

First trimester risk assessment follow-up;

Risk of fetal loss associated with invasive testing and
cervical length screening for preterm delivery

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ENGLISH SUMMARY

The overall topic of this PhD thesis is prenatal screening – first trimester risk assessment follow-up; first, assessing the risk of fetal loss associated with invasive testing following the current combined first trimester screening (cFTS) offer and, second, exploring the potential value of expanding the prenatal screening programme with CL screening to identify women at high risk of spontaneous preterm delivery (PTD) in a Danish population.

The thesis consists of two parts; a national registry-based study (Paper I) and a prospective longitudinal multicenter study (Paper II and III).

The first part consists of the national register-based study including 147 987 women identified in the Danish Fetal Medicine Database who had a singleton pregnancy and underwent cFTS from 2008–2010 (**Paper I**). The objective was to assess prospectively the risk of fetal loss associated with chorion villus sampling (CVS) and amniocentesis (AC) following cFTS. Propensity score stratification including information from cFTS was used to assess the risk of fetal loss with and without invasive tests. We found no significant difference in the risk of miscarriage or stillbirth for women who underwent CVS compared with those who did not, independent of analysis time-point after cFTS. Similarly, we found no significant difference in the risk of miscarriage or stillbirth following AC. The findings of this study indicate that the procedure-related risk of CVS and AC is very low, and this must be taken into consideration when counseling women at cFTS.

The second part is based on two papers from a prospective multicenter study on longitudinal CL screening at three time points between 11 and 24 weeks of pregnancy including more than 3400 unselected singleton pregnant women.

The objectives of **paper II** were to assess CL longitudinally in the first and second trimesters and to determine the proportion of women with short CL. Furthermore, Paper II assessed if women with a short CL at 19-24 weeks could be identified by ultrasound scanning at 11-14 weeks in relation to a potential implementation of universal CL screening in a Danish population. We

found a very low proportion of women with short CL (only 0.8 % with a CL \leq 25 mm at 19-21 weeks) in line with an estimated need to screen more than 1500 women to prevent one PTD. Furthermore, our findings indicate that first trimester CL assessment may not be of as high value for prediction of PTD as a short second trimester CL and cannot directly replace a CL measurement in the second trimester. Whether universal CL screening should be implemented in our low risk population must therefore depend on a cost-benefit analysis taking into account, the low proportions of women with short CL and of PTD.

The objective of **paper III** was to assess CL longitudinally in the first and second trimesters among singleton pregnant women with prior cervical conization. Additionally, Paper III examined the effect of CL \leq 25 mm as well as CL changes on the risk of spontaneous PTD in comparison with a control group of women with no history of conization. In the cohort of 214 women with prior cervical conization, we found a shorter mean CL even at the first time point of CL assessment (at 11-14 weeks). Likewise, the proportion of women with short CL was significantly higher at all three CL screening time points compared to the 3140 women with no history of conization. Although the women with conization had a higher risk of PTD, our findings imply that the effect of CL \leq 25 mm as well as percentage shortening of CL between time points on the risk of PTD was not as pronounced as for the control group of women with no prior conization. Our results indicate that if women with prior conization should be offered a routine CL assessment it might be best to add it to both routine ultrasound scans during pregnancy (11-14 weeks and 19-21 weeks, respectively) to assess shortening of CL. Overall, our findings support the theory that post-surgical cervical shortening is not the only explanation for the higher risk of spontaneous PTD among women with cervical conization. This information is of clinical importance regarding management and counselling of pregnant women with prior conization and short CL.