Göteborg, 2023

Ultrasound and molecular biomarkers for prediction of preterm delivery in different risk groups of singleton pregnancies

Akademisk avhandling, som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Järneken aula, Diagnosvägen 15 plan 0, den 1: a december, klockan 09.00.

av Tove Wikström

Fakultetsopponent: Ellika Andolf, Professor Emeritus, Karolinska Institutet, Stockholm

Huvudhandledare: Prof. Henrik Hagberg
Bihandledare: Prof. Bo Jacobsson, Prof. Lil Valentin, Prof. Ulla-Britt Wennerholm

Avhandlingen baseras på följande delarbeten:

I. Wikström, T., Hagberg, H., Jacobsson, B., Kuusela, P., Wesström, J., Lindgren, P., Fadl, H., Wennerholm, U. B., & Valentin, L. (2021). Effect of second-trimester sonographic cervical length on the risk of spontaneous preterm delivery in different risk groups: A prospective observational multicenter study. *AOGS, 100*(9), 1644–1655.

II. Wikström, T., Kuusela, P., Jacobsson, B., Hagberg, H., Lindgren, P., Svensson, M., Wennerholm, U. B., & Valentin, L. (2022). Cost-effectiveness of cervical length screening and progesterone treatment to prevent spontaneous preterm delivery in Sweden. *UOG*, *59*(6), 778–792.

III. Wikström, T., Abrahamsson, S., Bengtsson-Palme, J., Ek, J., Kuusela, P., Rekabdar, E., Lindgren, P., Wennerholm, U. B., Jacobsson, B., Valentin, L., & Hagberg, H. (2022). Microbial and human transcriptome in vaginal fluid at midgestation: Association with spontaneous preterm delivery. *Clin Transl Med 12*(9), e1023.

IV. Wikström, T., Kim SH, Leverin AL, Wennerholm UB, Jacobsson B, Valentin L, Bennett PR, Terzidou V, Hagberg H (2023). Association between specific miRNAs in serum at early gestation and spontaneous preterm delivery. *In manuscript.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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Ultrasound and molecular biomarkers for prediction of preterm delivery in different risk groups of singleton pregnancies

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Background: Preterm delivery (PTD) is the leading cause of death in children under five years of age. Spontaneous PTD (sPTD) might be partly preventable by treating asymptomatic women having a short cervical length (CL) with vaginal progesterone. Furthermore, the pathophysiology of spontaneous sPTD is insufficiently understood, limiting the prediction and prevention of the condition.
Aim: To investigate 1) CL as measured by transvaginal ultrasound (TVU) in the second trimester in different risk groups of asymptomatic women and the risk of sPTD; 2) the cost-effectiveness of different strategies to prevent sPTD including CL screening; 3) if there are differences in the vaginal metatranscriptome and human transcriptome between women with sPTD and women with term delivery; 4) whether a selection of nine specific miRNAs in maternal serum at gestational week 12-14 could serve as biomarkers for sPTD.
Methods: All four studies are based on the CERVIX-study, a prospective blinded multicentre study with the aim to estimate the diagnostic performance of CL (TVU) in asymptomatic women with a singleton pregnancy (*n*=11 072). In **Paper I** the study population was divided into three main risk groups: women at high risk of sPTD, nulliparous women with no risk factors for sPTD, and parous women with only term deliveries and no risk factors for sPTD. **Paper II** is a decision analytic model to estimate the cost-effectiveness of various CL screening strategies combined with treatment with vaginal progesterone to prevent sPTD. In **Paper III** vaginal sampling was performed prior to TVU at 18 to 20 weeks. Vaginal specimens were subjected to high throughput sequencing of both human and microbial RNA. In **Paper IV**, archived serum samples taken from participants in the CERVIX-study at gestational week 12-14 with a sPTD <34 weeks or who delivered at term were analyzed with RT-qPCR for nine miRNAs previously shown to be associated with sPTD.
Results: Paper I: the effect of CL shortening on the risk of sPTD <33 weeks was similar in all three risk groups, and the discriminatory ability was superior when measurements were performed at 21 to 23 weeks compared to at 18 to 20 weeks. In **Paper II** all suggested interventions gave better health outcomes in terms of less peri/neonatal mortality and more quality adjusted life years in a lifetime perspective when compared to the current situation in Sweden i.e., no screening and no treatment. In **Paper III** 17 human genes were significantly differently expressed in the preterm group when compared to the term group. In **Paper IV** none of the nine analyzed miRNAs was significantly differently expressed in those delivering <34 weeks compared to those delivering at term. Three miRNAs (miR-191-5p, miR-93-5p and miR-15-5p) were overexpressed in those delivering <28 to <32 weeks of gestation.
Conclusion: In asymptomatic women with singleton pregnancies, CL screening by TVU can be used for prediction of sPTD in both high and low risk pregnancies in a population with a low prevalence of sPTD. The method has a moderate discriminatory ability. CL screening by TVU followed by treatment with vaginal progesterone of those at increased risk of sPTD is probably cost-effective in a Swedish setting. Whether the identified human genes in vaginal fluid or miRNAs in maternal serum or plasma could serve as potential biomarkers in the future remains to be shown.

Keywords: cervical length measurement, preterm birth, second trimester, screening, cost-effectiveness analyzes, progesterone, human microbiome, transcriptome, gene expression profiles, microRNA

ISBN: **978-91-8069-317-2** (TRYCK)
ISBN: **978-91-8069-318-9** (PDF)