

ASSOCIATIONS OF ACETYLSALICYLIC ACID,
LOW-MOLECULAR-WEIGHT HEPARIN AND
NATTOKINASE USE WITH THE PRESENCE AND SIZE OF
SUBCHORIONIC HEMATOMA IN A PROSPECTIVE
COHORT

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Abstract

Subchorionic hematoma (SCH) is a frequent ultrasound finding in early pregnancy and may be associated with adverse obstetric outcomes, particularly when larger hematomas are present. In routine practice, SCH is sometimes diagnosed in women receiving antiplatelet or anticoagulant therapy, or supplements with potential effects on haemostasis, for other clinical indications. The aim of this study was to assess the association of acetylsalicylic acid 150 mg (ASA), low-molecular-weight heparin (LMWH) and Nataspin (nattokinase-containing supplement) use with the presence of SCH and with SCH size categories. This prospective observational cohort included 462 pregnant women examined between December 2020 and July 2025: 282 controls without SCH and 180 women with SCH. Hematoma size was available in 178 women with SCH and was categorized as small (0.6–1.4 cm; $n = 60$), medium (1.5–2.7 cm; $n = 72$) or large (2.8–5.8 cm; $n = 46$). ASA 150 mg was more frequent among women with SCH than among controls (23.3% vs. 5.7%, $p < 0.001$). LMWH use was also more common in the SCH group (11.1% vs. 1.4%, $p = 0.001$), whereas Nataspin was less frequent (2.2% vs. 23.4%, $p < 0.001$). Among women with SCH, ASA use increased with hematoma size (10.0%, 22.2%, and 43.5% in small, medium and large SCH, respectively; $p = 0.017$). LMWH was

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not associated with size category. The results should be interpreted as observational associations, since treatment allocation was influenced by clinical indications.

Key words: subchorionic hematoma, acetylsalicylic acid, ASA, low-molecular-weight heparin, nattokinase, pregnancy, hematoma size

Introduction. Subchorionic hematoma (SCH) is a collection of blood between the chorion and the uterine wall and is one of the most common sonographic findings in women presenting with bleeding during early pregnancy [1–3]. Its reported frequency varies according to the studied population, gestational age at diagnosis and symptom status. Several cohort studies and meta-analyses have linked SCH with a higher risk of pregnancy loss, preterm birth and placental complications, while hematoma size and sonographic features may modify the magnitude of this risk [4–8, 16–18].

At the same time, antiplatelet and anticoagulant prophylaxis are widely used in contemporary obstetric practice in women with thrombophilia, antiphospholipid syndrome, previous obstetric complications, assisted reproduction or increased risk of pre-eclampsia [9–11]. Low-dose acetylsalicylic acid is considered safe during pregnancy when used for appropriate indications [10], and low-molecular-weight heparin (LMWH) is recommended for prevention or treatment of venous thromboembolism in pregnancy when indicated [11]. Nevertheless, when SCH is detected, a frequent practical question is whether such therapy should be continued, reduced or temporarily withheld, especially in the presence of active bleeding or a larger hematoma. An additional uncertainty concerns nattokinase-containing supplements, for which obstetric evidence is limited despite described fibrinolytic and hemorheological properties in non-obstetric contexts [12–14].

The aim of the present study was to evaluate whether ASA, LMWH and Nataspin use are associated with the presence of SCH and with hematoma size categories.

Material and methods. This analysis was based on a prospective observational cohort conducted between December 2020 and July 2025. Two groups were formed: a control group without SCH ($n = 282$) and a group with SCH ($n = 180$). SCH was diagnosed by ultrasound examination in early pregnancy (Fig. 1). Women with a live embryo/fetus at the time of diagnosis and available follow-up according to the criteria of the dissertation protocol were included.

For size-based analysis, the maximum measured hematoma diameter in centimetres was used. Size data were available for 178 of the 180 women with SCH. Hematomas were categorized as small (0.6–1.4 cm; $n = 60$), medium (1.5–2.7 cm; $n = 72$) and large (2.8–5.8 cm; $n = 46$).

The analysed exposures were ASA 150 mg, LMWH (Fraxiparine/Clexane) and Nataspin (nattokinase-containing supplement), recorded as binary variables (yes/no) in the available dataset. Categorical variables were compared with the

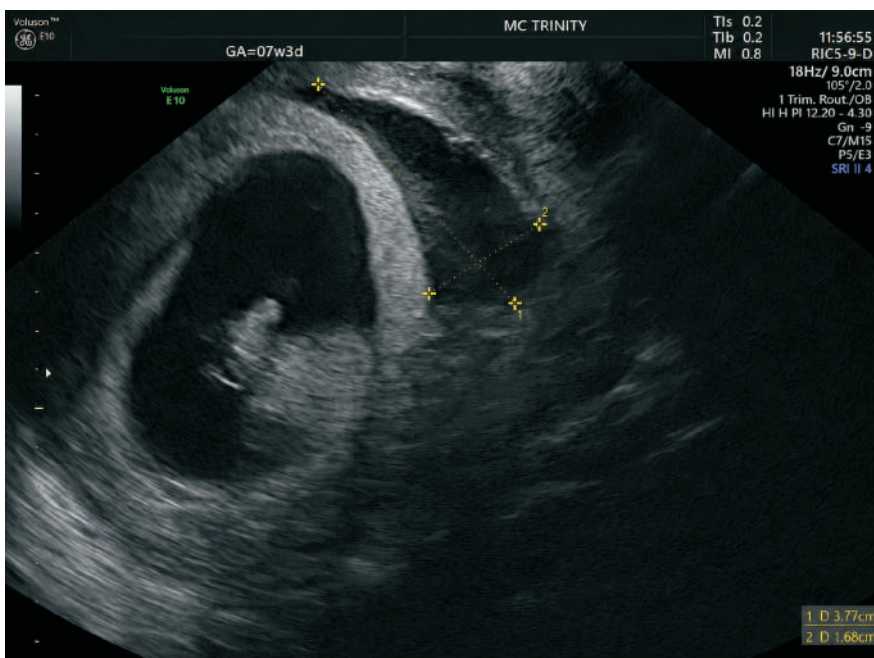


Fig. 1. Sagittal transvaginal ultrasound image of the uterus showing a subchorionic hematoma in a patient at 7+3 gestational weeks (personal archive)

chi-square test or Fisher's exact test when expected frequencies were small. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software.

Ethical considerations. The analysis was performed as part of a prospective observational dissertation protocol. No intervention beyond routine clinical care was performed. Patient data were anonymized before statistical analysis, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Results. The total analysed sample included 462 pregnant women, of whom 282 were controls without SCH and 180 had SCH. Mean maternal age was higher in the SCH group than in controls (32.01 ± 5.85 years, $n = 178$, vs. 28.25 ± 5.62 years, $n = 282$; $p < 0.001$). In the size-based SCH analysis, larger hematomas were more frequently observed in women older than 35 years ($p = 0.022$).

The use of ASA differed significantly between groups. ASA therapy was recorded in 42/180 women with SCH (23.3%) compared with 16/282 controls (5.7%; $p < 0.001$). LMWH was also more frequent in the SCH group (20/180, 11.1%) than in controls (4/282, 1.4%; $p = 0.001$). The opposite pattern was observed for Nataspin: it was recorded in 4/180 women with SCH (2.2%) and in 66/282 controls (23.4%; $p < 0.001$) (Table 1).

T a b l e 1

Use of ASA 150 mg, low-molecular-weight heparin and Nataspin according to SCH status

Variable	No SCH ($n = 282$)	SCH ($n = 180$)	p value
ASA 150 mg	16 (5.7%)	42 (23.3%)	< 0.001
LMWH	4 (1.4%)	20 (11.1%)	0.001
Nataspin	66 (23.4%)	4 (2.2%)	< 0.001

SCH, subchorionic hematoma; LMWH, low-molecular-weight heparin.

Among women with SCH and available size measurements, ASA use increased with hematoma size. ASA was recorded in 6/60 women with small SCH (10.0%), 16/72 with medium SCH (22.2%) and 20/46 with large SCH (43.5%). The association across size categories was statistically significant ($p = 0.017$). LMWH use did not show a significant association with SCH size (6.7%, 16.7% and 8.7% in small, medium and large hematomas, respectively; $p = 0.398$). Nataspin use in the SCH group was observed only among women with small hematomas (4/60, 6.7%), with no cases among medium or large hematomas. Because of the low number of exposed cases, this finding is best interpreted descriptively rather than as evidence of a treatment effect (Table 2).

T a b l e 2

Use of ASA 150 mg, low-molecular-weight heparin and Nataspin according to hematoma size among women with SCH

Variable	Small SCH ($n = 60$)	Medium SCH ($n = 72$)	Large SCH ($n = 46$)	p value
ASA 150 mg	6 (10.0%)	16 (22.2%)	20 (43.5%)	0.017
LMWH	4 (6.7%)	12 (16.7%)	4 (8.7%)	0.398
Nataspin	4 (6.7%)	0	0	descriptive

Size categories: small 0.6–1.4 cm, medium 1.5–2.7 cm, large 2.8–5.8 cm.

Discussion. The present analysis demonstrates different patterns of acetylsalicylic acid exposure, LMWH and Nataspin use in women with and without SCH, and different associations with hematoma size among women in whom SCH was present. The main findings are that ASA and LMWH were more commonly recorded in women with SCH, whereas Nataspin was substantially less common. Among women with SCH, ASA use increased with hematoma size, while LMWH showed no statistically significant association with size category.

These results require cautious interpretation. The study is observational and can identify associations but cannot establish causality. In routine clinical practice, ASA and LMWH are usually prescribed because of underlying risk factors, such as thrombophilia, previous reproductive or obstetric complications, assisted

reproduction or increased pre-eclampsia risk. Therefore, the higher frequency of these therapies in the SCH group may partly reflect a higher baseline risk profile rather than a direct causal effect of therapy on hematoma formation. The higher maternal age observed in the SCH group supports the possibility of confounding.

The size gradient observed for acetylsalicylic acid is clinically relevant. It may represent selection of higher-risk women into ASA therapy, differences in management after hematoma detection, or a true relationship that cannot be disentangled in the present dataset. A previous study in a reproductive medicine population reported a higher frequency of SCH among women taking low-dose aspirin [15], which is consistent with the direction of the present association. However, the current data do not justify a general recommendation to stop ASA automatically after SCH is detected. Such decisions should depend on the indication for ASA, the severity of bleeding, hematoma dynamics and the overall obstetric risk.

LMWH was more frequent among women with SCH than among controls, but it was not associated with hematoma size. This pattern suggests that LMWH may act mainly as a marker of clinical indication and baseline risk rather than as a factor related to hematoma enlargement. Nataspin showed the opposite distribution, being rare among women with SCH and absent in medium and large hematomas. The most plausible explanation is cautious clinical behaviour and avoidance of nattokinase-containing supplements when bleeding or hematoma is present. Although nattokinase has reported fibrinolytic properties [12–14], obstetric safety data are insufficient and no causal conclusion can be drawn from the present analysis.

The study has several limitations. Two women with SCH lacked size measurements and were excluded from the size-based analysis. The number of Nataspin-exposed women with SCH was small, limiting statistical interpretation. Detailed information on the indication for each therapy, timing of initiation, dose adherence and therapy modification after SCH diagnosis was not included in the present analysis. Despite these limitations, the findings are clinically relevant because they reflect real-world decision-making in early pregnancy.

Conclusion. In this prospective cohort, ASA and LMWH were significantly more frequent among women with SCH, whereas Nataspin use was significantly less frequent. Among women with SCH, ASA use increased with hematoma size, while LMWH was not associated with size category. Nataspin was recorded only in small hematomas. These findings describe associations observed in routine clinical practice and are likely influenced by clinical indications and baseline risk profile. The practical implication is that SCH in a woman receiving antithrombotic therapy requires individualized assessment rather than automatic discontinuation of all therapy.

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