Maternal environmental risk factors for congenital hydrocephalus: a systematic review

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OBJECTIVE Congenital hydrocephalus (CH) is one of the most frequent CNS congenital malformations, representing an entity with serious pathological consequences. Although several studies have previously assessed child-related risk factors associated with CH development, there is a gap of knowledge on maternal environmental risk factors related to CH. The authors have systematically assessed extrinsic factors in the maternal environment that potentially confer an increased risk of CH development.

METHODS The Cochrane Library, MEDLINE, and EMBASE were systematically searched for works published between 1966 and December 2015 to identify all relevant articles published in English. Only studies that investigated environmental risk factors concerning the mother—either during gestation or pregestationally—were included.

RESULTS In total, 13 studies (5 cohorts, 3 case series, 3 case-control studies, 1 meta-analysis, and 1 case report) meeting the inclusion criteria were identified. Maternal medication or alcohol use during gestation; lifestyle modifiable maternal pathologies such as obesity, diabetes, or hypertension; lack of prenatal care; and a low socioeconomic status were identified as significant maternal environmental risk factors for CH development. Maternal infections and trauma to the mother during pregnancy have also been highlighted as potential mother-related risk factors for CH.

CONCLUSIONS Congenital hydrocephalus is an important cause of serious infant health disability that can lead to health inequalities among adults. The present study identified several maternal environmental risk factors for CH, thus yielding important scientific information relevant to prevention of some CH cases. However, further research is warranted to confirm the impact of the identified factors and examine their underlying behavioral and/or biological basis, leading to the generation of suitable prevention strategies.

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KEY WORDS congenital hydrocephalus; risk factors; diabetes; maternal drug use; maternal hypertension; preeclampsia

HYDROCEPHALUS refers to the clinical condition resulting from the progressive expansion of the cerebral ventricles due to the deficient passage of CSF from the choroid plexus, the site of CSF synthesis, to its sites of absorption into the systemic circulation. Hydrocephalus that occurs in infancy, without an obvious extrinsic causal event, is commonly referred to as congenital hydrocephalus (CH) and is usually present at birth. On the other hand, when CH occurs in the context of a known postnatal causative factor, such as traumatic brain injury (TBI), infection, invasive mass, or hemorrhage, it is typically termed acquired hydrocephalus. However, a considerable number of cases cannot be clearly characterized, because several causative processes (e.g., intrauterine hemorrhages) can take place prenatally.

Congenital hydrocephalus can also be characterized as syndromic, when a specific clinical syndrome and/or genetic basis can be determined (e.g., APIS2-associated...
hydrocephalus). Syndromic forms of CH can be further divided into 2 categories: 1) hydrocephalus that accompanies other major congenital anomalies, with obvious clinical signs and imaging features (e.g., fibroblast growth factor receptor–associated craniosynostosis syndromes); and 2) hydrocephalus that is the principal abnormality, with no major additional physical findings (LICAM-associated hydrocephalus).26 Therapeutically, most cases of CH necessitate surgical treatment and demand continuous monitoring by practitioners in various medical specialties for a considerable length of time.

Congenital hydrocephalus is one of the most frequent CNS congenital malformations and is a condition with serious pathological consequences for the infant. Several child-related risk factors have been associated with the development of CH. These risk factors include male sex, preterm birth (< 28 weeks), birth weight (below the 10th percentile or above the 90th percentile), and being first-born.19 However, little is known about the maternal environmental risk factors (i.e., environmental factors that directly affect the mother and possibly cause hydrocephalus by indirectly affecting the fetus) related to CH. Although a small number of cohort and observational studies have previously reported possible maternal environmental risk factors, there is a paucity of systematic reviews to comprehensively analyze this issue.

Thus, our objective was to systematically search and assess extrinsic factors in the maternal environment that potentially confer an increased risk of CH development. Given that CH is an important cause of infant disability with substantial long-term health effects,14 defining and investigating potential risk factors related to maternal environmental characteristics would be a critical step in preventing some of these cases. To our knowledge, there is an older26 and a concurrent28 review assessing potential risk factors for adult hydrocephalus and CH. However, no study has adequately focused on maternal environmental risk factors related to CH.

Methods

A systematic review of maternal environmental risk factors for CH was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.18

Search Methods for Identification of Studies

The Cochrane Library, MEDLINE, and EMBASE databases were systematically searched for papers published between 1966 and December 2015, to identify all relevant articles published in English. Moreover, the references of retrieved papers and pertinent reviews were scrutinized to identify additional articles. In terms of the search strategy, we combined (“AND”) the searches for the terms “Hydrocephalus” and “Risk Factor” on the Ovid MEDLINE and Ovid EMBASE platforms to identify as many articles as possible. Furthermore, we used the term “Hydrocephalus” because nomenclature for CH has been diverse (e.g., congenital hydrocephalus, connal hydrocephalus, fetal hydrocephalus, infant-onset hydrocephalus) and nonspecific. Thus, we expanded our initial search and narrowed it down during subsequent steps of data collection and extraction.

Inclusion Criteria

Inclusion criteria in terms of participants, interventions, comparisons, outcomes, and study design are outlined in Table 1. Only studies investigating environmental risk factors concerning the mother either pregestationally or during gestation were considered for inclusion. Specifically, maternal environmental risk factors that were incorporated included extrinsic factors such as pathogens and/or infections, medication and/or illicit drug use, injuries, the socioeconomic environment, and prenatal care as well as maternal pathologies that can be modified by lifestyle changes. Thus, our aim was to identify environmental factors that 1) directly affect the mother and may contribute to hydrocephalus development by affecting the fetus, and 2) can be readily modified or avoided (e.g., through lifestyle changes and provision of health care), thus preventing CH development. Risk factors such as maternal age, ethnicity, maternal parity, gestational age, weight for gestational age, and mode of delivery were considered non-environmental and were not included in the present study.

Studies addressing hydrocephalus that was due to an obvious identifiable postnatal causal event (acquired hydrocephalus), such as brain trauma, infection (e.g., meningitis), invasive mass and/or tumors, or hemorrhage, were excluded from this review. Given that imaging in many infants with hydrocephalus demonstrates aqueductal stenosis as the possible cause,25 such cases, in the absence of an established genetic basis (LICAM-associated), were considered CH cases. Studies in which such cases were encountered were included in this review. Studies focusing on patients with an established genetic basis of hydrocephalus (syndromic forms) were excluded from this review. Definitions of syndromic cases were based on criteria defined by included studies.

<table>
<thead>
<tr>
<th>PICOS Criterion</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>Mothers: only environmental gestational or pregestational risk factors were included. Maternal age, maternal parity, gestational age, &amp; mode of delivery were excluded from the review (nonenvironmental). Neonates: studies emphasizing syndromic CH (established genetic basis) or acquired hydrocephalus associated w/ known causative postnatal factors (TBI, hemorrhage, invasive mass) were excluded. Studies analyzing hydrocephalus due to aqueductal stenosis were included.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>This review does not assess interventions for CH.</td>
</tr>
<tr>
<td><strong>Comparisons</strong></td>
<td>CH cases w/ a possible risk factor are compared w/ control CH cases (w/o the presumable risk factor) or none.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>This review does not assess outcomes for CH.</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Observational studies, systematic reviews, meta-analyses.</td>
</tr>
</tbody>
</table>

PICOS = participants, interventions, comparisons, outcomes, study design.
Data Collection and Extraction

Suitability for inclusion of studies (titles and abstracts were assessed initially, and full texts subsequently) was independently evaluated by 2 authors (M.P. and T.K.). Disagreements between authors were resolved by discussion, with the exception of 2 cases; in those, the issue was resolved by reference to a third party (A.V.K.). An extraction form was used for data acquisition. Where possible, the odds ratio, relative risk, and confidence interval were documented. In case reports, only putative risk factors were documented.

Results

Search Results and Description of Studies

The search yielded 520 studies (Cochrane Library, 9; MEDLINE, 473; EMBASE, 28; References, 10). After removing duplicates, 516 studies remained. Of these, 458 were considered irrelevant based on examination of the title and abstract. The majority referred to cases of idiopathic normal pressure hydrocephalus or to acquired hydrocephalus due to a known cause. A total of 58 full-text articles were assessed for inclusion. Of these, 35 were excluded due to “wrong topic,” 5 due to “not enough quantitative data,” 2 because “data were not extractable,” and 3 due to “wrong study type.” Finally, 13 studies (5 cohorts, 3 case series, 3 case-control studies, 1 meta-analysis, and 1 case report) met the inclusion criteria and were included in this review (Fig. 1).

Several presumable risk factors were identified from the studies that were found. The risk factors were subsequently divided into 7 different categories and were analyzed accordingly. Table 2 summarizes the characteristics of the included studies.

Risk Factors

Several maternal environmental risk factors were associated with the pathogenesis of CH. All of the identified risk factors will be analyzed below.

Congenital Infections

Congenital enterovirus 71 (EV71) and lymphocytic choriomeningitis (LCM) virus infection during gestation, perinatal infections with cytomegalovirus (CMV) and Toxoplasma gondii, and sexually transmitted disease at the time of delivery were identified. Congenital EV71 infection was assessed in 1 case report study. This study reported on a 28-year-old woman with a diagnosis of EV71 infection during pregnancy, whose obstetric ultrasonograms at 25 weeks of gestation revealed mild fetal hydrocephalus, among other abnormalities. An LCM virus infection, a rarely detected congenital infection, was investigated in 1...
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case series study,\textsuperscript{29} in which 26 cases of LCM virus infection were identified. All 26 patients had hydrocephalus, documented by CT or MRI. One case-control study suggested an association between CMV or \textit{T. gondii} and CH, with estimated ORs of 3.78 and 10.6, respectively, for the association.\textsuperscript{23} Sexually transmitted disease at the time of delivery was associated with 1.2% of pregnancies in which the infant developed CH according to a cohort study.\textsuperscript{27} Nevertheless, none of the identified associations were statistically significant.

Lifestyle-Modifiable Maternal Pathologies

There is a significant association between the following pathologies—maternal hypertension, preeclampsia, and maternal diabetes (pregestational and/or gestational)—and CH, according to one of the cohort studies.\textsuperscript{27} In a second cohort study, maternal diabetes and preeclampsia were investigated as risk factors but these associations did not reach significance.\textsuperscript{19} Furthermore, prepregnancy obesity had a statistically significant association with CH in a meta-analysis study (OR 1.68).\textsuperscript{24}

Maternal Medication

Maternal exposure to several drugs has been implicated in CH, including vaginal metronidazole treatment during the 2nd and 3rd month of pregnancy, and first-trimester exposure to maternal use of antidepressants (primarily selective serotonin reuptake inhibitors [SSRIs]), proton pump inhibitors (PPIs), nitrosatable drugs, or tribenoside. Vaginal metronidazole treatment was assessed by a case-control study,\textsuperscript{15} which showed an association between vaginal metronidazole use during the 2nd and 3rd month of gestation and CH (OR 10.7, 95% CI 1.1–104.5). Use of antidepressants during pregnancy was assessed in a cohort study as a risk factor for CH.\textsuperscript{20}

### Table 2. Characteristics of the 13 studies included in the literature review

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Type of Study</th>
<th>Presumable Risk Factor</th>
<th>Pts Exposed</th>
<th>Pts w/ CH</th>
<th>Pts w/ CH</th>
<th>RR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarren et al., 1978</td>
<td>Case series</td>
<td>Alcohol used during pregnancy</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Olshan &amp; Faustman, 1989</td>
<td>Cohort</td>
<td>Nitrosatable drugs during pregnancy</td>
<td>6061</td>
<td>12</td>
<td>6921</td>
<td>5</td>
<td>2.48 (0.85–7.24)</td>
</tr>
<tr>
<td>Wright et al., 1997</td>
<td>Case series</td>
<td>LCM virus infection during gestation</td>
<td>26</td>
<td>3</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Swayze et al., 1997</td>
<td>Case series</td>
<td>Alcohol used during gestation</td>
<td>26</td>
<td>3</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Chow et al., 2000</td>
<td>Case report</td>
<td>Congenital EV71 infection</td>
<td>1</td>
<td>1</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Carmichael et al., 2002</td>
<td>Cohort</td>
<td>First prenatal care after 8th mo of pregnancy*</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Kazy et al., 2005</td>
<td>Case-control</td>
<td>Vaginal metronidazole treatment during 2nd &amp; 3rd mos of pregnancy*</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Smithe et al., 2009</td>
<td>Meta-analysis</td>
<td>Maternal obesity*</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Kubicek et al., 2011</td>
<td>Case-control</td>
<td>Tribenoside treatment during 2nd &amp; 3rd mos of pregnancy*</td>
<td>174</td>
<td>4</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Jeng et al., 2011</td>
<td>Cohort</td>
<td>Low socioeconomic status*</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Simeone et al., 2013</td>
<td>Case-control</td>
<td>1. \textit{T. gondii} infection 2. CMV infection</td>
<td>NE</td>
<td>1.2%</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Munch et al., 2014</td>
<td>Cohort</td>
<td>1. Antidepressants used during pregnancy* 2. SSRIs used during pregnancy* 3. PPIs used during pregnancy 4. Maternal diabetes</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

NE = nonextractable; Pts = patients; STI = sexually transmitted infection. * Statistically significant. Applied only in studies in which statistical significance can be defined (case series and case reports are excluded).
Maternal environmental risk factors for congenital hydrocephalus

study, which highlighted a significantly increased risk of CH in children exposed to antidepressants during the first trimester compared with unexposed children (relative risk [RR] 2.52). This association remained significant (RR 2.7) when SSRIs were assessed alone. The same cohort study assessed PPI use during pregnancy and found that the relative risk of CH in children with exposure to PPI use during the first trimester of gestation was 2.35 compared with unexposed children. Nonetheless, this risk was comparable to that for syndromic CH. Hence, this finding is not considered significant. Other drugs that have been associated with CH are nitrosatable drugs taken anytime during pregnancy, with an elevated RR (2.48) evaluated in a prospective cohort study. Tribenoside, a drug used for the treatment of hemorrhoids, was assessed in a case-control study showing an increased risk of CH if treatment was offered during the 2nd or 3rd gestational month.

Maternal Use of Alcohol and Illicit Drugs

Alcohol use during gestation and its influence on CH development was assessed in 3 studies. A retrospective cohort study and 2 case series studies indicated greater use of alcohol among pregnant women whose infants developed CH. Illicit drug use was suggested as a risk factor for CH in 1 retrospective study. Specifically, an association with illicit drug use was identified in 3.9% of pregnancies in which the infant developed CH; significance, nevertheless, was not reached.

Trauma to Mother During Gestation

One cohort study indicated that 3% of mothers whose infants developed CH suffered a severe trauma during gestation. However, this finding was not statistically important.

Prenatal Care

Prenatal care has been significantly associated with the development of CH in 2 cohort studies. Specifically, the complete lack of prenatal care is strongly associated with CH and initiating prenatal care after the 8th month of gestation is also related to the development of CH (OR 2.1).

Low Socioeconomic Status

A large population-based cohort study evaluated socioeconomic status as a risk factor. Demographic and clinical characteristics were compared between infants with and without CH, referring to a specific population subgroup during a determinate period of time. This study showed that there is a significantly increased risk of CH in infants with low socioeconomic status (OR 1.5, 95% CI 1.4–1.6).

Discussion

The epidemiological characteristics of hydrocephalus are not well explored and understood. Nevertheless, previous estimates on the incidence of CH indicate approximately 3 cases per 1000 live births in the US and an overall prevalence of 0.5%. Although several previous epidemiological, clinical, and experimental studies assessing various individual risk factors for CH have been conducted, given the high complexity of this entity and its several potential etiologies, a complex multifactorial (genetic and environmental) etiology may be responsible for any or all subtypes of hydrocephalus.

Given that CH is an important cause of serious infant health disability that can lead to health inequalities among adults, assessing and investigating extrinsic factors in the maternal environment that potentially confer an increased risk of CH development would be a crucial step in preventing some of these cases.

We have identified some of these risk factors. Maternal medication or alcohol use during gestation; lifestyle-modifiable maternal pathologies such as obesity, diabetes, or hypertension; lack of prenatal care; and a low socioeconomic status were identified as significant maternal environmental risk factors for CH development. Additional risk factors such as TBI to the mother or maternal infections were also assessed in previous studies, but their significance in the pathogenesis of CH was not established.

Regarding maternal medication, a striking finding is the significant association between first-trimester use of antidepressants (the SSRIs in particular) and CH development that was indicated in a large cohort study. Given the widespread use of SSRIs and the evidence for adverse maternal (e.g., an increased risk of pregnancy-induced hypertension) and neurodevelopmental effects, this finding and its underlying biological and/or behavioral parameters warrant further investigation. A study by Munch et al. in 2014 indicated that, unlike SSRIs, first-trimester exposure to PPIs does not confer a substantial risk for CH. Instead, deficiencies in maternal nutrition were postulated as indirect underlying mechanisms. Several other medications taken during particular times of pregnancy and via specific routes of delivery were shown by the present analysis to increase the risk of CH. Vaginal, unlike oral, metronidazole use during the 2nd and 3rd month of gestation was shown to be associated with CH in a case-control study. Nevertheless, the small number of hydrocephalic cases and the lack of data on other maternal infections or use of additional medications presented significant limitations of this study. Other medication use included nitrosatable drugs during the first 4 months of pregnancy and tribenoside during the 2nd and 3rd months of pregnancy. However, given the small number of detected cases in the latter 2 studies, the established associations should be interpreted cautiously. The significant association between alcohol exposure during pregnancy and CH that was consistently reported by several of the identified studies is somewhat unsurprising given its known teratogenic potential.

The present review incorporated studies assessing lifestyle-modifiable (and thus readily preventable) maternal pathologies and their impact on CH. Significant associations were shown for chronic maternal hypertension, maternal diabetes (pregestational and/or gestational), and preeclampsia in one large cohort study but not in a second cohort study. Obesity was significantly associated with CH in a meta-analysis. Given that obesity, the metabolic syndrome, and related pathologies are reaching pandemic proportions, their impact on the development of hydrocephalus warrants further confirmation under both clinical and experimental settings. Preeclampsia, a hypertensive

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disorder of pregnancy, is distinguished from other pathophysiological processes by raised serotonin levels—and the use of antidepressants, albeit during the second trimester, has been shown to increase its risk.3

Regarding congenital infections, the associations of congenital EV71 and LCM virus infections with CH were identified in a case-control and a case series study, respectively.6,27 Thus, these findings can only be regarded as indicators for future research. Nevertheless, of note is the fact that both pathogens have been previously implicated in hydrocephalus during development or adulthood under clinical or experimental settings.1,27 In a case-control study, prenatal CMV and T. gondii infections were considered as risk factors for CH, but these associations did not reach statistical significance.23 The lack of significance was attributed to the limited number of analyzed samples and their quality, or to the relatively small proportion of cases that is related to these infections. In this context, it is worth noting that a recent study suggests an association between congenital T. gondii infection and specific anatomical patterns of CH,12 whereas a meta-analysis of fetal ultrasound findings indicates an association between CMV congenital infection and hydrocephalus (in 4.7% of pregnancies).4

Maternal sexually transmitted infection at the time of delivery was assessed by 1 study but no significant association was established.27 Two additional factors showing significant associations with CH development were related to prenatal care and socioeconomic status. Thus, complete lack of prenatal care significantly increased CH risk in the large cohort study published by Van Landingham et al. in 2008.8 A second large cohort study indicated that lack of early prenatal care, which is significantly associated with CH, may represent a general indicator of the social environment indirectly affecting maternal behavioral and exposure patterns rather than a mechanistic factor.1 In this context, it is noteworthy that a low socioeconomic status has been shown to significantly increase the risk of CH by a third large cohort study.14

Certain putative limitations of the present analysis need to be acknowledged. One such limitation concerns the heterogeneous nature of inclusion criteria for CH provided by the studies included in this review. Our intention was to exclude studies addressing CH with an established genetic basis, thus focusing on environmental risk factors. However, it should be pointed out that a complex multifactorial (genetic and environmental) etiology has been proposed as the basis for any or all subtypes of CH,6,26 and that genetic screening in patients with CH is typically initiated in the presence of major concurrent clinical findings.6 The 13 studies included in this systematic review have highlighted important factors associated with an increased risk of CH development. Nevertheless an additional point that needs to be made is that, aside from 1 meta-analysis,25 5 large cohort studies,2,5,13,18,20,26 and 3 case-control studies,4,10,15,17 the remaining evidence was drawn from 3 case series and 1 case report. Moreover, even in the large-scale cohort and case-control studies, assessment of individual risk factors for CH was based on a limited number of cases. Thus, the aforementioned findings should be interpreted cautiously and regarded as possible future avenues of research under epidemiological, clinical, and preclinical settings.1,10,15,20,30

Conclusions

The present study identified several maternal environmental risk factors for CH. Maternal medication or alcohol use during gestation; lifestyle-modifiable maternal pathologies such as obesity, diabetes, or hypertension; lack of prenatal care; and a low socioeconomic status were identified as significant maternal environmental risk factors for CH development. Other lines of evidence suggest that maternal infections and trauma to the mother during pregnancy represent additional potential risk factors. A better understanding of the impact of these factors in CH development and their underlying behavioral and/or biological mechanisms is warranted to firmly establish the identified associations and allow for future prevention strategies.

References

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Kalyvas, Kalamatianos. Acquisition of data: Kalyvas, Kalamatianos, Pantazi. Analysis and interpretation of data: Kalyvas, Pantazi. Drafting the article: Kalyvas, Pantazi, Lianos. Critically revising the article: Kalamatianos, Lianos, Stranjalis, Alexiou. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kalyvas. Study supervision: Stranjalis, Alexiou.

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