

# **Recurrent unexplained first-trimester miscarriage. Effects of acetylsalicylic acid, platelet aggregation and thyroid disease.**

Akademisk avhandling

som för avläggande av medicine doktorexamen vid Sahlgrenska akademien,  
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av

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## *Avhandlingen baseras på följande delarbeten*

- I. **Blomqvist L, Hellgren M, Strandell A.** 2018. Acetylsalicylic acid does not prevent first-trimester unexplained recurrent pregnancy loss: A randomized controlled trial. *Acta Obstet Gynecol Scand.* 2018;97:1365-1372.
- II. **Blomqvist L, Strandell A, Baghaei F, Hellgren M.** 2019. Platelet aggregation in healthy women during normal pregnancy - a longitudinal study. *Platelets.* 2019;30:438-444.
- III. **Blomqvist L, Strandell A, Jeppsson A, Hellgren M.** Platelet aggregation during pregnancy in women with previous recurrent first-trimester fetal loss, with and without acetylsalicylic acid treatment. Submitted.
- IV. **Blomqvist L, Filipsson Nyström H, Hellgren M, Strandell A.** Preconceptual thyroid peroxidase antibody positivity in women with recurrent pregnancy loss may be a risk factor for another miscarriage. In manuscript.

**SAHLGRENKA AKADEMIN  
INSTITUTIONEN FÖR KLINISKA VETENSKAPER**



# Recurrent unexplained first-trimester miscarriage. Effects of acetylsalicylic acid, platelet aggregation and thyroid disease.

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**Background/Aims:** Recurrent pregnancy loss (RPL) occurs in 1-2% of fertile couples and about 50% of cases are unexplained. Impaired placental circulation, increased platelet aggregation, immunological factors and thyroid autoimmunity have been suggested to be involved. Other placenta-mediated complications have been reduced by inhibition of platelet aggregation with acetylsalicylic acid (ASA). The effect of ASA on RPL has been unclear. These studies aimed at investigating the effect of ASA treatment on RPL and arachidonic acid (AA)-induced platelet aggregation in women with RPL, as well as the effect of thyroid function by analyzing Thyroid Stimulating Hormone (TSH) and thyroid peroxidase antibodies (TPO-ab).

**Methods:** Women (n=640) with at least three unexplained first-trimester miscarriages were screened for inclusion in a single-center, randomized, placebo-controlled trial (the ASA-RCT, Paper I). Four hundred women were given either 75 mg ASA or placebo daily, beginning at gestational week (gw) 6-7, when fetal heartbeat was detected by vaginal ultrasound. Treatment ended at the latest at gw 36. Treatment compliance was determined by analysis of AA-induced platelet aggregation using multiple electrode impedance aggregometry. All women underwent the same follow-up. Primary outcome was live birth rate (LBR).

In order to define reference values for the multiple electrode impedance aggregometry (the Multiplate analyzer), a longitudinal study was conducted including 79 healthy, non-smoking pregnant women with normal pregnancies (Paper II). Platelet aggregation induced by AA, adenosine diphosphate (ADP), thrombin receptor activating peptide 6 (TRAP) and collagen (COL) were determined four times during pregnancy and three months postpartum.

From the randomized population, 176 and 177 women, respectively, with normal AA-induced platelet aggregation before pregnancy and treated with ASA or placebo, were studied (Paper III). Platelet aggregation was determined before and during pregnancy and results in the randomized groups were compared with one another, as well as with those in the healthy controls from Paper II.

From the screened and eligible population, 495 women with complete thyroid test analyses [thyroid stimulating hormone (TSH), free thyroxine (T4) and thyroid peroxidase antibodies TPO-ab] before pregnancy were included. Risk factors for a new miscarriage were studied, in particular associations with TPO-ab and TSH in the upper normal range.

**Results:** In the ASA-RCT, all 400 randomized women completed the follow-up. LBR were 83.0% and 85.5% in the ASA and placebo groups, respectively. The mean difference was -2.5% (95% CI to -10.1% to 5.1%). The risk ratio was 0.97 (95% CI 0.89 to 1.06).

In the longitudinal study of platelet aggregation during normal pregnancy, activation of platelets by AA, ADP and TRAP resulted in a minor decrease in platelet aggregation during pregnancy, compared with postpartum. COL-induced platelet aggregation was unchanged. A minor increase in platelet aggregation as pregnancy continued was found related to ADP.

There were no significant differences in AA-induced platelet aggregation when placebo-treated women with RPL were compared with healthy women with normal pregnancies. ASA treatment significantly reduced platelet aggregation during pregnancy, compared with before pregnancy. Gradually increased platelet aggregation was seen in the majority of ASA-treated women as pregnancy progressed. There were only two complete non-responders to ASA.

Miscarriage occurred more often in women with than without TPO-ab (25.7% vs 17.5%). There was no association between TSH in the upper normal range and a new miscarriage. Potential risk factors for a new miscarriage were age, number of previous miscarriages and presence of TPO-ab.

**Conclusions:** ASA does not prevent a new miscarriage in women with at least three previous first-trimester miscarriages. AA-induced platelet aggregation seems to be similar in women with RPL and in healthy women with normal pregnancies. ASA, 75 mg daily, decreases AA-induced platelet aggregation in most women during pregnancy, but the effect diminishes as pregnancy progresses. TPO-ab, but not TSH in the upper normal range, may be associated with an increased risk of a new miscarriage.

**Key words:** Acetylsalicylic acid, recurrent miscarriage, platelet aggregation, pregnancy, early pregnancy, first-trimester, live birth, impedance aggregometry, thyroid stimulating hormone, levothyroxine, thyroid peroxidase antibody, arachidonic acid-induced platelet aggregation, platelet activators