Introduction

The placenta is the organ that links mother and fetus during pregnancy. It plays a crucial role in fetal growth and development by enabling the exchange of nutrients and oxygen from the mother to the fetus and removing fetal waste products.[1] The placenta is an endocrine organ, a site of synthesis and selective transport of hormones and neurotransmitters. In addition, the placenta forms a barrier to toxins and infective organisms.[2,3] In recent years, findings based on placental lesions have contributed to a better understanding of how the placenta functions. Less than optimal placental performance may result in morbidity or even mortality of both mother and fetus. Indeed, there are indications that placental lesions are the main cause of fetal death.[4] It is also becoming increasingly clear that impaired placental functioning can have major implications for the live-born infant. Awareness among pediatricians, however, of the benefit of placental findings for neonatal care, is limited. Usually, the results of placental examinations are only reported back to the obstetrician instead of also passing it on to the pediatrician. In our opinion, this is a missed opportunity. Information on placental lesions can often be helpful towards explaining an abnormal neonatal outcome and might have consequences for treatment.

This article provides a systematic review of the relation between placental lesions and neonatal mortality, morbidity, and neurological development. We summarized the literature published in English from January 1995 to October 2013. We refined our search results by selecting the appropriate articles from the ones found during the initial searches. The first selection was based on the title, the second on the abstract, and the third on the full article. The quality of the selected articles was determined by using the Newcastle-Ottawa Quality Assessment Scale.

Study appraisal and synthesis methods: We systematically searched the Pubmed database for literature on the relation between placental lesions and fetal and neonatal mortality, neonatal morbidity and neurological outcome. We conducted three separate searches starting with a search for placental pathology and fetal and neonatal mortality, followed by placental pathology and neonatal morbidity, and finally placental pathology and neurological development. We limited our search to full-text articles published in English from January 1995 to October 2013. We refined our search results by selecting the appropriate articles from the ones found during the initial searches. The quality of the selected articles was determined by using the Newcastle-Ottawa Quality Assessment Scale.

Conclusions: The placenta plays a key role in fetal and neonatal mortality, morbidity, and outcome. Pediatricians should make an effort to obtain the results of placental examinations.
and morbidity. Should this prove to be the case, this information is important for the pediatrician who should, therefore, be aware of and take into consideration the placental findings of their patients.

Methods

Literature search

This systematic review was conducted following the PRISMA guidelines for systematic reviews. A registered systematic review protocol is not available. Two independent researchers (AMR and AFB) searched the PubMed database for literature on the relation between placental lesions and perinatal mortality, neonatal morbidity, and neurological development. We limited our search to full-text articles published in English from January 1st 1995 to October 31st 2013. We conducted three separate searches starting with a search for placental lesions and fetal and neonatal mortality, followed by placental lesions and neonatal morbidity, and finally placental lesions and neurological development.

For the search on placental lesions and fetal and neonatal mortality, we used the terms ("placental pathology" AND "fetal death") OR ("placental pathology" AND "stillbirth") OR ("placental" AND "cause" AND "stillbirth") OR ("placental pathology" AND "mortality") .

For the search on placental lesions and neonatal morbidity, we used the terms ("placental pathology" AND "morbidity") OR ("placental pathology" AND "neonatal outcome") OR ("placental lesions" AND "morbidity") OR ("placental lesions" AND "neonatal outcome") OR ("placenta" AND "neonatal implications") OR ("placental" AND "lesions" AND "risk factor").

For the search on placental lesions and neurological development, we used the terms ("placental pathology" AND "neurological") OR ("placental pathology" AND "neurologic") OR ("placental pathology" AND "cerebral palsy") OR ("placental" AND "neurodevelopmental outcome") OR ("placental pathology" AND "follow up").

Subsequently, we refined our search results by selecting the appropriate articles from the ones found during the initial searches in three stages. The first selection was based on the title, the second on the abstract, and the third on the full-text article. Review articles on the subject of placental lesions and outcome were indicated as background articles. We did not use these articles in the tables, but we did use them in the text of our article. We were mainly interested in single births, therefore articles focusing primary on multiple births were excluded. In addition to the database search, we screened the reference lists of the selected articles, and the publications of important research groups in the field.

Quality assessment

We assessed the quality of all the selected studies by means of the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies. This assessment scale consists of three parts. For cohort studies these parts include selection, comparability, and outcome, for case-control studies selection, comparability, and exposure. The selection part consists of 4 items, with a maximum of 1 point per item. The comparability part has 1 item, with a maximum of 2 points for this item. Both the outcome and exposure parts consist of 3 items, with a maximum of 1 point per item. This provides a score, ranging from 0–9 points, with 9 points for the highest quality.

Results

Our first search for placental lesions and perinatal mortality resulted in 135 articles. The second search for placental lesions and neonatal morbidity resulted in 55 articles. Our third search for placental lesions and neurological outcome produced 67 articles. After removing duplicates, we had a total of 221 articles. We excluded 117 articles based on their titles. Reasons for exclusion were studies with patient populations from developing countries or studies focusing on multiple births. Abstracts or full-text articles were assessed of the remaining 104 articles. Sixty-three articles were additionally excluded for the following reasons: no placental pathology performed, no neonatal outcome, and the studies being out of scope. By analyzing the reference lists of the remaining 41 articles, and screening publications from important research groups in the field, we additionally included 14 articles. Finally, 55 studies were included in our systematic review (Figure 1), i.e. 18 studies on perinatal death [4–21], 19 on neonatal morbidity [22–40], and 18 on neurological outcome.[41–58] Characteristics and the quality assessment scores of these 55 articles are presented in Tables 1–3.

Placental pathology

Examination of the placenta can reveal a wide range of pathologies. For good reproducibility it is necessary that placental lesions are well defined. Committees of the perinatal section of the Society for Pediatric Pathology have proposed definitions for maternal vascular underperfusion, fetal vascular obstructive lesions (fetal thrombotic vasculopathy), and the amniotic infection syndrome.[59–61] Definitions and descriptions of additional pathologies can be found in various textbooks on the pathology of the placenta.[62–67]

Since we acknowledge the fact that most pediatricians are unfamiliar with placental lesions and because a wide variety of terminology is used in the literature, we classified placental lesions according to the underlying pathology as previously proposed together with their pathological descriptions in Table 4.[35,42,59–61,68–71] Placental lesions and perinatal mortality

Perinatal mortality is defined as death during the perinatal period. In the 10th Edition of the World Health Organization's International Classification of Diseases, the perinatal period is defined as death from 22 completed weeks of gestation up to 7 days after birth.[72] Fetal deaths form the largest group of perinatal mortality. In high-income countries one in every 200 infants that reaches 22 weeks' gestation or more, is stillborn.[73] Recently, the important role of the placenta in fetal deaths has become increasingly clear and several studies suggested that placental pathology is one of the main causes of fetal death (Table 5). This underscores the importance of examining the placenta, a fact sorely underestimated by obstetricians and general pathologists.[16]

In 30% of the cases the cause of stillbirth is unknown.[73] In the remainder, i.e. the proportion of cases with known cause, most stillbirths are caused by placental lesions (12–63%, Table 5), followed by infections and umbilical cord abnormalities. [73] For lower gestational ages (GAs) (20 to 24 weeks), an unknown cause of death is most prominent, followed by placental lesions. At higher GAs, the relative importance of unknown causes decreases and placental causes increase.[73]

Placental pathology consistent with maternal vascular underperfusion is the main contributor to fetal death, ranging from 34 to 38 percent.[4,8,14] This is most prominent during the preterm
period, in pregnancies complicated by hypertensive disorders, with a strong decline thereafter. During the term period, fetal death is mainly caused by developmental pathology of placenta parenchyma.\[4\] We can conclude that a pathological examination of the placenta is essential for clarifying causes of stillbirths.\[5,13,14,19\]

The older classification systems for perinatal mortality did not address placental pathology, or specific placental lesions, as a separate group. Only in the more recent classification systems is placental pathology included as a cause of fetal death. In all recent stillbirth studies placental pathology is designated as one of the main causes of fetal death.\[74,75\] The introduction of classification systems with placental pathology included as a separate group might be one of the reasons why recent studies identify placental pathology as one of the main causes of fetal death. Most of the placental lesions found in stillbirths, however, are also seen regularly after live, preterm or term, births.\[76\] The question arises whether placental lesions are also related to neonatal and neurological morbidity.

To summarize, in recent years the role of the placenta in fetal deaths has become increasingly clear. Placental pathology is one of the main causes of fetal death, with placental pathology consistent with maternal vascular underperfusion as the main contributor.

Placental lesions and neonatal morbidity

It has been suggested that placental lesions are also associated with neonatal morbidity, but the association is less clear than for fetal mortality. Placental lesions are suggested to be associated with illness severity shortly after birth, and with a wide range of neonatal problems (Table 6).

Illness severity shortly after birth can be determined by the presence of asphyxia, Apgar scores during the first minutes after birth, and by several clinical variables during the first 24 hours after birth. Perinatal asphyxia is described to be associated with placental lesions affecting fetal vascular supply. These lesions were umbilical cord complications (disrupted velamentous vessels, cord tear, hypercoiled cord, cord hematoma), chorioamnionitis with fetal vasculitis, and fetal thrombotic vasculopathy.\[31,35\] Low Apgar scores at 1 and 5 minutes are associated with ascending intrauterine infection and maternal vascular underperfusion.\[22,26\] Higher illness severity during the first 24 hours after birth, determined by the Score of Neonatal Acute Physiology Perinatal Extension (SNAPPE), is associated with placental pathological findings of fetal thrombotic vasculopathy and elevated nucleated red blood cells (a sign of hypoxia).\[38\]
### Table 1. Description of selected studies perinatal mortality.

| Reference                  | Country     | Study design     | Study population                      | Study period | Sample size | Blinding examiner | Definition placental lesions | Corrected for confounders | Quality assessment Selection | Quality assessment Comparability | Quality assessment Outcome/ exposure | Quality assessment Total |
|----------------------------|-------------|------------------|---------------------------------------|--------------|-------------|-------------------|-----------------------------|----------------------------|-------------------------------|----------------------------------|-----------------------------|---------------------|
| Incerpi et al. (1998) [5]  | USA         | Cohort Retrospective | Stillbirths >20 wk GA, >500 g BW | 1990–1994    | 745         | NS                | N                           | N                          | 2                             | 0                               | 3                  | 5                  |
| Ogunyemi et al. (1998) [6] | USA         | Case-control Retrospective | Stillbirths >25 wk GA. Case: stillbirth | 1985–1995    | 115 cases, 193 N controls | Y                 | Y                           | Y                          | 3                             | 2                               | 2                  | 7                  |
| Galan-Roosen et al. (2002) | The Netherlands | Descriptive Prospective | Stillbirths + neonatal death, >500 g BW | 1983–1992    | 151 stillbirths, N 88 neonatal death | N                 | N                           | N                          | 4                             | 0                               | 2                  | 6                  |
| Horn et al. (2004) [8]     | Germany     | Cohort Retrospective | Stillbirth >22 wk GA, >500 g BW        | NS           | 310         | N                 | N                           | N                          | 3                             | 0                               | 3                  | 6                  |
| Locatelli et al. (2005) [9]| Italy       | Cohort Retrospective | Live born / neonatal death <750 g BW  | 1998–2002    | 59          | Y                 | N                           | Y                          | 3                             | 2                               | 2                  | 7                  |
| Burke et al. (2007) [10]   | Australia   | Observational Retrospective | Intrapartum death, all GA            | NS           | 20          | N                 | N                           | N                          | 4                             | 0                               | 3                  | 7                  |
| Zanconato et al. (2007) [11]| Italy      | Cohort Retrospective | Stillbirth >22 wk GA, >500 g BW        | 2000–2006    | 59          | N                 | N                           | N                          | 4                             | 0                               | 2                  | 6                  |
| Vergani et al. (2008) [12] | Italy       | Cohort Retrospective | Stillbirth >22 wk GA, >500 g BW        | 1995–2007    | 154         | N                 | N                           | N                          | 4                             | 0                               | 3                  | 7                  |
| Heazell et al. (2009) [13] | UK          | Cohort Retrospective | Stillbirths                           | 2006–2007    | 71          | N                 | N                           | N                          | 3                             | 0                               | 3                  | 6                  |
| Kidron et al. (2009) [14]  | Israel      | Cohort Retrospective | Stillbirth 23–40 wk GA, Singletons    | 1994–2005    | 120         | N                 | Y                           | N                          | 4                             | 0                               | 3                  | 7                  |
| Korteweg et al. (2009) [4] | The Netherlands | Cohort Prospective Multi-center | Antepartum death >20 wk GA | 2002–2006    | 750         | N                 | Y                           | N                          | 4                             | 0                               | 3                  | 7                  |
| Bonetti et al. (2011) [15] | Italy       | Cohort Retrospective | Stillbirth >22 wk GA, >500 g BW        | 2000–2004    | 132         | N                 | N                           | N                          | 3                             | 0                               | 3                  | 6                  |
| Tellefsen et al. (2011) [16] | Norway    | Cohort Retrospective | Perinatal death >22 wk GA –7d post partum | 2004–2008    | 104         | N                 | N                           | N                          | 4                             | 0                               | 3                  | 7                  |
| VanderWielen et al. (2011) [17] | USA      | Cohort Prospective Multi-center | Perinatal death + terminated pregnancies | NS           | 20 wk 330, ≤20 wk 73, 24 h pp 13 | N                 | N                           | N                          | 4                             | 0                               | 3                  | 7                  |
### Table 1. Placental Pathology and Neonatal Outcome

| Country          | Study design     | Study population | Study period                | Sample size | Corrected for confounders | Blinding placental examiner | Quality assessment | Quality assessment Outcome/exposure | Quality assessment Comparability | Quality assessment Total | Study population |
|------------------|------------------|------------------|-----------------------------|-------------|---------------------------|----------------------------|---------------------|-------------------------------|---------------------------|----------------------|-------------------|
| USA              | Cohort           | Stillbirth ≥20 wk GA | 2006–2008                  | 512         | Y                         | N                          | 8                   |                               |                           |                      |                   |
|                   | Prospective      | Stillbirth ≥20 wk GA | 2006–2008                  | 1025        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   | Multi-center     | Stillbirth ≥20 wk GA | 2002–2008                  | 1925        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥18–19 wk GA | if GA was uncertain     |             | N                         | N                          | 1                   |                               |                           |                      |                   |
| Korteweg et al.  | Cohort           | Stillbirth ≥22 wk GA | 1990–2003                  | 377 cases   | Y                         | N                          | 2                   |                               |                           |                      |                   |
|                   | Prospective      | Stillbirth ≥22 wk GA | 1990–2003                  | 377 cases   | Y                         | N                          | 2                   |                               |                           |                      |                   |
|                   | Multi-center     | Stillbirth ≥500 g BW | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥500 g BW | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥500 g BW | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |
|                   |                    | Stillbirth ≥22 wk GA | 1998–2009                  | 1089        | N                         | N                          | 3                   |                               |                           |                      |                   |

**Reference**

- The stillbirth collaborative research group (2011)[18]
- Korteweg et al. (2012)[19]
- Helgadottir et al. (2013)[20]
- Bring et al. (2013)[21]

**Abbreviations:** wk - weeks; GA - gestational age; BW - birth weight; NS - not stated; pp - post partum

- "outcome" for cohort studies, "exposure" for case-control studies.
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Lung development and neonatal respiratory problems, such as neonatal respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD), are associated with placental inflammation. There are indications that the incidence of RDS is reduced in infants exposed to chorioamnionitis (ORs 0.1–0.6, 95% CI: 0.02–0.8).[23,29,37,77] This beneficial effect may be explained in several ways. It can be explained by advanced lung maturation in terms of an early elevation of interleukin-1 beta (IL-1β) in lung lavage fluid in the presence of chorioamnionitis, which stimulates the release of corticotrophin-releasing factor and corticosteroids. [78,79] These hormones enhance the production of cortisol which results in accelerated lung maturation and, therefore, a decrease in the incidence of RDS.[80] Lung maturation is also explained with animal models of fetal inflammation. Chorioamnionitis in the fetal lung induces elevated IL-1, which in turn increases the amounts of surfactant proteins in parallel with increases in surfactant lipids in bronchoalveolar lavages. The lung mesenchymal tissue decreases, which increases the epithelial surface area and airspace volume of the lung. This results in a more mature lung structure that contains more surfactant, has increased compliance, and supports better gas exchange.[77,81,82]

Besides potentially a beneficial effect on lung function immediately after birth, an ascending intrauterine infection can also have a detrimental effect on the preterm lung, particularly in the long-term.[77] Chorioamnionitis can promote BPD, with ORs ranging from 2.0–7.4 (95% CI: 1.2–31.2).[23,26,37,40,77,83] BPD results from multiple antenatal and postnatal factors (hits) contributing to disease progression.[84] Despite a healthier initial condition [less RDS], the pulmonary status worsens during the postnatal period.[83] This is explained by an increased susceptibility of the lung to postnatal injurious events (second hits).[83–86]

Even so, the relation between respiratory problems and chorioamnionitis is difficult to assess, since it is confounded by a variety of prenatal factors.[85]

Necrotizing enterocolitis (NEC) is a challenging problem in the neonatal care of, mainly, preterm infants. The etiology of NEC is still poorly understood, but it is believed to be multifactorial.[37] Several studies found an association between NEC and placental lesions, in particular fetal vascular obstructive lesions (fetal thrombotic vasculopathy, congested villi, coagulation-related lesions) with ORs ranging from 2.6 to 9.10 (95% CI: 1.13–15.08).[26,32,33] The presence of ischemia has been proposed as an explanation for the etiology of NEC. Placental vasculopathy, which causes uteroplacental insufficiency, may cause fetal circulatory adaptive changes to hypoxia, which may result in bowel ischemia predisposing to NEC.[26]

Retinopathy of prematurity (ROP) is also associated with placental lesions, in particular with inflammatory lesions with ORs ranging from 1.8 to 3.1 (95% CI: 1.02–9.5).[26,36,37,77,88] ROP affects preterm infants and is caused by disorganized growth of retinal blood vessels which may result in scarring and retinal detachment. The etiology of ROP is likely to be a multihit phenomenon. At least part of the multihit is an inflammation-related pathogenesis, which is thought to be mediated by cytokines and growth factors present in the newborn’s systemic circulation.[39] The severity of ROP also correlates positively with ascending intrauterine infection.[88]

Fetal cardiac abnormalities are also thought to be associated with placental lesions. A six-fold increase in fetal cardiac abnormalities is reported in the presence of fetal thrombotic vasculopathy.[34] The most common cardiac abnormalities found in its presence are ventricular and atrial septal defects, cardiomegaly, and coarctation of the aorta. It is hypothesized that the relation may be explained by a causal link between the two
| Reference                  | Country | Study design | Study population | Study period | Sample size | Blinding placental examiner | Definitions placental lesions | Corrected for GA | Quality assessment | Outcome/ exposure | Quality assessment Co-C | Quality assessment Total |
|---------------------------|---------|--------------|------------------|--------------|-------------|-----------------------------|-----------------------------|----------------|------------------|------------------|------------------------|------------------------|
| Beebe et al. (1996) [22]  | USA     | Cohort       | Retrospective    | High risk population, all GA | 1989–1992    | 1252          | Y                           | Y                          | Y                | 3                | 2                | 2                       | 7                      |
| Watterberg et al. (1996) [23] | USA     | Case-control | Prospective      | Intubated infants <2000 gram. Case: RDS | 1987–1989    | 38 cases, 15 controls | Y                           | Y                          | N                | 3                | 0                | 3                       | 6                      |
| Baergen et al. (2001) [24] | USA     | Case-control | Retrospective    | All GA. Case: ELUC | 1977–1995    | 926 cases, 200 controls | Y                           | Y                          | N                | 3                | 2                | 3                       | 8                      |
| Redline et al. (2002) [25] | USA     | Cohort       | Retrospective    | VLBW infants <32 wk GA | 1995–1997    | 371           | Y                           | reference previous article | Y                | 3                | 2                | 3                       | 8                      |
| Ogunyemi et al. (2003) [26] | USA     | Cohort       | Retrospective    | Preterm infants 24-32 wk GA | 1992–2000    | 774           | NS                          | Y                          | Y                | 4                | 2                | 3                       | 9                      |
| Ariel et al. (2004) [27]  | Israel  | Cohort       | Prospective      | Infants from pregnancies with preeclampsia, placental abruption or RUGR | 1996–2004    | 64            | Y                           | Y                          | N                | 3                | 0                | 3                       | 6                      |
| Holcroft et al. (2004) [28] | USA     | Cohort       | Retrospective    | Preterm infants admitted NICU <34 wk GA | 1999–2002    | 259           | NS                          | Y                          | Y                | 4                | 2                | 3                       | 9                      |
| Richardson et al. (2006) [29] | Canada  | Cohort       | Retrospective    | Preterm infants 25-34 wk GA | 1995–2003    | 660           | NS                          | Y                          | Y                | 3                | 2                | 3                       | 8                      |
| Mehta et al. (2006) [30]  | USA     | Cohort       | Retrospective    | Preterm infants admitted NICU ≤34 wk GA | 1999–2001    | 165           | Y                           | N                          | Y                | 3                | 1                | 2                       | 6                      |
| de Laat et al. (2006) [31] | The Netherlands | Case-control | Prospective      | All GA. Cases: overcoiling / undercoiling UC | 2002–2003    | 885           | Y                           | Y                          | Y                | 3                | 1                | 3                       | 7                      |
| Beaudet et al. (2007) [32] | Canada  | Cohort       | Retrospective    | NICU population placental pathology report available | 1996–1997    | 1296          | Y                           | NS                         | Y                | 3                | 2                | 3                       | 8                      |
| Dix et al. (2010) [33]    | Switzerland | Case-control | Retrospective    | Infants with NEC, all GA. Case: NEC | 1994–2005    | 77 cases, 769 controls | NS                          | Y                          | Subanalyses GA | 2                | 0                | 3                       | 5                      |
| Saleemuddin et al. (2010) [34] | USA     | Case-control | Retrospective    | Infants with FTV, all GA. Case: FTV | 1990–2007    | 113 cases, 216 controls | Y                           | Y                          | Y                | 3                | 2                | 3                       | 8                      |
| Wintermark et al. (2010) [35]            | Canada  | Cohort       | Prospective      | Infants with HIE undergoing induced hypothermia ≥36 wk GA | 1996–1997    | 23            | Y                           | Y                          | N                | 4                | 0                | 3                       | 7                      |
| Reference       | Country | Study design | Study population | Study period | Sample size | Blinding placental examiner | Definitions placental lesions | Corrected for GA | Quality assessment Selection 4pt | Quality assessment Comparability 2pt | Quality assessment Outcome/exposure a 3pt | Quality assessment Total 9pt |
|-----------------|---------|--------------|------------------|--------------|-------------|-----------------------------|-------------------------------|----------------|---------------------------------|-----------------------------------|--------------------------------------|------------------|
| Moscuzza et al. (2011) [36] | Italy   | Cohort study Retrospective Single-center | NICU population placental pathology report available | 2007 | 122 | NS N N N 2 0 | 3 5 |
| Sato et al. (2011) [37] | Japan   | Cohort Retrospective Single-center | NICU population <30 wk GA | 2000–2008 | 302 | NS Y Y Y 3 1 | 3 7 |
| Roescher et al. (2011) [38] | The Netherlands | Cohort Retrospective Single-center | NICU population <32 wk GA | 2006 | 40 | Y N N N 4 0 | 3 7 |
| Chen et al. (2011) [39] | USA     | Cohort Prospective Multi-center | ELGAN 23-27 wk GA | 2002–2004 | 1064 | Y Y Y Y 4 2 | 3 9 |
| Perrone et al. (2012) [40] | Italy   | Cohort Prospective Single-center | Preterm infants <32 wk GA | 2008–2001 | 105 | NS Y N N 4 0 | 2 6 |

a: 'outcome' for cohort studies, 'exposure' for case-control studies.
b: Bell stage II and more.

Abbreviations: GA - gestational age; RDS - respiratory distress syndrome; ELUC - excessively long umbilical cord; VLBW - very low birth weight; NS - not stated; IUGR - intrauterine growth restriction; NICU - Neonatal Intensive Care Unit; UC - umbilical cord; NEC - necrotizing enterocolitis; FTV - fetal thrombotic vasculopathy; HIE - hypoxic ischemic encephalopathy; ELGAN - extremely low gestational age newborns.
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| Reference          | Country | Study design | Study population | Study period | Sample size | Blinding placental examiner | Definitions placental lesions for GA | Corrected for GA | Quality assessment Selection 4pt | Quality assessment Comparability 2pt | Quality assessment Outcome/exposure 3pt | Quality assessment Total 9pt |
|-------------------|---------|--------------|------------------|--------------|-------------|----------------------------|--------------------------------|-----------------|-------------------------------|-----------------------------------|-------------------------------------|------------------------|
| Redline et al. (1998) [41] | USA     | Case-control Retrospective Single-center | NICU population <1500 g BW. Cases: NI at 20 m | 1983–1991 | 60 cases, 59 controls | Y                           | Y                             | N               | 2                             | 0                                 | 3                                   | 5                      |
| Redline et al. (2000) [42] | USA     | Case-control Retrospective Single-center | Term infants. Cases: NI. Controls: meconium | 1990–1997 | 40 cases, 176 controls | N                           | Y                             | Y               | 1                             | 2                                 | 3                                   | 6                      |
| Viscardi et al. (2001) [43] | USA     | Case-control Retrospective Single-center | NICU population all GA. Cases IUGR | 1991–1996 | 94 cases, 145 controls | Y                           | Y                             | Y               | 2                             | 2                                 | 3                                   | 7                      |
| Adams-Chapman et al. (2002) [44] | USA     | Case-control Retrospective Single-center | NICU population <37 wk GA. Cases: MFI | 1990–1998 | 21 cases, 42 controls | N                           | N                             | Y               | 3                             | 2                                 | 2                                   | 7                      |
| McDonald et al. (2004) [45] | Ireland | Case-control Retrospective Single-center | Term infants. Cases: NE | 1987–1998 | 93 cases, 387 controls | N                           | S                             | NS              | 2                             | 2                                 | 2                                   | 7                      |
| Redline (2005) [46] | USA     | Case-control Retrospective Single-center | Term infants. Cases: NI | 1995–2000 | 125 cases, 250 controls | Y                           | N                             | Y               | 3                             | 2                                 | 2                                   | 7                      |
| Polam et al. (2005) [47] | USA     | Case-control Retrospective Single-center | NICU population 22–29 wk GA. Cases: AIUI | 1997–2000 | 102 cases, 75 controls | Y                           | Y                             | Y               | 3                             | 2                                 | 2                                   | 7                      |
| Redline et al. (2007) [48] | USA     | Cohort Retrospective Single-center | NICU population ELBW infants <1 kg BW | 1992–1995 | 129 | Y                           | Y                             | Y               | 3                             | 2                                 | 3                                   | 8                      |
| Reiman et al. (2008) [49] | Finland | Cohort Retrospective Single-center | Preterm infants <32 wk GA or <1500 g BW | 2002–2006 | 121 | Y                           | Y                             | Y               | 3                             | 1                                 | 3                                   | 7                      |
| Suppiej et al. (2008) [50] | Italy   | Cohort Retrospective Single-center | NICU population <32 wk GA | 1998–2001 | 104 | N                           | S                             | N               | 2                             | 0                                 | 1                                   | 3                      |
| Chau et al. (2009) [51] | Canada  | Cohort Prospective Single-center | Preterm infants 24–32 wk GA | 2006–2008 | 92 | NS                          | N                             | N               | 3                             | 2                                 | 3                                   | 8                      |
| Leviton et al. (2010) [52] | USA     | Cohort Prospective Multicenter | ELGAN <28 wk GA | 2002–2004 | 1246 | N                           | N                             | Y               | 4                             | 1                                 | 3                                   | 8                      |
| Elbers et al. (2010) [53] | Canada  | Cohort Retrospective Multicenter | Term + late preterm ≥34 wk GA. All neonatal stroke | 1992–2006 | 12 | NS                          | Y                             | Y               | 2                             | 0                                 | 3                                   | 5                      |
| Rovira et al. (2011) [54] | Spain   | Cohort Retrospective Single-center | Preterm infants <32 wk GA, <1500 g BW | 2002–2004 | 177 | NS                          | Y                             | Y               | 4                             | 2                                 | 3                                   | 9                      |
| Reference          | Country     | Study design          | Study population | Study period | Sample size | Blinding placental examiner | Definitions placental lesions for GA | Corrected for GA | Quality assessment Selection 4pt | Quality assessment Comparability 2pt | Quality assessment Outcome/exposure 3pt | Quality assessment Total 9pt |
|-------------------|-------------|-----------------------|------------------|--------------|-------------|-------------------------------|-------------------------------------|----------------|----------------------------------|----------------------------------------|----------------------------------------|-------------------|
| Chang et al. (2011) [55] | Canada      | Cohort Retrospective Single-center | IUFD 27–41 wk GA | 2001–2007 | 37          | Y                            | Y                                    | Y              | 3                               | 1                                       | 3                               | 7                 |
| Blair et al. (2011) [56] | Australia   | Case-control Prospective Multi-center | Late preterm + term ≥ 35 wk GA. Cases: CP | 1980–1995 | 445 cases, 497 controls | N                            | Y                                    | N              | 4                               | 0                                       | 1                               | 5                 |
| Van Vliet et al. (2012) [57] | The Netherlands | Cohort Retrospective Single-center | Preterm infants ≥ 32 wk GA. AIUI+MVU | NS          | 72          | Y                            | Y                                    | Y              | 4                               | 2                                       | 2                               | 8                 |
| Hayes et al. (2012) [58] | Ireland     | Case-control Retrospective / prospective Single-center | Term infants ≥ 36 wk GA. Cases: NE | 2001–2008 | 141 cases, 309 controls | Y                            | N                                    | Y              | 2                               | 2                                       | 3                               | 7                 |

*a: ‘outcome’ for cohort studies, ‘exposure’ for case-control studies.
b: Subgroup of placentas of both cases and controls were blinded re-reviewed.

Abbreviations: NICU - Neonatal Intensive Care Unit; BW - birth weight; NL - neurologic impairment; GA - gestational age; IUGR - intrauterine growth restriction; MFI - maternal floor infarction; NE - neonatal encephalopathy; AIUI - ascending intrauterine infection; ELBW - extremely low birth weight; ELGAN - extremely low gestational age newborns; IUFD - intrauterine fetal death; CP - cerebral palsy; MVU - maternal vascular underperfusion.
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lesions.[34] The presence of one lesion may lead to the establishment of the other, through abnormal blood flow which serves as the common denominator. Another theory is that a common genetic variation underlies both placental fetal thrombotic vasculopathy and abnormal development of the heart.[34]

This theory is supported by studies in mice which have shown that common genetic variation underlies both placental fetal thrombotic vasculopathy and abnormal development of the heart.[34] In addition, ascending intrauterine infection and fetal thrombotic vasculopathy as the most important placental finding with respect to neonatal morbidity.[22,26,34] This may pave the way for early interventions serving to prevent morbidity. Before such interventions can be defined, however, detailed knowledge of the pathophysiological mechanisms that lead to neonatal morbidity is required.

### Placental lesions and neurological morbidity

Many prospective and retrospective studies have been conducted on placental lesions and neurological morbidity (Table 7). Some of the studies focused on early brain development, while others focused on neurological and functional outcome as determined by follow-up testing. However, it is difficult to conduct correlative studies between placenta lesions and neurologic or psychiatric

### Table 4. Overview of placental pathology relevant for understanding perinatal morbidity and mortality.

| Diagnosis                                      | Pathology and explanation                                                                 | Outcome                                                                 |
|------------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Maternal vascular underperfusion (MVU)         | Inadequate spiral artery remodeling or spiral artery pathology (decidual vasculopathy). Commonly seen in pregnancies complicated with pre-eclampsia. Expressed by parenchymal pathology such as placental hypoplasia, increased syncytiot knots, villous agglutination, increased perivillous fibrin, distal vilous hypoplasia, abnormal vilous maturity, infarction, retrolental hematoma.[59] | Fetal death [4,8,14], CP [48,56]                                      |
| Umbilical cord complications                   | Obstruction or disruption of the umbilical cord blood flow (e.g. umbilical cord prolapse, entanglement, knots, disrupted velamentous vessels, hyper/hypo-coiling). Can lead to fetal placental vascular stasis resulting in FTV.[35] | Fetal death [21,31], fetal anomalies [24], asphyxia [31,35], low Apgar score at 1–5 minutes [24,31], RDS [24] |
| Fetal thrombotic vasculopathy (FTV)            | Thrombosis, recent or remote, in the umbilical cord, chorionic plate or stem villus vessels and/or secondary degenerative pathology in the fetal vasculature distal to by thrombosis obliterated vessels (e.g. avascular chorionic vili). Expressed by hemorrhagic endovasculopathy, intimal fibrin cushions, fibromuscular hypertrophy, villous stromal-vascular karyorhexis.[60] | Stillbirth [34], asphyxia [35], † illness severity first 24h (38), NEC [32,33], fetal cardiac abnormalities [34], ventriculomegaly [52], PVL [43], NI [41,42], CP [46] |
| Distal vilous immaturity/vilous maturation defect | Maturation defect of the third trimester placenta characterized by enlarged chorionic vili with increased numbers of capillaries, macrophages, and fluid and decreased formation of vasculosyncytial membranes. As a result the diffusion distance between intervillous space and fetal capillaries is increased.[68] | Fetal death [4], asphyxia in diabetic pregnancy [68] |
| Villitis of unknown etiology (VUE)             | Chronic lymphohistiocytic inflammation of the stem- and chorionic villi, with or without obliteratorive vasculopathy of stem villus vessels.[69] | Neonatal infection [22], NI [42,46], NE [45,58]                                      |
| Ascending intrauterine infection (AIUI)         | Acute chorioamnionitis and choriitis (maternal response). The degree of severity can be staged and graded.[61] | Intrapartum death [10], Low Apgar score at 1–5 minute [22,26,35], neonatal infection [22,26,30,36], ↓ RDS [23,29,37], BPD [23,26,37,40], ↓ NEC [32], ROP [26,36,37,39], IVH [26,32,36,37,47], ventriculomegaly [52], CP [52], NE [45,58] |
| Chronic deciduitis                             | Chronic lymphohistiocytic inflammation of placental villi.[70]                           | Intrapartum death [10], Low Apgar score at 1–5 minute [22,26,35], neonatal infection [22,26,30,36], ↓ RDS [29,37], BPD [23,26,40], NEC [32], ROP[26,36,39], IVH [26,30,32,36,47], brain lesions [49], NI [42,46,54], NE [45,58], disability in development at 2y [54] |
| Fetal hypoxia                                  | Elevated nucleated red blood cells (NRBCs). Only rare NRBCs are normal after the first trimester. [42] | † illness severity first 24h [38], NI [42] |
| Chorangiosis                                   | Diffuse increase in the number of villous capillaries                                  |

Abbreviations: CP - cerebral palsy; RDS - respiratory distress syndrome; NEC - necrotizing enterocolitis; PVL - periventricular leukomalacia; NI - neurological impairment; NE - neonatal encephalopathy; BPD - bronchopulmonary dysplasia; ROP - retinopathy of prematurity; IVH - intraventricular hemorrhage.

doi:10.1371/journal.pone.0089419.t004
| Placenta | Placental lesion | Ref. | Outcome measure: Perinatal death | Association found proportion*/OR (95% CI) | No association found/ non placental | Remarks |
|----------|-----------------|------|-------------------------------|---------------------------------|-----------------------------------|---------|
| Placenta | Not specified   | [11] | Stillbirth                     | Proportion 0.42 (0.31–0.53)     | 53% placenta negative            | Placenta new insight |
| Placenta |                  | [14] | Stillbirth                     | Proportion 0.33 (0.25–0.41)     | Direct cause death               |         |
| Placenta |                  |      |                               | Proportion 0.47 (0.38–0.56)     | Major contributor                |         |
| Placenta |                  | [13] | Unexplained stillbirth         | OR 0.17 (0.04–0.70)             | After placental assessment stillbirth less likely to be unexplained |         |
| Placenta |                  | [16] | Explanation perinatal death    | Proportion 0.73 (0.64–0.81)     | 12% placenta no connection       | Could explain death |
| Placenta |                  |      |                               | Proportion 0.51 (0.41–0.66)     | death                           | Cause explained by placental examination alone |
| Placenta |                  | [12] | Stillbirth                     | Proportion 0.12–0.40 (0.08–0.48)| Different classification systems |         |
| Placenta |                  | [4]  | Stillbirth                     | Proportion 0.65 (0.61–0.69)     | Placental lesions main cause fetal death |         |
| Placenta |                  | [15] | Stillbirth                     | Proportion 0.22 (0.15–0.30)     | 51% no placental cause           | Secondary main condition |
| Placenta |                  | [17] | Stillbirth                     | Proportion 0.42 (0.37–0.47)     | 19.9% fetal, 13% maternal, 31.9% no cause | Proportion placental/cord causes stillbirth |
| Placenta |                  | [18] | Stillbirth                     | Proportion 0.24 (0.20–0.28)     | 29.3% obstetric condition, 13.7% fetal abnormalities, 12.9% infection, 10.4% umbilical cord abnormalities | Placental second common cause stillbirth. Placenta main cause (26.1%) in antepartum deaths. |
| Placenta |                  | [19] | Test determine cause death     | Proportion 0.96 (0.94–0.97)     | 72.6% autopsy, 29.0% genetic analysis | Placental examination most valuable test for determination of cause stillbirth |
| Placenta |                  | [9]  | placental pathology in survivors and neonates who died | Proportion 0.61–0.69 | No differences in placental pathology between survivors and neonates who died. |         |
| Placenta |                  | [6]  | Stillbirths                    | OR: 2.43 (1.12–5.26)            | Positive placental pathology in 66% of stillbirths versus 44% in controls. |         |
| Placenta |                  | [8]  | Stillbirth                     | Proportion 0.62 (0.56–0.67)     | Leading cause intrauterine death  |         |
| Placenta |                  | [5]  | Evaluation Stillbirth          | Proportion 0.30 (0.26–0.34)     | Most important aspects stillbirth evaluation: placenta and autopsy |         |
| Placenta |                  | [20] | Stillbirth                     | Proportion 0.50 (0.45–0.55)     | 19.4% unknown                   | Main cause of death. Placenta 18% associated condition death |
| Placenta | Acute/subacute pathology | [7] | Stillbirth + neonatal death | Proportion 0.32 (0.27–0.38) | 23% congenital malformation, 16% infection, 8% prematurity, 7% unclassifiable | Most probable cause stillbirth |
| Placenta | Chronic/ progressive pathology | [7] | Stillbirth + neonatal death | Proportion 0.21 (0.16–0.27) | Third most probable cause stillbirth |         |
| AIUI     | Ascending intrauterine infection | [10] | Intrapartum death | Proportion 0.35 (0.18–0.57) | 50% other (UC entanglement) | Proportion AIUI in intrapartum death |
| AIUI     |                  | [15] | Stillbirth                     | Proportion 0.23 (0.16–0.31)     | Major relevant condition associated with death. Chorioamnionitis diagnosed by bacterial cultures |         |
| MVU      | Maternal vascular underperfusion | [14] | Stillbirth                     | Proportion 0.35 (0.27–0.44)     | Direct/major contributor fetal death |         |
| MVU      |                  | [4]  | Stillbirth                     | Proportion 0.34 (0.30–0.38)     | Most important placental lesions in fetal death |         |
| MVU      |                  | [8]  | Stillbirth                     | Proportion 0.38 (0.31–0.45)     | Main contributor placental lesions to death |         |
outcomes in the child.[90] Neurological outcomes are not evident immediately after birth, but only long after most placentas have been discarded. Placentas, especially those of term infants, are not routinely sent to the pathologist for examination.[55,90] Unless immediately after birth, but only long after most placentas have outcomes in the child.[90] Neurological outcomes are not evident within the brain that have been implicated in the pathogenesis of cystic PVL and CP. Therefore, if low gestational age resulting from maternal infection in itself plays a direct role in the pathogenesis of CP, then adjusting for its effect will falsely diminish the observed association between chorioamnionitis and CP.[91]

Neonatal encephalopathy has mainly an antepartum, rather than an intrapartum, etiology. An important antepartum factor is placental pathology.[45,58] Placental lesions consistent with fetal thrombotic vasculopathy (OR 4.63, 95% CI: 2.01–10.68) and AIUI with a fetal response (funisitis) (OR 22.54 95% CI: 11.07–45.91) are both associated with neonatal encephalopathy.[45,58] Another less strongly associated placental lesion is accelerated villous maturation (disturbed uteroplacental flow) with an OR of 3.35 (95% CI: 1.48–7.63). Elbers et al. studied placental pathology in relation to neonatal stroke.[33] They systematically described their findings in twelve cases of neonatal stroke, ten of which had placental lesions. They found the following types of lesions: thromboinflammatory process in six cases, sudden catastrophic event in five cases, decreased placental reserve in three cases, and stressful intrauterine environment in two cases. They suggested that multiple risk factors are involved in neonatal stroke, and that placental pathology may be a contributing factor.[53]

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Table 5. Cont.

| Placenta | Placental lesion                  | Ref. | Outcome measure: Perinatal death | Association found proportion/*OR (95% CI) | No association found/ non placental | Remarks                       |
|----------|----------------------------------|------|----------------------------------|----------------------------------------|-----------------------------------|-------------------------------|
| UC       | Umbilical cord lesions           | [15] | Stillbirth                        | Proportion 0.05 (0.02–0.10)             |                                   | Proportion UC pathology in stillbirth |
| UC       | Umbilical cord complication      | [21] | Stillbirth                        | Proportion 0.08 (0.06–0.10)             |                                   | Significant more in term stillbirth (9.75) compared to preterm stillbirth (6.4%) |
| UC       | Undercoiling umbilical cord      | [31] | Fetal death                       | OR 3.35 (1.48–7.63)                     |                                   |                               |
| UC       | Overcoiling umbilical cord       | [31] | Fetal death                       | Not significant. OR 2.43 (0.68–8.66)    |                                   |                               |
| UC       | Excessive long UC                | [24] | Fetal/neonatal death              | Not significant. OR 2.75 (0.65–36.14)   |                                   |                               |

*proportion placental lesions in perinatal death.

Abbreviations: AIUI - ascending intrauterine infection; MVU - maternal vascular underperfusion; UC - umbilical cord.

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Table 6. Results of selected studies on neonatal morbidity.

| Placental lesion specified | Ref. | Outcome measure | Associations found OR (95% CI) | Association found other | No association found | Remarks |
|---------------------------|------|-----------------|------------------------------|--------------------------|----------------------|---------|
| Maternal + fetal response | [22,26,35] | Low Apgar score | Proportion AIUI: 0.35 95%CI (0.19–0.53) [35] | Apgar 1–5 minutes, asphyxia. |
| AIUI (not specified) | [38] | Illness severity first 24h | No relation | |
| AIUI | [22,26,30,32,36] | Neonatal infection | Effect size r = 0.31 [36] | No relation [32] | EOS + LOS + nosocomial infection |
| AIUI | [23,26,32] | RDS | OR 0.11 (0.02–0.63) | No relation [26,32] |
| AIUI | [23,26,32,40] | BPD | OR 2.0–7.4 (1.20–31.16) | No relation [32] |
| AIUI | [25] | BPD | OR 0.7 (0.4–0.9) | Unadjusted GA ns |
| AIUI | [26,30,32,36,40] | PDA | Effect size r = 0.25 [36] | No relation [32,30] |
| AIUI | [26,36,39,40] | ROP | Effect size r = 0.52 [36] | No relation [40] | In combination with micro-organisms [39] |
| AIUI | [26,32,40] | NEC | OR 3.80 (1.67–8.67) | No relation [26,40] |
| AIUI | [28] | Fetal metabolic acidosis | No relation | |
| AIUI | [22] | Liver disorders | No relation | |
| AIUI | [22] | Anomalies* | No relation | |
| Maternal response | [28] | Fetal metabolic acidosis | No relation | |
| AIUI | [29,37] | RDS | Proportion RDS: 0.44 95% CI (0.35–0.53) [29] | Significant less than control group |
| AIUI | [29,37] | BPD | Proportion: 0.22 95% CI (0.10–0.42) | Proportion AIUI |
| AIUI | [29,37] | IVH | Proportion: 0.47 95% CI (0.40–0.55) | Significant less than control group |
| AIUI | [29,37] | PDA | Proportion: 0.47 95% CI (0.40–0.55) | Significant less than control group |
| AIUI | [29,30] | IVH | No relation [29] |Adjusted for GA not significant [29] |
| AIUI | [37] | ROP | No relation | Stage AIUI |
| AIUI | [37] | NEC | No relation | Stage AIUI |
| Fetal response | [29] | RDS | Proportion: 0.47 95% CI (0.40–0.55) | Significant less than control group |
| MVU | [26,32] | Neonatal infection | | |
| MVU | [26,32,40] | NEC | OR 4 (1.7–9.2) | No relation [32,40] |
| MVU | [25,26,32,40] | BPD | | |
| MVU | [26,32] | RDS | | |
| MVU | [26,32,40] | PDA | | |
| MVU | [26,40] | ROP | | |
| MVU | [22] | Liver disorders | OR 2.2 (1.2–4.2) | Only with abruption |
| MVU | [22] | Low Apgar score 1 min | Apgar <7 (1+5 min) |
| MVU | [26,32] | Illness severity first 24h | No relation |
| MVU | [26,32,40] | NEC | No relation [32,40] |
| MVU | [25,26,32,40] | BPD | No relation |
| MVU | [26,32] | RDS | No relation |
| MVU | [26,32,40] | PDA | No relation |
| MVU | [26,40] | ROP | No relation |
| MVU | [22] | Liver disorders | | |
| MVU | [22] | Low Apgar score 1 min | No relation |
| Placental lesion specified | Ref. | Outcome measure | Associations found OR (95% CI) | Association found other | No association found | Remarks |
|---------------------------|------|-----------------|-------------------------------|-------------------------|---------------------|---------|
| MVU                       | [22] | Neonatal infection | No relation |                         |                     |         |
| MVU                       | [22] | Anomalies*        | No relation |                         |                     |         |
| FTV                       | [34] | NRFHT            | OR 3.01 (1.54–5.78)           |                         |                     |         |
| FTV                       | [34] | Fetal cardiac abnormalities | OR 8.02 (3.02–21.26) |                         |                     |         |
| FTV                       | [34] | CNS abnormalities | No relation |                         |                     |         |
| FTV                       | [35] | Asphyxia         | Proportion: 0.26 95% CI (0.13–0.46) | Proportion FTV |                     |         |
| FTV                       | [38] | Illness severity first 24h | Median scores illness severity significantly ↑ | Higher illness severity |                     |         |
| FTV                       | [32,33] | NEC             | OR 4.34–9.10 (1.80–15.08)    |                         |                     |         |
| FTV                       | [27] | Fetal thrombophilia | No relation |                         |                     |         |
| FTV                       | [32] | Nosocomial infection | No relation |                         |                     |         |
| FTV                       | [32] | RDS              | No relation                 |                         |                     |         |
| FTV                       | [32] | BPD              | No relation                 |                         |                     |         |
| FTV                       | [32] | PDA              | No relation                 |                         |                     |         |
| FTV                       | [32] | IVH              | No relation                 |                         |                     |         |
| VUE                       | [22] | Low Apgar score 1 min | No relation |                         |                     |         |
| VUE                       | [38] | Illness severity first 24h | No relation |                         |                     |         |
| VUE                       | [22] | Neonatal infection | OR 2.3 (1.1–5.1)          |                         |                     |         |
| VUE                       | [22] | Liver disorders   | No relation                 |                         |                     |         |
| VUE                       | [22] | Anomalies*        | No relation                 |                         |                     |         |
| Deciduitis                | [38] | Illness severity first 24h | No relation |                         |                     |         |
| Deciduitis                | [32] | Nosocomial infection | No relation |                         |                     |         |
| Deciduitis                | [32] | RDS              | No relation                 |                         |                     |         |
| Deciduitis                | [25,30,32] | BPD          | No relation                 |                         |                     |         |
| Deciduitis                | [32] | NEC              | No relation                 |                         |                     |         |
| Deciduitis                | [30,32] | PDA              | No relation                 |                         |                     |         |
| Deciduitis                | [30,32] | IVH              | No relation                 |                         |                     |         |
| Deciduitis                | [30] | ROP              | No relation                 |                         |                     |         |
| UC                        | [35] | Asphyxia         | Proportion UC: 0.39 95% CI (0.22–0.59) | Less in control group |                     |         |
| UC                        | [24] | Apgar 1 min      | Effect size r = –0.09       | Lower Apgar scores     |                     |         |
| UC                        | [24] | Apgar 5 min      | Effect size r = –0.07       | Lower Apgar scores     |                     |         |
| UC                        | [24] | NRFHS            | OR 4.91 (1.71–15.91)        |                         |                     |         |
| UC                        | [24] | Fetal anomalies  | OR 13.10 (1.95–256.26)      |                         |                     |         |
| UC                        | [24] | Respiratory distress | OR 2.86 (1.09–8.17)    |                         |                     |         |
| UC                        | [31] | Low Apgar 5 min  | OR 3.14 (1.47–6.70)         |                         |                     |         |
| UC                        | [31] | Asphyxia         | OR 4.16 (1.30–13.36)        |                         |                     |         |
| Marker                    | [38] | Illness severity | Median scores illness severity significantly ↑ | Higher illness severity |                     |         |
| Marker                    | [36] | LOS              | No relation                 |                         |                     |         |
| Marker                    | [36] | PDA              | No relation                 |                         |                     |         |
process that harmed the vasculature of the placenta causing infarction, the same process may also have directly harmed either the fetal cerebral vasculature or the brain.[56]

Results on the association between placental pathology and long-term neurological outcome, including developmental tests and functional outcome, are also inconsistent between studies. In preterm infants it is thought that neurological impairment is
| Placental lesion | Placental lesion specified | Ref. | Outcome measure | Associations found OR (95% CI) | Association found other | No association found | Remarks |
|-----------------|---------------------------|------|-----------------|------------------------------|-------------------------|----------------------|---------|
| AIUI Maternal + fetal response | [26,32,36,40,47] | IVH | OR 1.7–3.5 (1.2–23) | \( r^2 = 0.71 \) [36] | No relation [40] | No association found | Stage/grade AlUI also not associated with WMI |
| AIUI Not specified | [51] | WMI | | No relation | | Stage/grade AlUI also not associated with WMI |
| AIUI | [43] | Ultrasound abnormalities | | No relation | | IVH, PVL, infarction |
| AIUI | [55] | Neuronal karyorrhexis or white matter gliosis | No data (\( p<0.05 \)) | Neuropathology in stillbirths |
| AIUI | [47] | Neurodevelopment | | No relation | | Age: 12–24m BSID-II |
| AIUI | [50] | Speech abnormalities | OR: 5.1 (1.35–19.4) | 18months |
| AIUI | [59] | Hearing loss | OR 11.6 (1.3–105.9) | 18months |
| AIUI | [59] | Motor development | No relation | 18months |
| AIUI Maternal response | [29,54] | IVH | OR 2.4 (1.0–5.6) | No relation [29] | Adjusted for GA not significant [54] |
| AIUI | [52] | Venticulomegaly | OR 1.4–1.5 (1.01–2.4) | No relation |
| AIUI | [48,52,54] | CP | OR 2.3–3.4 (1.1–7.4) | No relation [48,54] |
| AIUI | [58] | Neonatal encephalopathy | OR 2.02 (1.16–3.74) | RRR 3.3 (1.1–10.4) [58] | Adjusted for confounders not significant [45] |
| AIUI | [49] | Brain lesions | | No relation | IVH, cPVL, ventriculomegaly |
| AIUI | [41] | Neurologic impairment | | No relation | VLBWI |
| AIUI | [54] | Motor abnormalities | OR 3.68 (0.95–14.28) | 24 m Bayley-II or Brunet-Lezine scale |
| AIUI | [54] | Any grade disability | | No relation | 24months |
| AIUI | [54] | Speech abnormalities | | No relation | 24months |
| AIUI | [54] | Hearing loss | | No relation | 24months |
| AIUI | [48] | Neurocognitive function | | No relation | ELBWI follow-up 8y |
| AIUI Fetal response | [29,30,54] | IVH | OR 2.0–2.3 (1.0–5.5) | No relation [29] | Adjusted for GA not significant [54] |
| AIUI | [51] | WMI | | No relation |
| AIUI | [52] | Ventriculomegaly | | No relation | OR 1.4 (0.9–2.2) [52] |
| AIUI | [48,52,54] | CP | OR 4.32 (0.91–20.44) | No relation [48,52] | OR 1.7 (0.8–3.7) [52] |
| AIUI | [41,42,46] | Neurologic impairment | OR 2.9–13.2 (1.2–144) | No relation [41] |
| AIUI | [43,58] | Neonatal encephalopathy | OR 22.54 (11.07–45.91) | RRR 20.7–34.6 (1.8–232.9) [58] |
| AIUI | [49] | Brain lesions | OR 2.46 (1.13–5.41) | Adjusted for GA not significant | IVH, cPVL, ventriculomegaly |
| AIUI | [54] | Moderate to severe disability | OR 4.08 (1.16–14.44) | 24months |
| AIUI | [54] | Speech abnormalities | OR 2.89 (1.19–7.04) | 24months |
| AIUI | [54] | Hearing loss | | No relation | 24months |
| AIUI | [48] | Neurocognitive function | | No relation | ELBWI follow-up 8y |
| Placental lesion | Placental lesion specified | Ref. | Outcome measure | Associations found OR (95% CI) | Association found other | No association found | Remarks |
|-----------------|---------------------------|------|----------------|-------------------------------|-------------------------|----------------------|---------|
| MVU             | Maternal vascular underperfusion | [26,32,40] | IVH           |                               |                         | No relation          |         |
| MVU             | [52] | Venticulomegaly | OR 0.5 (0.3–0.96) |                               |                         |                      |         |
| MVU             | [45] | Neonatal encephalopathy | OR 3.86 (1.36–10.92) |                               |                         |                      |         |
| MVU             | [53] | Neonatal stroke | Proportion 0.25 (0.09–0.53) | 3 placentas of 12 infants with neonatal stroke |                         |                      |         |
| MVU             | [41] | Neurologic impairment | OR 3.7–9.2 (1.0–51) | Only chorionic plate thrombi | [41] |                      |         |
| MVU             | [48,52] | Neurodevelopment 7/8y | OR 4.1–7.4 (1.3–17.9) | Adjusted for GA not significant | [42] | With oblative fetal vasculopathy |         |
| MVU             | [45,58] | Neurodevelopment | OR 2.11 (1.16–3.83) | RRR 17.7 (5.0–60.8) [58] | Adjusted for confounders not significant |         |
| FTV             | [32] | Venticulomegaly | OR 2.1 (1.2–3.9) |                             |                         |                      |         |
| FTV             | [48,52] | CP | OR 7.4–10.1 (1.6–46.3) | No relation | OR 1.5 (0.3–6.6) | [52] |                      |         |
| FTV             | [41,42,46] | Neurologic impairment | OR 3.7–9.2 (1.0–51) | Only chorionic plate thrombi | [41] |                      |         |
| FTV             | [42,46] | Neurologic impairment | OR 4.1–7.4 (1.3–17.9) | Adjusted for GA not significant | [42] | With oblative fetal vasculopathy |         |
| FTV             | [45,58] | Neonatal encephalopathy | OR 2.11 (1.16–3.83) | RRR 17.7 (5.0–60.8) [58] | Adjusted for confounders not significant |         |
| VUE             | [43] | Ultrasound abnormalities | OR 5.41 (1.42–20.54) | IVH, PVL, infarction |                             |                      |         |
| VUE             | [44] | CP | OR 14 (2–163) | Age:22–29months |                             |                      |         |
| Deciduitis      | [32] | Ventriculomegaly | OR 2.1 (1.2–3.9) |                             |                         |                      |         |
| Deciduitis      | [48,52] | CP | OR 7.4–10.1 (1.6–46.3) | No relation | OR 1.5 (0.3–6.6) | [52] |                      |         |
| MFI             | Maternal floor infarction | [43,44] | Ultrasound abnormalities | No relation | IVH, PVL, infarction |                             |         |
| MFI             | [44] | WMI | OR 3.7 (1.1–12.7) |                             |                         |                      |         |
| MFI             | [44] | Neurodevelopment | OR 14 (2–163) | Age:22–29months |                             |                      |         |
| Marker          | Elevated NRBCs | [36] | Venticulomegaly | OR 2.1 (1.2–3.9) |                             |                      |         |
| Marker          | [55] | Neurologic impairment | OR 5.7 (1.5–21.0) |                             |                         |                      |         |
| Marker          | Stressful intrauterine environment | [33] | Neonatal stroke | Proportion 0.17 (0.05–0.45) | 1 case ↑ NRBCs and 1 case chorangiosis |                             |         |
| Other           | Villus edema | [48] | Neurocognitive function | OR 4.7 (1.1–19.2) | ELBW follow-up | By |                      |         |
| Other           | [41] | Neurologic impairment | OR 5.7 (1.5–21.0) |                             |                         |                      |         |
| Placental lesion specified | Outcome measure | Associations found OR (95% CI) | Association found other | No association found | Remarks |
|---------------------------|-----------------|-------------------------------|-------------------------|---------------------|---------|
| Other                     | Neonatal encephalopathy | OR 4.63 (2.01–10.68) | No data (p<0.05) | Neuropathology in stillbirths |
| Other                     | Neuronal karyorrhexis | | | |
| Other                     | IVH              | OR 2.57–2.19 (1.01–6.58) | | |
| Other                     | IVH              | No relation | | |
| Other                     | Meconium staining | | | |
| Other                     | IVH              | No relation | | |
| Other                     | Meconium-associated vascular necrosis | Neurologic impairment | OR 4.8–8.2 (2.0–29.0) | Adjusted for GA not significant [42] |
| Other                     | Meconium phagocytosis | Neonatal encephalopathy | RRR 7.2–9.8 (2.3–42.4) | | |
| Other                     | Chorioamnioniotic hemosiderosis | Neurologic impairment | OR 74.8 (6.3–894) | | |
| Other                     | Sudden catastrophic event | Neonatal stroke | Proportion 0.42 (0.19–0.68) | Retropelacental hematoma and umbilical cord occlusion |
| Other                     | Thrombo-inflammatory process | Neonatal stroke | Proportion 0.5 (0.25–0.75) | Acute chorioamnionitis, chronic villitis, chorionic vessel thrombi, avascular villi |

* = effect size.

Abbreviations: IVH - intraventricular hemorrhage; WMI - white matter injury; PVL - periventricular leukomalacia; BSID - Bayley scales of infant development; GA - gestational age; CP - cerebral palsy; cPVL - cystic periventricular leukomalacia; ELBW - extremely low birth weight infant; VLBW - very low birth weight infant; MDI - mental development index; PDI - psychomotor development index; WISC - Wechsler Intelligence Scale for Children; MABC - movement assessment battery for children; CBCL - Children Behavior Checklist.

Abbreviations placental lesions: AIUI - ascending intrauterine infection; MVU - maternal vascular underperfusion; FTV - fetal thrombotic vasculopathy; VUE - villitis of unknown etiology; MFI - maternal floor infarction; NRBCs - nucleated red blood cells.

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Discussion/Conclusion

The placenta plays a key role in fetal and neonatal mortality, morbidity, and outcome. Placental lesions are one of the main contributors to fetal death. In these cases placental lesions consistent with maternal vascular underperfusion are most important. Although less clear-cut, several neonatal problems are also associated with placental lesions. Regarding neonatal morbidity and neurological outcome, placental lesions with ascending intrauterine infection (with a fetal component) and fetal thrombotic vasculopathy, constitute the greatest problem.

To our surprise we noticed a difference in the description of placental lesions between studies on perinatal death and studies on neonatal outcome. The majority of studies on placental pathology and stillbirth only focus on the presence or absence of placental lesions in general, but they do not examine the relation between specific placental lesions and stillbirth. Studies concerning placental lesions and neonatal or neurological outcome do specify the lesions, finding several relations between specific placental lesions and outcome. Characterizing placental lesions in more detail in stillbirth studies may provide additional information concerning the cause of death.

Most studies report on associations between placental lesions and outcomes but this does not necessarily reflect a causal relation. There is still need to clarify pathophysiological mechanisms. One of these proposed mechanisms include gene-environment interactions. Placental lesions might already have their onset early in pregnancy, due to changes in placental genes, leading to epigenetic alterations. Causes for these placental epigenetic changes may include a non optimal intrauterine environment, due to a maternal disease or adverse insults to the intrauterine environment.

This may in turn cause placental dysfunction and hence adverse neonatal outcome. We thus have to take into account that multiple interactions from maternal, placental, and fetal health play a role in the etiology of perinatal death and neonatal morbidity. Future research must consider statistical tools to better address interactions among these multiple variables, such as a mixed-effect regression analyses for example.

There are several limitations to our systematic review. Firstly, there is a potential risk of publication bias. Studies finding negative results regarding placental lesions and outcome might not be published. This may lead to an overestimation of associations between placental lesions and outcomes. Secondly, we included studies from the past 18 years. Earlier studies might have had different results. Finally, most studies included in this review were conducted in high-risk populations. Studies in a low- or moderate-risk group may reveal different results.

A final point we would like to address is an urgent need for increasing awareness among pediatricians for placental lesions and neonatal outcome. The obstetrician sends the placenta to the pathologist for histological examination. The results of the examination are reported back to the obstetrician. In most cases the pediatrician is unaware of the results of the placental examination. In the light of the accumulating evidence, however, that placental pathology is associated with perinatal mortality, neonatal morbidity, and neurological outcome, pediatricians should make an effort to obtain the results of placental examinations. Placental pathology, ascending intrauterine infection, and fetal thrombotic vasculopathy in particular, may help to identify the group of neonates at risk of adverse neonatal outcome. Monitoring these infants more closely could be helpful. Knowledge of the pathophysiological mechanisms leading to neonatal mortality and morbidity may lead the way to finding early intervention strategies to improve infants’ morbidity and outcome.

Supporting Information

Checklist S1 PRISMA flowchart of identified articles published between January 1995 and October 2013.

(DOC)
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Author Contributions

Wrote the paper: AMR. Designed the structure of the manuscript: AMR. AT JJHME AFB. Literature search: AMR. AFB. Drafted the initial manuscript: AMR. Drafted the ‘placental pathology’ section: AT. Reviewed and revised initial manuscript: AT JJHME AFB. Approved the final manuscript as submitted: AMR. AT JJHME AFB.

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