

Meta-analysis of subchorionic hemorrhage and adverse pregnancy outcomes

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Key Words: subchorionic hemorrhage, pregnancy, ultrasonography, bleeding, systematic review

Abstract

The purpose of this study was to determine whether subchorionic hemorrhage is associated with increased adverse pregnancy outcomes of preterm delivery, spontaneous abortion, and abruption. PUBMED databases were searched for case control, cohort, and cross-sectional human studies that investigated the relationship of ultrasound-detected subchorionic hemorrhage and adverse outcomes of preterm delivery, spontaneous abortion, and abruption. Data were extracted by two independent investigators. Nine studies were included in the pooled meta-analysis. Relative risk estimates (RR) and 95% confidence intervals (CI) were pooled across studies. Subchorionic hemorrhage was associated with preterm delivery (pooled RR = 1.64; 95% CI 1.41-1.89), spontaneous abortion (pooled RR = 2.59; 95% CI 2.34-3.25), and abruption (pooled RR = 3.16; 95% CI 2.32 – 4.31). This study suggests that early pregnancy subchorionic hemorrhage may increase the risk of preterm delivery, spontaneous abortion, and abruption. Women may be advised of increased adverse outcomes associated with subchorionic hemorrhage.

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Introduction

Ultrasonographic detection of subchorionic hemorrhage during pregnancy (especially in those with first trimester bleeding) is a relatively common finding. The incidence rate has been reported between 1.3-62% depending on the patient population that was studied.^{1,2,3,4} A number of studies have investigated the association between the presence of subchorionic hemorrhage and adverse pregnancy outcomes. Nonetheless, the clinical significance of subchorionic hemorrhage and its effect on pregnancy outcomes remains controversial.

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Previously published studies show conflicting results. Some investigators have found associations between subchorionic hemorrhage and multiple adverse pregnancy outcomes, including preterm labor, spontaneous abortion, abruption, intrauterine growth restriction, intrauterine fetal demise, preeclampsia, and preterm rupture of membranes,^{1,2,4-8} while others have found no association.^{3,9} In addition, none of the prior studies controlled for other well known risk factors for adverse pregnancy outcomes, such as prior preterm labor, obesity, trauma, advanced age, chronic hypertension, and fetal chromosomal abnormalities. These inconsistent results combined with low quality investigations have made it challenging for clinicians to provide appropriate counseling to pregnant mothers with subchorionic hemorrhage regarding the risks to the pregnancy.¹⁰

The objective of this study was to perform a meta-analysis of all available literature from observational studies to resolve conflicting reports of the association between subchorionic hemorrhage and adverse pregnancy outcomes. This analysis focused on the most frequently reported adverse outcomes associated with subchorionic hemorrhage: premature delivery, spontaneous abortion, and abruption.

Methods for Review

Literature Search

PUBMED databases were searched for articles with keywords related to “subchorionic hemorrhage”, “first trimester”, “pregnancy”,

“ultrasonography”, and “bleeding”, and were limited to human subjects. Cohort, case-control, and cross-sectional studies were considered eligible for this meta-analysis if they compared subchorionic hemorrhage to adverse pregnancy outcomes of preterm delivery, spontaneous abortion, and/or abruption. References of extracted articles and review articles were also searched. This search was repeated on PUBMED for articles published between January 1981 and July 2011. Titles and abstracts from 40 articles were screened to exclude case reports, commentaries or editorials, and animal studies. If eligibility was unclear, the article was reviewed in detail. An abstraction form summarizing study design, study population, variable definitions, and relevant raw and adjusted data was completed for each article. Among the initial 40 articles published in English, 9 studies met eligibility requirements and reported outcome data of preterm delivery, spontaneous abortion, and abruption. Studies were excluded if they were case reports (n=6), case series (n = 20), and/or reviews (n = 5). Among the included studies, all either reported results for “ever” vs. “never”, or contained data that allowed computation for “ever” vs. “never” preterm delivery, spontaneous abortion, or abruption and exposed to subchorionic hemorrhage.

Data Extraction

Data were abstracted that pertained to reported study design, definitions listed for subchorionic hemorrhage, hematoma volume descriptions, adverse pregnancy outcomes of preterm delivery (defined as the number of preterm births before 37 weeks of gestation),

spontaneous abortion, abruption, and statistical analysis. Two independent reviewers abstracted data for each article and the two sets of data were compared for agreement. Inconsistencies were re-reviewed three times for consensus. The author was responsible for final decisions on disagreements. Covariate adjusted estimated relative risks (RRs) were utilized in the meta-analysis when reported, under the assumption that the data were properly adjusted for confounders. When available, the variances were calculated based on the reported confidence intervals (CIs) from adjusted models. Otherwise, the natural log of the RR and its variance was calculated from reported data.¹¹ For studies that did not report RRs and CIs, crude estimates were calculated based on the distribution of cases and controls reporting percentages among the relevant adverse outcomes. All studies were included in the primary analysis. Because two studies included both subchorionic hemorrhage and retroplacental hemorrhage in the evaluation of adverse pregnancy outcome, a separate analysis was performed on studies that limited their analysis to subchorionic hemorrhage.

Statistical Analysis

For dichotomous factors, both fixed-effects and random-effects models were utilized to obtain pooled RR and 95% CIs.^{11,12} Fixed-effects models assume that risk is homogeneous across included studies, while random-effects models assume that the risks are random draws from a more heterogeneous set of studies. Therefore, random-effects models are more conservative and lead to conclusions

about all studies in the hypothetical population of studies.^{11,12} Statistical tests of heterogeneity were performed to assess the appropriateness of fixed-effects analysis.¹² Estimates from fixed- and random-effects models were similar when heterogeneity tests were non-significant ($p > 0.20$). Because the primary interest was adverse outcomes associated with subchorionic hemorrhage, after completing the primary pooled analysis, two studies that combined retroplacental hemorrhage and subchorionic hemorrhage were excluded and the pooled analysis was subsequently repeated.

Results

Characteristics of the pooled studies and populations studied are detailed in Table 1.¹⁻⁹ All articles were ultrasonographic cohort studies. Five studies similarly defined subchorionic hemorrhage as evidence of fluid dissecting the chorionic membrane away from the myometrium at a position removed from the placenta.^{1,2,5,6,9} Two studies combined retroplacental hemorrhage and subchorionic hemorrhage,^{2,4} while two other studies failed to include a definition of subchorionic hemorrhage.^{3,4}

In four studies,^{1,2,3,5} the volume of the hematoma was related to the outcome of the pregnancy. Each of these investigations measured volume using different techniques and definitions. One assessment found that patients with hematoma greater than 60 ml had increased risk of preterm delivery.⁵ A second study reported that large subchorionic hemorrhages (at least 25% of the size of the gestational sac) as

compared to small subchorionic hemorrhages ($\leq 5\%$ of the size of the gestational sac) were associated with increased risk of stillbirth, and total

adverse outcome.¹ Nagy et al,² and Pedersen et al,^{2,3} found no association between the size of the hematoma and adverse outcome.

Table 1: Clinical outcome of pregnancies complicated by subchorionic hemorrhage

Author, year, country	Gestational age in (weeks)	Cases with SCH N	Control Group N	Outcomes of Pregnancy		Comments
				Cases with SCH N (%)	Control Group N (%)	
Ball et al, 1996, USA	5 – 22	238 *	648 (- VB)*	8 (3) PTD 16 (7) SA 8 (3) A	20 (97) PTD 13 (2) SA 2 (.03) A	No association between SCH & PTD Larger SCH associated with increased odds of total adverse outcome & stillbirth
Nagy et al, 2003, Hungary	5-12	187	6488	30 (16) PTD 9 (5) A	459 (7) PTD 56 (.009) A	No association between size of hematoma and adverse outcome
Pedersen et al, 1990, Denmark	9 – 20	62	280	7 (11)PTD 7 (11) SA	32 (11) PTD 28 (10) SA	No association between size of hematoma and adverse outcome
Ylostalo et al, 1984, Finland	12-33	16	10	5 (31) A	1 (10) A	Median duration of pregnancy shorter in patients with a hematoma (34 vs. 39 weeks). Included 2 cases with retroplacental hematoma
Johns et al, 2003, UK	5-14	51	78	5 (9) PTD 1(2) A	6 (8) PTD 2(3) A	
Sauerbrei et al, 1986, Canada	10-20	30	30	7 (23) PTD 3 (10) SA	3 (10) PTD 0 (0) SA	Hematoma > 60 ml increased risk of PTD
Borlum et al, 1989, Denmark	9 – 24	80	286	7 (9) PTD 13 (16) SA	16 (6) PTD 16 (6) SA	Volume of SCH was < 30 ml in 85% of the patients
Goldstein et al, 1983, USA	9 – 16	10	40	2 (2) SA	0 (0) SA	Size of SCH not related to pregnancy outcome
Norman et al, 2010, USA	17 – 22	1081	63966	168 (16) PTD** 39 (4) A	6603 (11) PTD** 377 (.006) A	

N = number of studies, SCH = subchorionic hemorrhage, VB = vaginal bleeding, PTD = preterm delivery, SA = spontaneous abortion, A = abruption

*Analysis of PTD < 36 weeks & control group without vaginal bleeding

** Analysis of PTD < 37 weeks

Table 2: Pooled relative risk estimates for subchorionic hemorrhage and adverse pregnancy outcomes

<i>Adverse Outcome</i>	<i>N</i>	<u>Fixed-Effects Model</u>			<u>Random- Effects Model</u>	
		<i>RR</i>	<i>95% CI</i>	<i>Homogeneity p-value</i>	<i>RR</i>	<i>95% CI</i>
Preterm Delivery						
All studies	7	1.64	1.41-1.89	0.2841	1.67	1.32-2.10
Excluding those with retroplacental hemorrhage	6	1.53	1.31-1.79	0.7918	1.53	1.31-1.79
Spontaneous Abortion						
All studies	5	2.59	1.78-3.76	0.1843	2.60	1.48-4.54
Abruption						
All studies	5	3.16	2.32-4.31	0.0993	3.85	2.0-7.42
Excluding those with retroplacental hemorrhage	3	2.73	1.93-3.86	0.1159	3.22	1.05-9.88

Two studies stratified preterm deliveries into two different categories:¹ 1) < 34 weeks and < 37 weeks;² or 2) < 30 weeks and < 36 weeks.^{1,8} Only those groups close to the general definition of preterm delivery (< 37 weeks) were included in the pooled analysis. Table 2 reports the pooled estimated RRs for adverse outcomes using both fixed- and random-effects models for all studies. Also included are the pooled estimated RRs for adverse outcomes after restricting the two studies that combined subchorionic hemorrhage and retroplacental hemorrhage. Preterm delivery rates were reported in 7 of the 9 studies.^{1-3,6,8,9} Figure 1 presents the individual study and pooled estimates for preterm delivery rates using the fixed-effects model. This analysis reveals a significantly increased estimated RR of preterm delivery associated with subchorionic hemorrhage (RR = 1.64; 95% CI = 1.41-1.89).

Spontaneous abortion rates were reported in five of the nine studies.^{1,2,5-7} Each investigation reported increased percentages of spontaneous abortion in the cases with subchorionic hemorrhage as compared to the control groups. Figure 2 presents the pooled estimated RR for the rate of spontaneous abortion using the fixed-effects model (RR = 2.59, 95% CI = 1.78-3.76). Data for abruption rates were available in five of the nine studies.^{1,2,4,8,9} Figure 3 presents individual and the pooled estimated RR for the rate of abruption in the cases using the fixed-effects model (RR = 3.16; 95% CI 2.32 – 4.31).

When the analysis was restricted to studies where exposure to subchorionic hemorrhage was reported without including retroplacental hemorrhage, the pooled fixed-effects estimated RRs for subchorionic hemorrhage and preterm delivery decreased from 1.64 to 1.53 (n = 6; heterogeneity p = 0.79); and the pooled RRs for sub-chorionic hemorrhage and abruption decreased

from 3.16 to 2.73 (n = 3, heterogeneity p = 0.12). Analyses of spontaneous abortion were not affected.

Comment

The pooled analyses clarify the magnitude of association between subchorionic hemorrhage and increased risk of preterm labor, spontaneous abortion, and abruption. Study results revealed that women with subchorionic hemorrhage had a greater than 2-fold increase in spontaneous abortion, and a greater than 3-fold increase in the risk of abruption. The RR of preterm delivery was 1.5-times greater in women with subchorionic hemorrhage as compared to controls. Furthermore, even with the analysis restricted to studies that did not

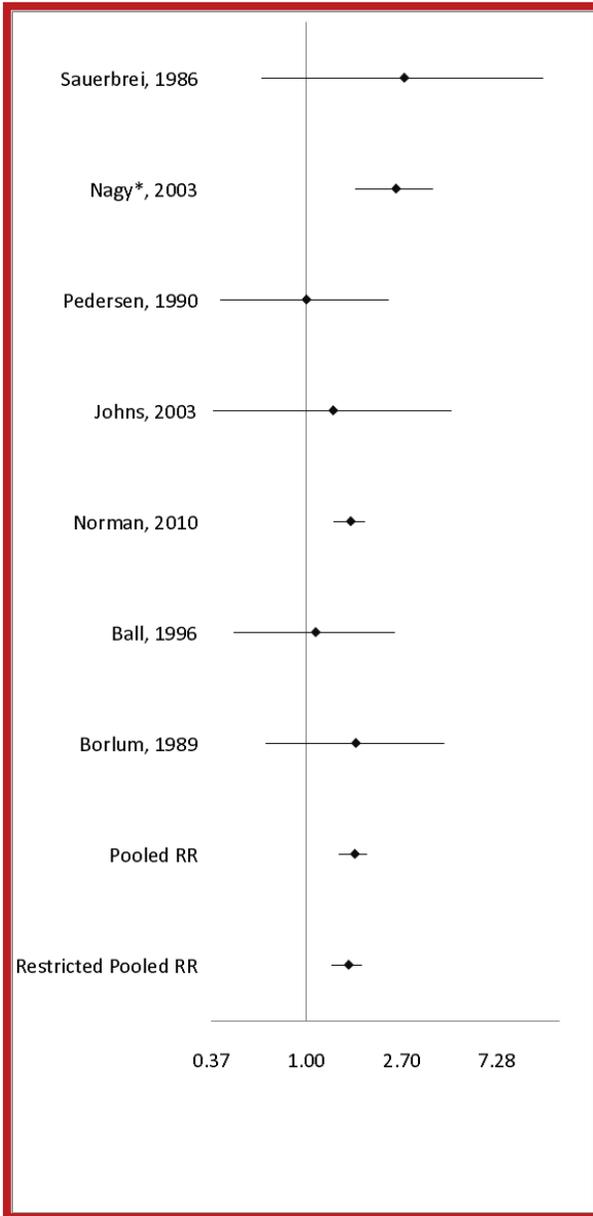


Figure 1: Forest plot of the association of subchorionic hemorrhage and preterm delivery estimated relative risks and 95% confidence intervals by study.

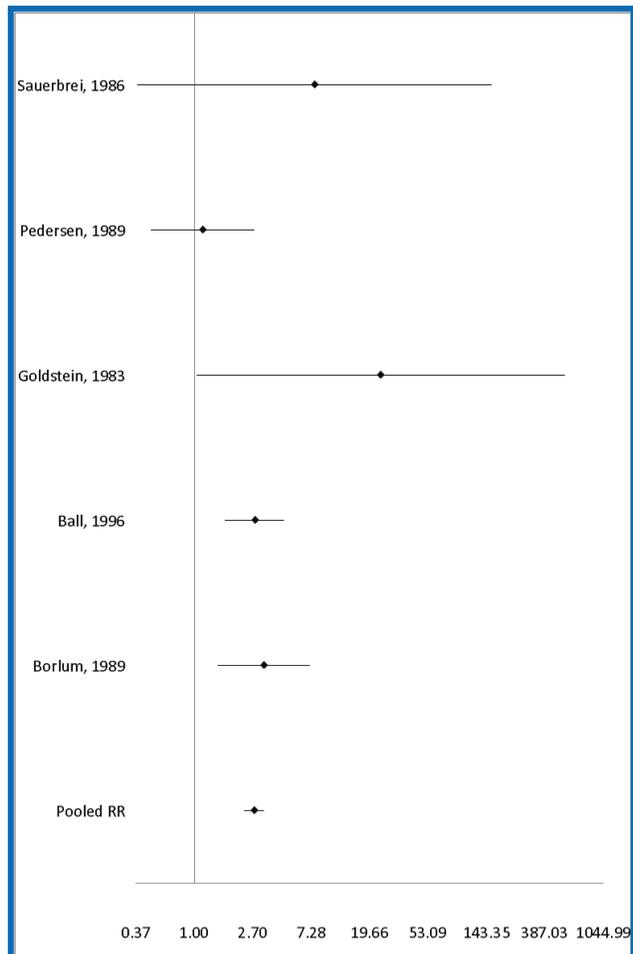


Figure 2: Forest plot of the association of subchorionic hemorrhage and spontaneous abortion estimated relative risks and 95% confidence intervals by study.

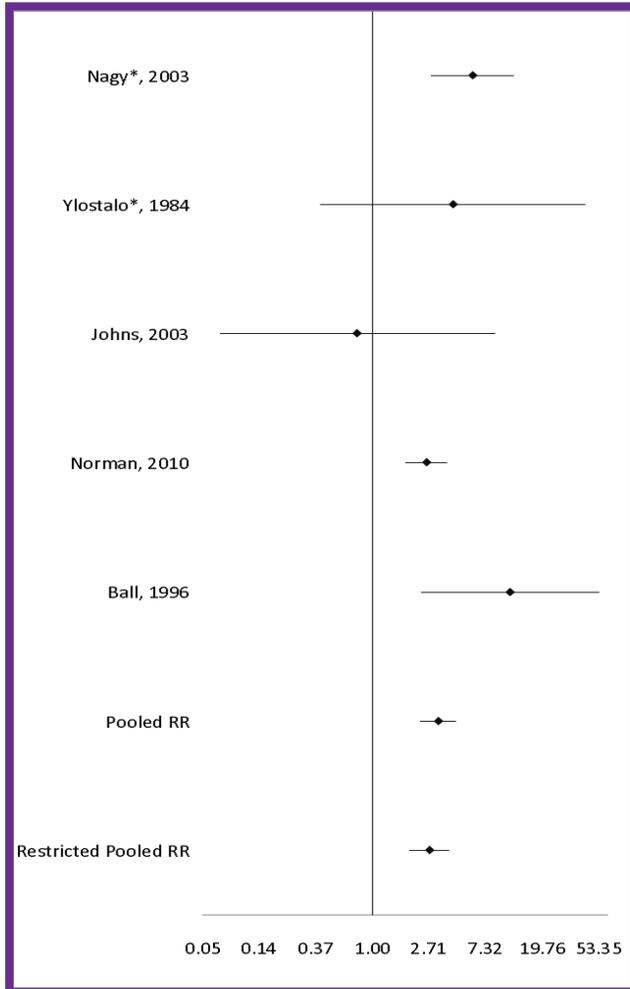


Figure 3: Forest plot of the association of subchorionic hemorrhage and abruption estimated relative risks and 95% confidence intervals by study.

only in comparison to the control group without vaginal bleeding, yet the analysis included control groups with and without vaginal bleeding. In addition, among the nine studies analyzed, there are several issues with inconsistent definitions of subchorionic hemorrhage, hematoma volume discrepancies, and variations in outcome measures. The early studies focused primarily on the adverse outcome of spontaneous abortion. Among these studies, there are discrepancies in the definition of spontaneous abortion. Some evaluated only first trimester or second trimester abortion, while others examined fetal loss at any gestational period. For the purposes of this meta-analysis, spontaneous abortion was included as a dichotomous event that may have occurred in the first or second trimester.

Prior literature has suggested that larger hematomas are associated with increased risk of preterm delivery, but this association could not be analyzed since only three studies conducted analysis of subchorionic hemorrhage volume, and none of these studies defined volume in the same manner. In addition, multiple studies stratify preterm delivery into two or more different groups based on gestational weeks gained prior to delivery, thereby making the results more difficult to interpret and more difficult to pool for analysis. In an attempt to reduce selection bias, for this meta-analysis, preterm delivery groups were included that were closer to term gestational age.

Two studies included both subchorionic hemorrhage and retroplacental hematoma in the inclusion criteria and reported the combined adverse

include retroplacental hematomas, exposure to subchorionic hemorrhage had a significant effect on both preterm delivery and abruption.

Several inconsistencies were identified among the studies. Two studies used as controls women with vaginal bleeding and no subchorionic hematoma,^{3,9} while others used asymptomatic women or both. Ball et al.¹ found a significant relative risk of spontaneous abortion

pregnancy outcome results.^{2,4} The presence of a retroplacental hematoma may create an area of weakness for placental abruption to occur, thereby confounding the results of the analysis. After restricting the analysis to only those studies that did not include retroplacental hematomas, the estimated RR of abruption was still highly significant at 2.73, and is therefore not likely due to bias.

A prior systemic review published in 1993 by Pearlstone et al.,¹³ included 14 studies, of which only five had controls. Without performing meta-analysis, the authors concluded that subchorionic hemorrhage was associated with spontaneous abortion and preterm delivery. The authors noted the limitations of the prior studies, including the fact that five of the studies were without control groups. To improve validity, only studies with controls were included in this study, and meta-analyses were performed in order to pool RR estimates. All known studies were combined in order to increase power and to achieve a more precise risk estimate for the adverse pregnancy outcomes.

Despite these strengths, meta-analyses are dependent on the quality of the individual studies, individual review, and publication bias. While a rigorous literature review was performed to identify all eligible studies, it is possible that some studies were missed including unpublished studies. In addition, several of the studies used in the meta-analysis were conducted during the early stages of obstetrical ultrasound technology.³⁻⁷ Imaging interpretation was more difficult in these early studies as compared to more recent studies, and may have led

to misclassification bias of cases. Additionally, the differences in definitions of the study populations and eligible subjects described above may have added to the heterogeneity between studies.

Conclusion

In summary, this meta-analysis indicates that subchorionic hemorrhage is significantly associated with increased risk of preterm delivery, spontaneous abortion, and abruption. Although there are no specific management interventions to prevent the adverse outcomes, based on this meta-analysis, women with subchorionic hemorrhage should receive more precise counseling as to the risks to their pregnancy and should be instructed to notify their physicians of early warning symptoms such as vaginal bleeding, cramping, and abdominal pain.

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