), but also due to the possibility of recurrence in future pregnancies such as in alloimmune thrombocytopenia.[13]

Most frequently the hemorrhage occurs in the periventricular white matter, mainly in the germinal matrix, and the blood clot appears as an echogenic collection similar to the normal choroid plexus that progressively develops a complex texture in the following days with some degree of enlargement of the lateral ventricles (Figure 1). Small hemorrhages may undergo spontaneous resolution over time, while large hemorrhages frequently cause aqueductal obstruction and severe ventricular enlargement. They can also be associated with infarction and destruction of the white matter surrounding the ventricles and result in a porencephalic cyst.[14] Other types of ICH are infratentorial hemorrhage and subdural hematoma, which are more difficult to recognize antenatally (Figure 2). The infratentorial hemorrhage appears as an echogenic collection into the posterior fossa and is difficult to differentiate from a primary ischemic cerebellar lesion; it usually causes a hypoplasia of the cerebellar hemisphere.[6,7] Subdural hematomas usually appear as a large complex mass, associated with midline shift and compression of the hemispheres similarly to tumors from which they are usually difficult to be differentiated.[15]

Despite its importance, however, robust estimates of perinatal mortality and morbidity of fetuses affected by intracranial hemorrhage diagnosed antenatally is yet to be available. The

aim of this systematic review and meta-analysis was to ascertain the perinatal mortality and morbidity, as well as the long-term neurodevelopmental outcomes of fetuses with ICH, so that clinicians can provide accurate counselling to parents.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to an a-priori designed protocol for systematic reviews and meta-analysis. Medline, Embase, Clinicaltrials.gov and Cochrane Library databases were searched electronically in July 2020, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for “fetus” and “hemorrhage” (Supplementary Table 1). The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA[16] and MOOSE[17] guidelines were followed. Reference lists of relevant articles and reviews were hand searched for additional reports. The study was registered with the PROSPERO database (Registration Number: CRD42020197333).

Inclusion criteria, primary and secondary outcomes

The inclusion criteria were studies reporting the outcomes of fetuses, newborns and infants after an antenatal diagnosis of ICH. The primary outcomes were perinatal death (PND) defined as the sum of intra-uterine death (IUD) and neonatal death (NND).

The secondary outcomes were:

- Termination of pregnancy (TOP)
- IUD, defined as fetal loss after 20 weeks’ gestation.
- NND, defined as the death of the newborn up to 28 days of life
- Need for surgery/shunting at birth, defined as the need for brain surgery or ventriculo-peritoneal shunting after birth due to hydrocephalus
- Cerebral palsy, defined according to the European Cerebral Palsy Network and classified as diplegia, hemiplegia, quadriplegia, dyskinetic, or mixed
- Mild neurodevelopmental delay, defined according to the specific psychometric tests used by each author to evaluate the included children
- Severe neurodevelopmental delay, defined according to the specific psychometric tests used by each author to evaluate the included children
- Intact survival, defined as survival free from neurological complications

All these outcomes were explored in the overall population of fetuses with ICH. Furthermore, we planned to perform sub-group analysis according to the location of the hemorrhage:

- Intra-axial hemorrhage, defined as an ICH within the brain itself and including supra-tentorial (intra-ventricular and intra-parenchymal) and infra-tentorial hemorrhage.
- Extra-axial hemorrhage, defined as an ICH that occurs within the skull but outside of the brain tissue, and including epidural, subdural and sub-arachnoid hemorrhage
- Complex ICH, defined as an ICH occurring simultaneously in different locations.

Finally, IVH was classified according to Papile et al.[18] into:

- Grade I: limited to subependymal matrix
- Grade II: defined as clots inside the lateral ventricle with no ventriculomegaly or ventriculomegaly less than 15mm at the lateral ventricular atrium
- Grade III: diagnosed when blood clots affected one or both lateral ventricles together with ventriculomegaly exceeding 15mm at the lateral ventricular atrium
- Grade IV: including Grades I–III hemorrhages with hemorrhage in a large part of the periventricular parenchyma

We therefore performed a sub-group analysis among intraventricular (IVH) hemorrhages according to their severity, i.e. mild (IVH I and II) and severe (IVH III and IV).

Study selection, data collection and quality assessment

Only studies reporting the outcomes in fetuses with a prenatal diagnosis of ICH were considered eligible for inclusion. Cases associated with other major structural anomalies on ultrasound were not included, because as coexisting anomalies are likely to impact the short and long-term outcomes of these fetuses. We also excluded ICH cases in monochorionic diamniotic twin pregnancies as the outcome of these pregnancies is likely to reflect the complications of monochorionic diamniotic pregnancies rather than ICH itself. Pediatric and surgical series reporting only symptomatic cases or those undergoing exclusively surgery were also excluded, because such cases are likely not to reflect the natural history of the disease. We excluded studies with less than three cases. Studies published before 2000 were excluded, as we considered that advances in prenatal imaging techniques, improvements in the diagnosis and definition of brain anomalies make these less relevant. Finally, studies not providing a clear classification of the anomaly were not considered suitable for the inclusion in the current review.

Three authors (FGS, JZ and SI) independently reviewed each potentially relevant record based on the title and abstract. Agreement regarding potential relevance was reached by consensus. Full texts were retrieved for each potentially relevant citation. The same authors independently reviewed the full text of each selected study to assess eligibility for inclusion

and, using a standardised extraction form, independently extracted relevant data regarding study characteristics and pregnancy outcomes. Discrepancies between the authors were resolved by discussion with a fourth author (AK).

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 case-control or 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 outcome of interest. 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 the 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, its length and the 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.[19]

Case series were evaluated with a modified version of NOS, which is based on 8 questions in the domains of selection, ascertainment, causality and reporting (Supplementary Table 2). Although a formal score could be assigned giving a binary response to each question, the numeric representation of methodological quality was not considered appropriate as recommended, the overall final judgment was made based on questions 1, 2, 3, 7 and 8, which were deemed most critical in this specific clinical scenario.[20]

Statistical analysis

We used meta-analyses of proportions to combine data and reported pooled proportions and their 95% confidence intervals (CI). 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 that no heterogeneity was observed, whereas values >50% are associated with substantial heterogeneity. Due to the clinical heterogeneity among studies, a random effects model was used for all meta-

analyses.[21] Egger's test was used to assess potential publication bias and funnel plots were created for visual inspection.[22] Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than 10, as the tests lack power to detect real asymmetry in this scenario.[23] The analysis was performed using Statsdirect 3.0.171 (Stats Direct Ltd) and Revman 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) statistical software.

RESULTS

General characteristics of the study

A total of 723 articles were identified, 36 were assessed with respect to their eligibility for inclusion (Supplementary Table 3), and 16 studies (Table 1) were included in the systematic review (Table 1; Figure 3). These 16 studies[6-9,24-35] included 193 fetuses with ICH. No randomized controlled trials were available for inclusion; data for this review were only derived from observational cohort studies or case-series.

Detailed information on ultrasound appearance of ICH were reported only by 8 studies (87 fetuses).[6,8,24-26,28,30-31] ICH presented as ventriculomegaly in 41% (36/87) of cases, hyperechogenic appearance of the lateral ventricles or within the brain parenchyma in 23% (21/87) and 8% (7/87) of cases, respectively.

The results of the quality assessment of the included studies using NOS or its modified version are presented in Table 2. The cohort studies showed an overall good score regarding the selection and comparability of the study groups, and for ascertainment of the outcome of interest; the case series were judged to be mainly of low quality. The main weaknesses of these studies were their retrospective design, small sample size, heterogeneity of outcomes observed, times of postnatal follow-up and prenatal management.

Synthesis of the results

All fetuses with ICH

Fifteen studies (187 fetuses)[6-9, 24-26, 28-35] reported the incidence of mortality in fetuses with a prenatal diagnosis of ICH. Overall, PND occurred in 14.6% (95% CI 7.3-24.0), while the corresponding figures for IUD and NND were 10% (95% CI 6.2-14.6) and 7.2% (95% CI 4-11.2), respectively. Parents opted for pregnancy termination in 18.9% (95% CI 7.0-35) of the cases.

Complete information on postnatal outcome was reported in 13 studies (160 fetuses).[6, 8-9, 24-26, 30, 32-35] and were computed upon the number of liveborn new-born. Postnatal shunt placement was required in 27.6% (95% CI 12.5-45.9) of children.

Of the total of 94 fetuses (12 studies), 32% exhibited CP at the age of two. When classifying infant follow up, 16.7% of children were reported to have mild NDD and a further 31.1% (109

fetuses, 14 studies) as having severe adverse neurodevelopmental outcome (Table 3). CP was attributed as severe NDD in most cases.

Subgroup analysis according to the location of ICH and severity

Data reporting on primary and secondary outcomes according to the location of ICH are presented in Table 4. PND occurred in 13.3% (95% CI 5.7-23.4) of fetuses with intra-axial hemorrhage. When stratifying the analysis according to the location of the hemorrhage, PND occurred in 10.3% (95% CI 4.4-18.4) of fetuses with intra-ventricular, 13.8% (95% CI 0.9-32.9) with intra-parenchymal and 21.3% (95% CI 6.4-41.9) with complex hemorrhage.

Regarding the postnatal outcome, 24.7% (95% CI 11-41.2) of fetuses with intra-axial hemorrhage required shunt placement after birth and 27.1% (95% CI 17.1-38.4) experienced cerebral palsy. Mild and severe neurodevelopmental delay were observed in 15% (95% CI 6.9-25.6) and 32.3% (95% CI 19.7-46.3) of cases, respectively, while 51.9% (95% CI 36-67.4) experienced a normal neurodevelopmental outcome. When stratifying the analysis according to the site of the intra-axial hemorrhage, shunt placement after birth was required in 33.7% (95% CI 14.6-56.2) of children with a prenatal diagnosis of intra-ventricular and in 50.3% (95% CI 13.1-87.3) of those with intra-parenchymal hemorrhage (Table 5), while the corresponding figures for cerebral palsy was 23.8% (95% CI 11.3-39.1) and 70.8% (95% CI 30.2-97.7), respectively. Severe neurodevelopmental delay was reported in 30.5% (95% CI 14.6-49.3) of children with a prenatal diagnosis of intra-ventricular and in 100% (95% CI 51.3-100) of those with intra-parenchymal hemorrhage, while the corresponding figures for normal neurodevelopmental outcome were 53.7% (95% CI 40.8-66.3) and 0% (95% CI 0-48.7), respectively.

Although limited by the small number of included fetuses, subgroup analysis for mortality and postnatal outcomes according to the severity of intra-ventricular hemorrhage are reported in Supplementary Table 4 and Figure 4. PND occurred in 13.3% (95% CI 0.9-36.6) of fetuses with mild IVH (n=11) and 8.8% (95% CI 1.6-21.1) of fetuses with severe IVH (n=32); looking at the postnatal outcome, 21.9% (95% CI 16.5-55.9) and 27.5% (95%CI 5.3-58.7) fetuses with mild (n=6) or severe (n=29) IVH needed a shunt or surgery at birth, respectively. A normal outcome was recorded for 100% (95%CI 62.3-100) of fetuses with mild IVH compared to 42.7% (95%CI 25.2-61.3) of fetuses with severe IVH.

Finally, only four studies (8 fetuses) [6-7, 24-25] reported the outcome for extra-axial hemorrhage. PND occurred in 26,7% (95% CI 5.3-56.8); one child underwent shunt placement and all those who survived had a normal postnatal outcome.

DISCUSSION

Main findings

The findings from this systematic review showed that fetuses with a prenatal diagnosis of ICH are at high risk of perinatal mortality and adverse longer term neurodevelopmental outcome. PND occurred in 14.6% of these fetuses and in 18.9% of cases parents opted for TOP. Among those born alive, 27.6% required shunt placement after birth and 32.0% had cerebral palsy. Importantly, normal postnatal outcome was reported in half of all included cases. Subgroup analysis according to the location of the hemorrhage was limited by the relatively small number of included cases, but suggested that shunt placement after birth was required in similar numbers of children with intra-ventricular and intra-axial hemorrhage. In contrast, cerebral palsy and severe neurodevelopmental delay were much lower in children with a prenatal diagnosis of intra-ventricular rather than intra-parenchymal hemorrhage, with normal neurodevelopmental outcome in 54% and 0%, respectively. Robust evidence on the incidence of mortality and postnatal outcome in fetuses with extra-axial hemorrhage could not be extrapolated due to the small number of cases.

Interpretation of the findings

Clinical outcomes after ICH vary according to several factors such as gestational age (which affects the maturity of the brain), location and extent of the lesion, presence of concurrent disorders and the underlying etiology. Intra-axial hemorrhages were more commonly reported compared to extra-axial; among the former, the IVH were the most frequently reported ICH. In fact, the most common sonographic abnormality found in the fetal ICH setting is ventricular enlargement, a non-specific sign. Other possible ultrasound features include increased periventricular white matter echogenicity, hyperechoic clots, avascular intracranial masses, porencephaly and hydranencephaly. IVH most commonly arises from capillaries in the subependymal germinal matrix which usually starts to involute at 20-26 weeks and is generally absent at term; these capillaries are quite immature vessels and poorly supported by connective tissue and this might explain why IVH are the most common hemorrhage diagnosed in utero and in the preterm infants. [1, 36]

The clinical outcomes of these hemorrhages are mainly dependent on the severity of bleeding, presence of concurrent white matter injury, post-hemorrhagic ventriculomegaly and parenchymal infarctions. In fact, when stratifying according to the severity of IVH, we found normal postnatal outcome recorded in less than half of infants with severe fetal IVH,

compared to all those with mild IVH. Similarly, in preterm infants with severe IVH, i.e. accompanied by severe ventriculomegaly (III) and/or white matter injury (grade IV), there was a strong association with cerebral palsy, impaired mental and motor development and visual dysfunction.[37]

Intraparenchymal hemorrhages have different outcomes according to the site of the lesion, such as corticospinal tract versus central gray matter, their extension and severity, such as isolated and unilateral compared to multiple or bilateral lesions. Despite their importance, they were less frequently reported compared to IVH.

The underlying etiology may also play a role in influencing the outcome. However, in our systematic review, no subgroup analysis according to etiology could be performed because no specific etiologic factor could be identified in 58.9% of the fetuses. Among fetuses with ICH due to unknown etiologies and reporting on morbidity outcomes (n=99), 67.7% were born alive and of these 31.3% had neurodevelopmental delay and 23.9% needed a shunt at birth. The most commonly recognized etiology in our review was FNAIT (22.3%, n=45/202) due to the large number of fetuses (n=43/202) available for the analysis from the international FNAIT registry,[35] followed by infective causes (4.5%, n=9/202).

In our review, no genetic causes were found as causative for ICH although they are increasingly reported as etiologic factors of ICH in neonates.[1] In particular, mutations in COL4A1 and COL4A2 have been linked to neonatal ICH due to the role of these collagens chains in maintaining vascular tone and endothelial integrity. The possible role of these mutations was also reported prenatally in a case report by Lichtenbelt et al.,[38] but when systematically assessed in four fetuses with fetal IVH by Kutuk et al., no mutations in these genes were found.[39] Recently, Itai et al.[40] reported on COL4A1/2 mutations in 218 individuals and only in 14 cases ultrasound/MRI findings were suggestive of features commonly associated with COL4A1/2 variants, i.e. destructive lesions or cerebral haemorrhage.

With increasing understanding and access to genomic medicine as well as rapidly decreasing costs there is great scope to investigate the etiology of ICH in the next decade. Especially, rather than looking at individual mutations, whole genome or whole-exome sequencing (WES) may become more accessible than before. In fact, Hausman-Kedem et al.[41] performed WES in 26 cases of perinatal ICH and found a likely causative variant in 4 subjects, thus supporting the WES use in this context.

Strengths and limitations

This is the first systematic review exploring the outcomes after a prenatal diagnosis of ICH. The detailed and systematic literature search and multitude of outcomes explored represent the main strengths of our work. Nevertheless, the relatively small number of constituent studies, their retrospective non-randomized design, and differences among the included populations in gestational age at diagnosis, outcome definition, prenatal management, and time at follow-up of fetuses with ICH represent limitations.

Differences in post-natal assessment and time of follow-up of these children will affect any attempt of pooling data in systematic reviews, and this holds true for any condition that may affect neuro-development. Very early assessment may not accurately predict neurodevelopmental outcomes; in contrast late evaluation will be influenced by socioeconomic, parenting, environmental, and educational factors, which may significantly impact developmental measures explored. Nevertheless, methods for correcting for such postnatal exposures exist. It should also be noted that few of the included studies specifically reported the type of neurodevelopmental assessment adopted, and we call upon researchers to ensure such longer-term follow up is conducted, using standardized tools. Nevertheless, our work represents the most up-to date assessment of the totality of the evidence for this important condition.

Implications for clinical practice and research

Prenatal diagnosis of ICH has been increasing over the last years thanks to the improvement in prenatal imaging and the more frequent use of fetal MRI in cases of suspected CNS lesions on prenatal ultrasound.[5-9] Despite so, many cases of ICH remain undiagnosed: in fact, in many countries no universal third trimester scan is offered to women without risk factors.[42] Even when it is performed, fetal ICH may still occur after the scan and therefore not being diagnosed. However, its recognition still represents an important clinical challenge both for diagnostic work-up and counselling. Apart from imaging, identifying the underlying etiology of the condition is a priority, and should include detailed maternal history, evaluation of possible trauma, a complete record of maternal drug use (both illicit and prescribed), evaluation of possible vertical transmission of maternal infections and recognition of feto-neonatal alloimmune thrombocytopenia. This is important for management of the index pregnancy but also has implications for recurrence in future pregnancies.

The evaluation of the severity of the condition, through the use of fetal MRI when feasible, is also important for the possible implications for pregnancy management, especially in those countries where the termination of pregnancy is allowed beyond 24 weeks. Our review showed a high prevalence of cerebral palsy and/or neurodevelopmental delay at follow-up and these figures, although derived from a small number of fetuses, might help in counselling the couple. On the other hand, in countries where termination of pregnancy cannot be offered beyond 24 weeks, the management of complex and severe cases becomes difficult. In fact, diagnosis of fetal ICH is more common in the third trimester,[9,24] and it often occurs in patients with a previous apparently normal routine anomaly scan at 20 weeks. In these cases, the estimation of severity and consequently the long-term outcomes might influence the types of care offered at birth. Moreover, the recommended mode of delivery may differ according to the severity of ICH in these fetuses: a caesarean section is often offered to avoid additional bleeding due to the head compression during vaginal delivery.[4]

As shown in supplementary Table 3, several cases series were published over the last 20 years on fetal ICH: however, many of them were excluded because they reported data on less than three cases, and therefore, providing anecdotal rather that generalizable information. Moreover, although we chose to evaluate outcomes on the prognosis of these fetuses such as mortality, cerebral palsy or neurodevelopmental delay, many studies were excluded as the outcomes of interest were not reported. This highlights the need of developing a Core Outcome Set (COS) within women's health as recommended by "The CoRe Outcomes in Women's and Newborn health (CROWN) initiative" (www.crown-initiative.org) in order to harmonize outcome reporting in women's health research, reduce waste in research by selecting those outcomes that are more relevant and applicable in most research settings and promote the routine collection of such data. Moreover, the standardization in reporting of outcomes would increase generalizability and meaningful pooled analysis. Moreover, as the prenatal diagnosis of fetal ICH is rare, multicentre registries would be useful in collecting data on large number of cases including the potential for detailed genomic analysis.

Conclusions

Fetuses and children with ICH in the prenatal period have increased risk of perinatal mortality and morbidity. PND occurred in 14.6% of fetuses with ICH, 27.6% of surviving fetuses required shunt and 32% developed cerebral palsy. This meta-analysis reports on the

key mortality and morbidity outcomes, according to the location (intra or extra-axial) and severity of bleeding. Due to the rarity of the condition, multicentre prospective registries should be promoted to collect high-quality data.

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FIGURE LEGENDS

Figure 1. Fetal unilateral intraventricular hemorrhage diagnosed at 22 weeks' gestation as depicted on 2 D ultrasound (1a), multiplannar 3D neurosonography (1b) and MRI (1c)

Figure 2. Schematic diagram of different types of hemorrhage.

Figure 3. PRISMA flow-chart of the included studies.

Figure 4. Flow-chart illustrating outcomes for mild and severe intraventricular hemorrhage.

Table 1 – List of the included studies

First Author (publication year)	Country	Type of study	Study period	Cases affected by fetal intracranial hemorrhage (n)	Locations/Type of hemorrhage (n)	Etiologies (n)	Outcomes observed	Length of follow-up
Abdelkadar (2016)[24]	Egypt	Prospective case series	2011-2015	20	Subdural (2), IVH (16), Complex (3)	Unknown (17); Preeclampsia (1); oral anticoagulant therapy (1); Previous affected fetus (1)	Mortality, Morbidity	No follow-up
Adiego (2019)[9]	Spain	Retrospective case series	2005-2016	14	IVH II (2), IVH III (3), IVH IV (7), Complex (2)	Unknown (14)	Mortality, Morbidity	28 months (range 3–96)
Elchalal (2005)[6]	Israel	Retrospective case series	June 1996 - May 2004	29	Subdural (2), IVH II (5), IVH III (3),Intraparenchymal (6), Subependymal hemorrhage (3), Other (5),	Unknown (27), IUGR (1), Rhesus alloimmunization (1)	Mortality, Morbidity	30 – 48 months

					Cerebellar (1), Complex (4)			
Folkerth (2001)[25]	USA	Retrospective case series	NS	3	Subdural (3)	Unknown (3)	Mortality, Morbidity	24 months
Ghi (2003)[7]	Italy	Retrospective case series	1981-2003	14	IVH II (4), IVH III (4), IVH IV (3), Infratentorial (2), Subdural (1)	Unknown (8), Maternal trauma (2), FNAIT (1), Rh alloimmunization (2), hydrops (1)	Mortality, Morbidity	11.6 months (range 1-48)
Huang (2006) [26]	Taiwan	Retrospective case series	2 years period (NS)	3	IVH III (1), Intraparenchymal (1), Choroidal (1)	Preeclampsia (2), Unknown (Choroidal hemorrhage) (1)	Mortality, Morbidity	20 months
Kutuk (2014)[8]	Turkey	Retrospective case series	2009-2012	6	IVH IV (1), Intraparenchymal (3), Complex (2)	Unknown (4), IUGR (2)	Mortality, Morbidity	9.4 months (range 6–15)
Luciano (2007) [27]	Italy	Prospective cohort study	2000-2003	6	IVH III (2); IVH IV (4)	Unknown (4), FNAIT (1), Maternal hypotension (1)	Morbidity	24 months
Maisonneuve (2019) [28]	France	Retrospective cohort study	2005-2016	4	Cerebellar (4)	Parvovirus B19 (4)	Mortality, Morbidity	Range 3-30 months
Manganaro (2012) [29]	Italy	Retrospective Case series	2006-2010	14	IVH (7), Intraparenchymal (1), Cerebellar	CMV (1), Unknown (13)	Mortality, Morbidity	NS (Imaging follow-up)

					(1), Complex (3), Extra-axial haematoma associated with dural sinus malformation (2)			
Martino (2015) [30]	Italy	Retrospective case series	2001-2014	17	Cerebellar (17)	CMV (1), Parvovirus B19 (1), Unknown (15)	Mortality, Morbidity	53 months (range 24–104)
Morioka (2006) [31]	Japan	Retrospective case series	1997-2004	5	IVH III (1), IVH IV (4)	Unknown (5)	Mortality, Morbidity	Range 9 months – 8 years
Ozduman (2003) [32]	USA	Retrospective case series	2003	4	IVH (1), Subependymal hemorrhage (1), Complex (2)	Unknwon (4),	Mortality, Morbidity	9 months
Strigini (2001)[33]	Italy	Retrospective case series	1996-1999	5	Subependymal hemorrhage (1) Hemorrhagic cyst (1), IVH (1), Complex (2)	Maternal Trauma (5)	Mortality, Morbidity	Range 6 months - 1 year
Tavil (2016) [34]	Turkey	Retrospective case series	Jan 1994-Jan	6	IVH III (1), IVH IV (4), Intraparenchymal	Unknown (6)	Mortality, Morbidity	42.8 ± 39.4 months (0.25–108 months)

			2014		(1)			
Tiller (2013) [35]	Norway	Observational cohort study	2001-2010	43	ICH (43)	FNAIT (43)	Mortality, Morbidity	Till discharge

CMV: Cytomegalovirus; FNAIT: Fetal-Neonatal Auto Immune Thrombocytopenia; IVH: Intra-ventricular Hemorrhage; ICH: Intracranial Hemorrhage, IUGR: Intra-uterine growth restriction,

Table 2 - Quality assessment of the included studies according to Newcastle–Ottawa Scale (NOS)*or to modified Newcastle-Ottawa, Pierson and Bradford Hill scales for case series**.

Author	Year	Selection	Comparability	Outcome
Abdelkadar[24]**	2016	Moderate quality		
Adiego[9]**	2017	High quality		
Elchalal[6]**	2005	High quality		
Folkerth[25]**	2001	Low quality		
Ghi[7]**	2003	Moderate quality		
Huang[26]**	2006	Low quality		
Kutuk[8]**	2014	Low quality		
Luciano[27]*	2007	★★★	★	★★
Maisonneuve[28]*	2018	★★★	★	★★
Manganaro[29]**	2012	Moderate quality		
Martino[30]**	2016	High quality		
Morioka[31]**	2006	Low quality		
Ozduman[32]**	2003	Low quality		
Strigini[33]**	2001	Low quality		
Tavil[34]**	2016	Moderate quality		
Tiller[35]*	2013	★★★	★	★★★

* Cohort/Case-control studies assessed according to Newcastle-Ottawa Scale (NOS) (assessment based on selection/comparability/exposure-outcome. Highest scores are 4 for selection, 2 for comparability and 3 for exposure-outcome).[19]

**Case series/reports assessed with a tool that published at BMJ Evidence-Based-Medicine Journal on April 2018 (Supplementary Table 2). Authors specifically mention about not to use an aggregate score for this tool on the other hand making overall judgment like we do (low or high quality) is much more appropriate.[20]

Table 3: Pooled proportions of the different outcomes reported in the present systematic review in fetuses affected by Intracranial hemorrhage.

Outcome	Studies	Fetuses	Pooled proportions	I^2 (%)
Mortality				
Perinatal death	15	31/187	14.63 4 (7.3-24.0)	58.4
Intrauterine death	15	16/187	9.98 (6.2-14.6)	0
Neonatal death	15	15/187	7.16 (4.0-11.2)	47.1
Termination of pregnancy	15	42/187	18.91 (7.0-35.0)	83.1
Postnatal outcome				
Need for surgery or shunt	14	25/109	27.58 (12.5-45.9)	73.2
Cerebral palsy	12	29/94	31.97 (22.2-42.6)	13.97
Mild neurodevelopmental delay	14	22/109	16.72 (8.4-27.2)	42
Severe neurodevelopmental delay	14	35/109	31.09 (19.0-44.7)	52.3
Normal outcome	14	53/109	53.60 (38.6-68.2)	58.2

a: computed upon the number of alive new-born. Cases lost-to follow-up excluded

Table 4: Pooled proportions for mortality according to the location of Intracranial hemorrhage.

Outcome	Studies	Fetuses	Pooled proportions	I^2 (%)
Intra-axial hemorrhage				
Perinatal death	14	16/161	13.28 (5.7-23.4)	61
Termination of pregnancy	14	33/161	17.82 (6.0-34.1)	81.4
Intrauterine death	14	11/161	7.98 (4.4-12.5)	0
Neonatal death	14	5/161	7.66 (2.7-14.8)	47.4
Supratentorial hemorrhage				
Intraventricular hemorrhage				
Perinatal death	11	7/78	10.32 (4.4-18.4)	10.5
Termination of pregnancy	11	22/78	22.55 (8.4-40.9)	65.9
Intrauterine death	11	2/78	5.23 (1.5-11.0)	0
Neonatal death	11	5/78	7.36 (2.0-15.8)	28.2
Grade I-II				
Perinatal death	3	1/11	13.27 (0.9-36.6)	0
Termination of pregnancy	3	3/11	27.52 (4.5-60.4)	30.4
Intrauterine death	3	1/11	13.27 (0.9-36.6)	0
Neonatal death	3	0/11	0 (0-24.2)	0
Grade III-IV				
Perinatal death	7	2/32	8.83 (1.6-21.1)	8.6
Termination of pregnancy	7	10/32	29.05 (7.9-56.8)	61.7
Intrauterine death	7	1/32	6.78 (1.0-17.2)	0
Neonatal death	7	1/32	5.69 (0.7-15.5)	0
Intraparenchymal hemorrhage				
Perinatal death	5	1/12	13.75 (0.9.-32.9)	18
Termination of pregnancy	5	7/12	53.07 (23.4-81.6)	23.8
Intrauterine death	5	1/12	13.75 (09.-32.9)	18

Neonatal death	5	0/12	0 (0-25.5)	0
Complex hemorrhage				
Perinatal death	6	3/16	21.29 (6.4-41.9)	0
Termination of pregnancy	6	4/16	26.20 (9.5-47.8)	0
Intrauterine death	6	3/16	21.29 (6.4-41.9)	0
Neonatal death	6	0/16	0 (0-22.8)	0
Infra-tentorial hemorrhage				
Perinatal death	5	2/24	12.35 (2.8-27.3)	0
Termination of pregnancy	5	4/24	22.12 (5.3-46.1)	22.5
Intrauterine death	5	2/24	12.35 (2.8-27.3)	0
Neonatal death	5	0/24	0 (0-13.6)	0
Extra-axial hemorrhage				
Perinatal death	4	2/8	26.72 (5.3-56.8)	0
Termination of pregnancy	4	3/8	36.90 (11.3-67.4)	0
Intrauterine death	4	2/8	26.72 (5.3-56.8)	0
Neonatal death	4	0/8	0 (0-33.2)	0

Table 5: Pooled proportions for postnatal outcomes according to the location of Intracranial hemorrhage.

Outcome	Studies	Fetuses	Pooled proportions	I^2 (%)
Intra-axial hemorrhage				
Need for surgery or shunt	14	20/98	24.68 (11.0-41.2)	67.4
Cerebral palsy	13	25/93	27.09 (17.1-38.4)	24.8
Mild neurodevelopmental delay	14	19/98	15.02 (6.9-25.6)	39.2
Severe neurodevelopmental delay	14	33/98	32.29 (19.7-46.3)	48.1
Normal outcome	14	45/98	51.85 (36.0-67.4)	57.7
Supratentorial hemorrhage				
Intraventricular hemorrhage				
Need for surgery or shunt	11	17/52	33.74 (14.6-56.2)	63.4
Cerebral palsy	11	12/52	23.77 (11.3-39.1)	33.3
Mild neurodevelopmental delay	11	4/52	10.63 84.1-19.8)	0
Severe neurodevelopmental delay	11	16/52	30.52 (14.6-49.3)	49.2
Normal outcome	11	28/52	53.66 (40.8-66.3)	0
Grade I-II				
Need for surgery or shunt	3	1/6	21.86 (16.5-55.9)	0
Cerebral palsy	3	0/6	0 (0-37.7)	0
Mild neurodevelopmental delay	3	0/6	0 (0-37.7)	0
Severe neurodevelopmental delay	3	0/6	0 (0-37.7)	0
Normal outcome	3	6/6	100 (62.3-100)	0
Grade III-IV				
Need for surgery or shunt	8	7/28	27.53 (5.3-58.7)	67.6
Cerebral palsy	6	7/19	32.22 (11.5-57.6)	27.2
Mild neurodevelopmental delay	7	2/24	12.67 (3.1-27.4)	0
Severe neurodevelopmental delay	7	11/24	45.76 (26.8-65.4)	9
Normal outcome	7	20/24	42.73 (25.2-61.3)	0
Intraparenchymal hemorrhage				
Need for surgery or shunt	3	2/4	50.29 (13.1-87.3)	51.6

Cerebral palsy	3	3/4	70.77 (30.2-97.7)	0
Mild neurodevelopmental delay	3	0/4	0 (0-48.7)	0
Severe neurodevelopmental delay	3	4/4	100 (51.3-100)	0
Normal outcome	3	0/4	0 (0-48.7)	0
Complex hemorrhage				
Need for surgery or shunt	3	2/6	39.31 (2.6-86.5)	49.2
Cerebral palsy	3	4/6	68.75 (29.2-96.6)	20.1
Mild neurodevelopmental delay	3	2/6	36.22 (8.1-71.1)	0
Severe neurodevelopmental delay	3	1/6	19.91 (1.1-53.5)	0
Normal outcome	3	3/6	48.75 (8.3-90.3)	41.8
Infra-tentorial hemorrhage				
Need for surgery or shunt	4	0/16	0 (0-18.2)	0
Cerebral palsy	4	2/16	16.47 (3.5-36.5)	0
Mild neurodevelopmental delay	4	2/16	16.47 (3.5-36.5)	0
Severe neurodevelopmental delay	4	3/16	22.42 (4.4-48.9)	17.5
Normal outcome	4	11/16	68.88 (39.0-91.9)	25.4
Extra-axial hemorrhage				
Need for surgery or shunt	3	1/3	37.06 (2.0-84.6)	18.9
Cerebral palsy	3	0/3	0 (0-56.9)	0
Mild neurodevelopmental delay	3	0/3	0 (0-56.9)	0
Severe neurodevelopmental delay	3	0/3	0 (0-56.9)	0
Normal outcome	3	3/3	100 (43.1-100)	0

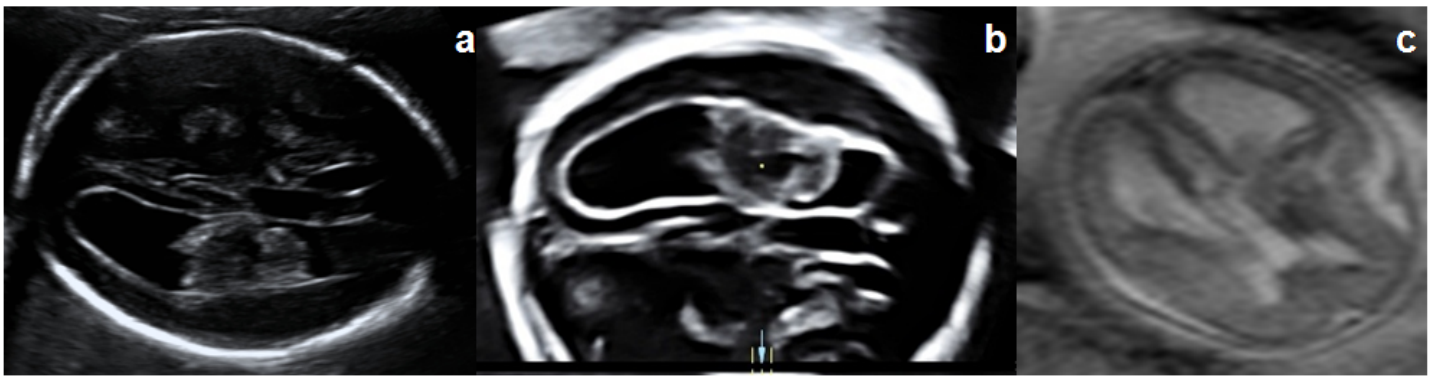

Figure 1

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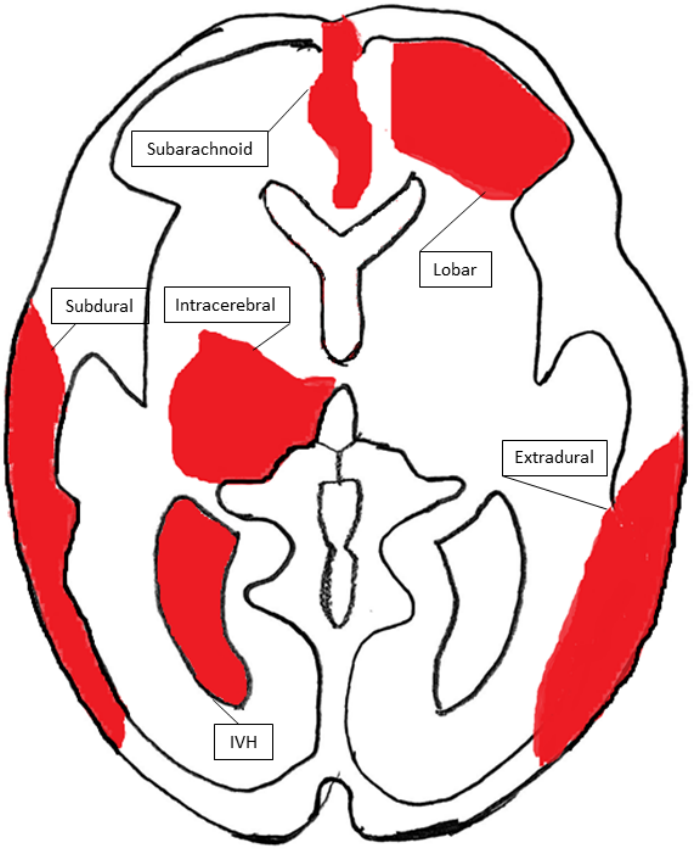

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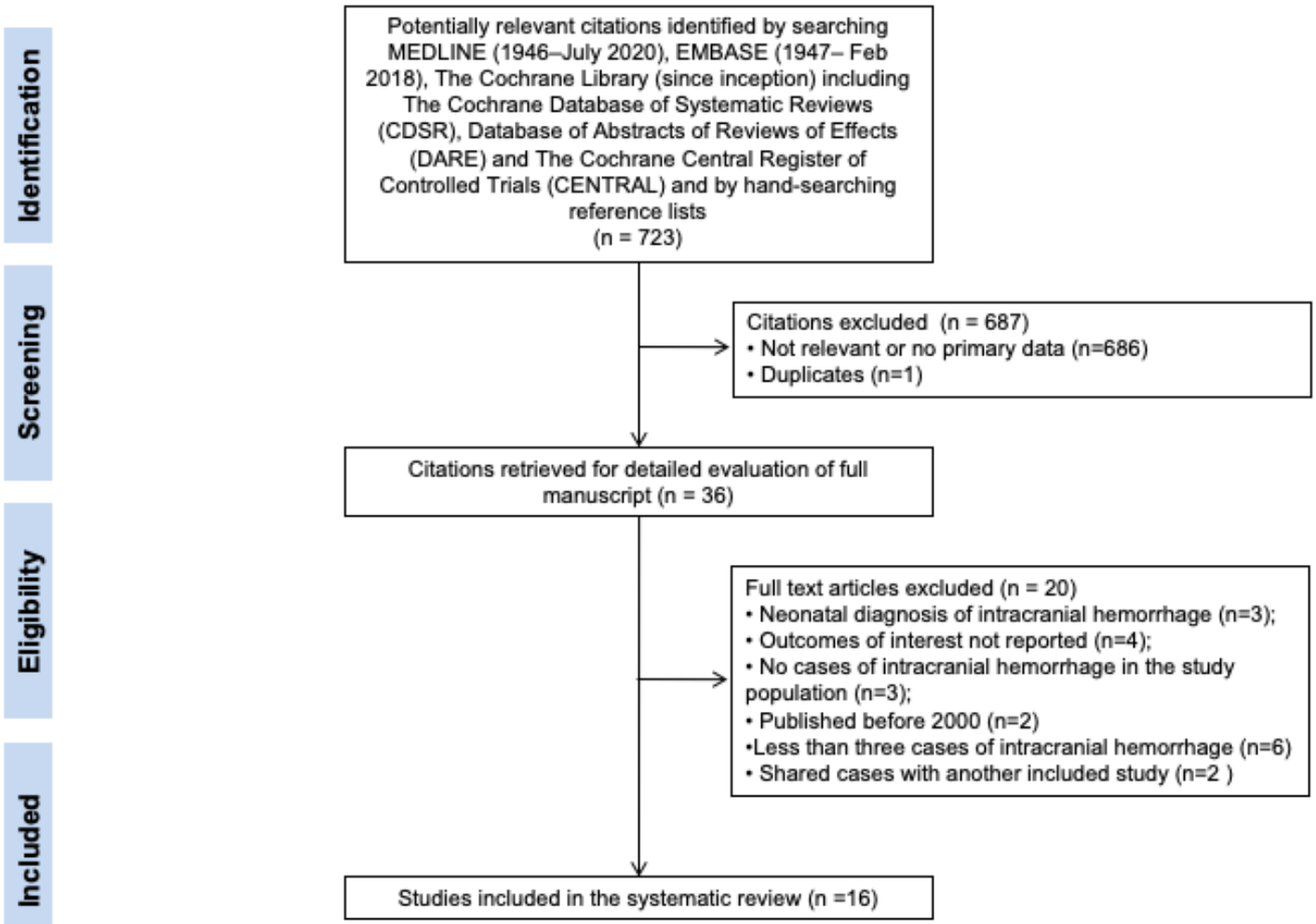

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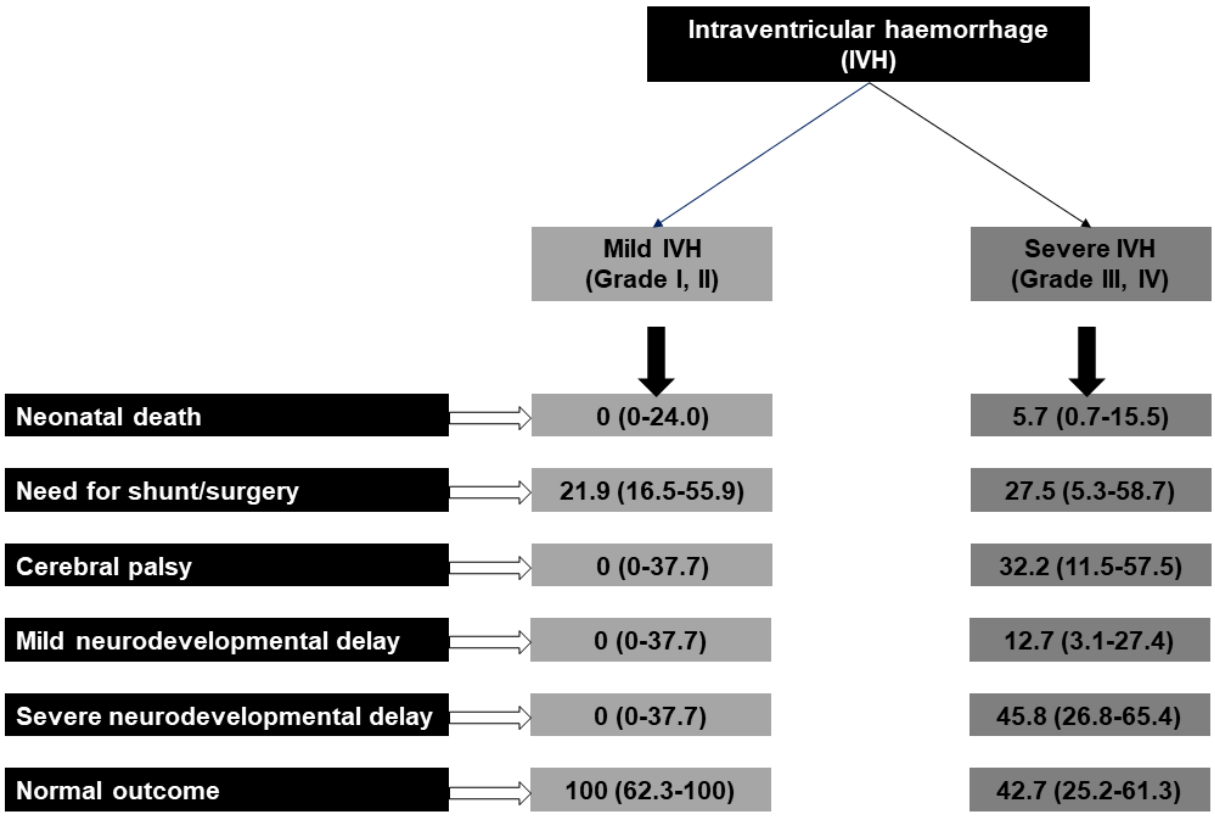

Figure 3

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