Purpose and aims

The general aim is to collect information to estimate if screening for preterm birth (PTB) with cervical length measurements at mid-gestation using ultrasound and prophylactic progesterone treatment if the cervix is short is potentially cost-effective in Sweden

The specific aims are to - in a Swedish population -

1) estimate the prevalence of ”short” cervix as measured by vaginal ultrasound at mid-gestation in asymptomatic women with a singleton pregnancy
2) find the optimal cervical length cutoff to predict PTB in asymptomatic women with a singleton pregnancy
3) estimate the sensitivity and specificity with regard to PTB of ”short” cervix as measured by vaginal ultrasound (using different measurement techniques and definitions) at mid-gestation in asymptomatic women with a singleton pregnancy
4) define the optimal gestational weeks (in the window from 18 to 23 gestational weeks) to measure cervical length to predict PTB in asymptomatic women with a singleton pregnancy
5) investigate if a shortening of the cervix between gestational week 18-20 and 21-23 is more predictive of PTB than a single measurement of cervical length in asymptomatic women with a singleton pregnancy
6) based on the results of 1), 2), 3) 4) and 5) and knowledge of the prevalence of PTB in singleton pregnancies in Sweden calculate the sample size of a Swedish randomized controlled trial to investigate the effect on PTB and neonatal outcome of screening asymptomatic women with a singleton pregnancy with ultrasound measurement of cervical length followed by progesterone treatment if the cervix is “short”

Survey of the field

Preterm birth (PTB) is defined by the World Health Organization (WHO) as birth at 36 gestational weeks + 6/7 (gw 36+6) or earlier [1]. The prevalence of PTB is 5-8% in most developed countries [2] but is much higher (12%) in the USA [3, 4]. In Sweden the PTB rate is about 5% in singleton pregnancies and about 40% in multiple pregnancies [5]. In the USA, the PTB rate differs between women of different race/ethnicity. It is highest in black non-hispanic women (16.8%) and lowest in white non-hispanic women (10.5%)(figures from 2011) [3]. These differences might be explained by genetic differences or differences in socio-economic status, antenatal care, genital infections, nutritional status, maternal risk behavior or stress.

PTB is the most common cause of neonatal mortality and morbidity in most western countries. It explains 60-80 % of all neonatal mortality and almost 50% of later neurological handicap [6]. Mortality and morbidity are inversely related to gestational age at birth [4, 6, 7]. PTB inflicts social and psychological trauma to families affected [4, 8] and is associated with extremely high costs for society [4, 9, 10]. An effective screening test to identify women at high risk of PTB would be of value, provided that there is an effective method to prevent PTB in the high risk group identified at screening.

Measurement of cervical length using vaginal ultrasound seems to be a suitable screening method for PTB: the shorter the cervix at mid-gestation the higher the risk. This applies to both to women with singleton and multiple pregnancies [11, 12, 13]. While there seems to be no effective method to prevent PTB in twin pregnancies (neither progesterone treatment, cerclage or the Arabin pessary have proven to be effective[14]), daily treatment with vaginal progesterone seems to reduce the rate of PTB in asymptomatic women with a singleton pregnancy and a short cervix as measured by ultrasound at 20 -24 weeks [15, 16]. It has been suggested, that universal screening of all pregnant women with ultrasound measurement of cervical length followed by progesterone treatment if the cervix is short should be introduced [17]. However, there is currently insufficient scientific evidence to introduce such a screening program in Sweden for the following reasons:

1) The promising results of prophylactic progesterone treatment in asymptomatic women with a singleton pregnancy and short cervix as measured by ultrasound at mid-gestation were obtained mainly in two in randomized controlled trials performed in countries where the rate of PTB is likely to be higher than in Sweden and race/ethnicity distribution is different [15,18]. One trial was done in Belarus, Chile, India, Czech republic, Israel, Italy, South Africa, Ukraine, Russia, and the USA [15]. It included 32091 asymptomatic women with a singleton pregnancy of whom 2.3% had an ultrasonographically short cervix (10-20 mm at 19-23 gestational weeks). Of the women with a short cervix randomized to treatment with vaginal progesterone or placebo, 31% were Afro-american and 33% Asian. The other trial was conducted in Brazil, Chile, Greece and UK [18]. It included 24620 asymptomatic women with a singleton or multiple pregnancy. Of these, 1.7% had an ultrasonographically short cervix ($\leq$15 mm at 20-25 gestational weeks). Of the women with a short cervix randomized to treatment with vaginal progesterone or placebo, 55% were black and 1% carried a twin pregnancy. The rate of spontaneous PTB < 34 weeks in the screened population was 2.1%. In Sweden the total rate of PTB <33 weeks in singleton pregnancies is 0.9% [5].

2) The prevalence of sonographically “short cervix” (irrespective of whether it is defined as $\leq$15mm, $\leq$ 20 mm, $\leq$ 25 mm or $\leq$ 30 mm) at mid-gestation in asymptomatic women with a singleton pregnancy seems to be 10 to 30 times lower in the Nordic countries/Northern Europe than in southern Europe, the UK or on other continents (possibly with the exception of Japan)[11, 12, 15, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28]. For example, in an observational study from Finland [19] only 0.3% (13/3697) of asymptomatic women with a singleton pregnancy had a cervix $\leq$25 mm (a commonly used cut-off to define a high risk group)at mid-gestation, in an

unpublished study from Gothenburg the corresponding figure was 0.5% (11/2122; Bo Jacobsson, personal communication), and similar results have been reported from the Netherlands (professor Ben Mol; personal communication). In studies conducted in southern Europe, in the UK, or on other continents than Europe the corresponding rate was 3.2% [21], 6.4% [24], 8.0% [11], 10% [12] and 10.7% [22]. It is not known if these differences are explained by population differences or by differences in measurement technique, for example whether or not the isthmus uteri was included in the measurement of cervical length. In most studies the technique used for cervical length measurement is not well described.

3) The reported sensitivity and specificity with regard to PTB of sonographically "short cervix" at mid-gestation in asymptomatic women with a singleton pregnancy varies greatly between observational studies and were low in a study from Finland. It is difficult to sum up published results, because the definitions both of "short cervix" and PTB differ between studies [11, 12, 19, 21, 22, 23, 26, 27]. The sensitivity for PTB < 32-34 weeks seems to be 50-60% if short cervix is defined as <20mm or <25 mm [11, 22, 23]. For PTB < 35 weeks sensitivity varies between 6% and 37% if short cervix is defined as <20mm or <25 mm [12 , 19, 21, 27], and between 19% and 54% if short cervix is defined as <30mm [12, 19, 21, 26]. In the study from Finland [19] cervical length < 25 mm and < 30 mm had sensitivity of only 7% and 19%, respectively, with regard to PTB < 35 weeks. This is lower than in all other studies.

4) The causes and pathophysiology of PTB are insufficiently known[4]. There are likely to be several different causes, and their prevalence are likely to differ between populations. It is fully possible that the cervix is shortened at mid-gestation only if certain causes are present, and that progesterone treatment prevents PTB only when there is a specific cause of short cervix.

Whether a screening program for PTB using ultrasound measurement of cervical length followed by progesterone treatment if the cervix is short will be effective depends on

- the rate of PTB in the population screened
- the prevalence of short cervix in the population screened
- the proportion of women giving birth preterm that have a short cervix (i.e., the sensitivity of the test)
- the proportion of women NOT giving birth preterm that do NOT have a short cervix (i.e., the specificity of the test)
- the proportion of women that accept to be screened
- the proportion of women with a short cervix that accept and complete prophylactic treatment
- by how much treatment reduces the rate of PTB, neonatal morbidity and mortality

Project description

Study design:

Swedish prospective observational multicentre study

Study population:

Eligibility criteria: asymptomatic women ≥ 18 years old with a live singleton pregnancy, who are able to understand oral and written information (information leaflets are available in Arabic, Bosnian, Croatian, Serbian, English, Farsi, Spanish and Somali language).

Exclusion criteria: fetal malformation, rupture of membranes, current vaginal bleeding, ongoing miscarriage, cerclage in situ, current progesterone treatment at the time of recruitment

Sample size:

11000 women; 100 of these women (0.9% of 11000 [5]) are expected to give birth before 33+0 gestational weeks, which gives a reasonable 95%CI for estimated sensitivity of "short cervix" to predict PTB before 33+0 gestational weeks.

Work plan/Study design:

Pregnant women are given oral and written information about the study at their antenatal care unit, at their first trimester ultrasound scan (if they attend) and at their second trimester ultrasound scan. Eligible women who give written consent are examined with vaginal ultrasound to measure cervical length as described below: once at 18+0 to 20+6 gestational weeks and once 3 weeks later at 21+0 to 23+6 gestational weeks. Gestational age is determined using ultrasound fetal biometry [29]. At inclusion, information is collected from the women on demographic background variables (age, parity, ethnicity), previous gynecological and reproductive history (cervical surgery, late miscarriage, i.e. miscarriage between gestational weeks 14+0 to 21+6, PTB of a singleton pregnancy, PTB of a multiple pregnancy, PTB being defined as birth at gestational week 22+0 to 36+6). If necessary, the information provided by the women is checked from their hospital records. Women who decline to have their cervix measured are asked to give us written consent to collect information on demographic background variables, gynecological and reproductive history and on the outcome of their current pregnancy (this is to make it possible to check for selection bias). The number of women declining permission to collect and use information for the study purpose and the number of women not eligible are noted but no information on these women is collected for study purpose (see data collection system below). The women themselves and all medical staff are blinded to the results of the cervical length measurements. However, an ultrasound finding of bulging amniotic membranes is disclosed.

The ultrasound examinations. The ultrasound examinations of the cervix are carried out by specially trained midwives, who have undergone standardized theoretical education and practical training. A certification system specifically designed for this project is in place.

The ultrasound examinations are performed vaginally with the women in the lithotomy position with an empty urinary bladder. The vaginal ultrasound probe is slowly introduced into the vagina until the cervix becomes visible. Care is taken not to exert undue pressure on the cervix: the anterior and posterior lips of the cervix should appear equally thick. Ideally, the cervical canal should be horizontal in the image. The length of the closed cervical canal (the line made by the interfaces of the mucosal surfaces) is measured as a straight line between the internal and external cervical os. If the isthmus is present its length is measured separately. A third measurement is taken from the external cervical os to the apparent (virtual) inner cervical os created by the opposition of the anterior and posterior

isthmus. The measurements are illustrated in Figure 1. Each measurement is taken three times, and all three are recorded. Images are stored for quality assessment.

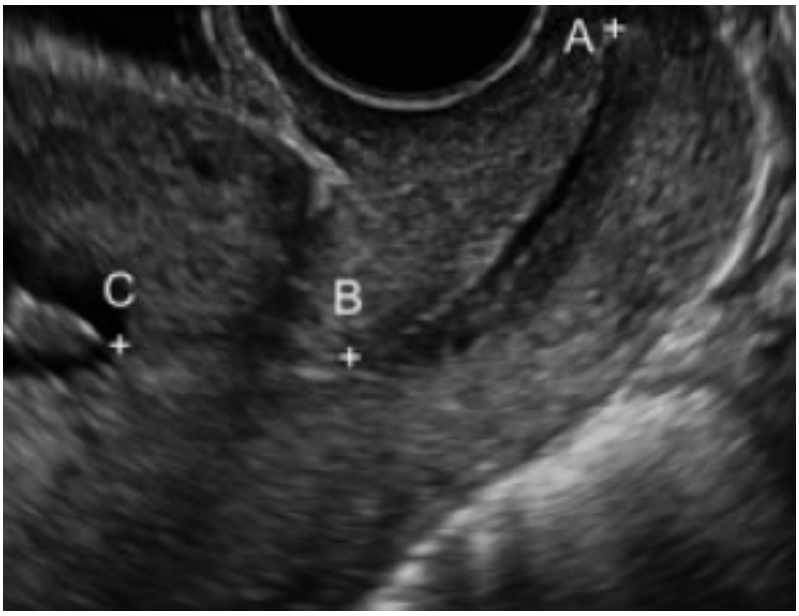

Figure 1. Ultrasound image of the cervix obtained with vaginal ultrasound. A, outer cervical os; B, inner cervical os; C, the virtual inner cervical os created by the opposition of the anterior and posterior isthmus. The following measurements are taken: A-B (length of the closed cervical canal); B-C (length of the isthmus); A-C. A fourth measurement result is obtained by adding (A-B) and (B-C).

Equipment. All participating centers have access to high quality ultrasound scanners and examination rooms necessary for the project, but one center needs a gynecological chair to make it possible to place the woman in the lithotomy position.

Data collection. Data are entered into a dedicated, web-based secure electronic data-collection system specifically developed for the study by MedScieNet AB, Stockholm, Sweden. The prospectively collected clinical information and the results of the cervical length measurements are entered into it. Information is also entered that a woman is not eligible or has refused to give us permission to use information for the study purpose, but no identification information or other information is entered into the database for these women. This means that we will be able to retrieve information on the number of women not eligible and the number of women that declined participation, but it will not be possible to identify these women.

Statistical analysis. At completion of the study, information on the outcome of pregnancy (gestational age at delivery, spontaneous start of labor) will be retrieved for the women included in the study from the clinical electronic obstetric record systems of the participating centres and/or from the Swedish pregnancy register. The following *end points* will be analysed:

The ability of sonographic cervical length to predict PTB <33+0 gestational weeks (*main outcome variable*) will be expressed as the area under the receiver operating characteristic curve (ROC), sensitivity, specificity, positive and negative likelihood ratios with their 95% CI. These calculations will be made separately for each of the three measurements of cervical length (A-B, A-C, and [(A-C) + (B-C)]; see Figure 1), separately for the minimal, maximal and mean value for each of the three measurements, and separately for measurements taken at 18+0 to 20+6 weeks and 21+0 to 23+6 weeks. Using the ROC curves we will identify the optimal method for measuring cervical length (which measurement, which gestational week) and the optimal cervical length cutoff of the optimal

method to predict PTB <33+0 gestational weeks. The ability of a change in cervical length between the first (at 18+0 to 20+6 weeks) and second (at 21+0 to 23+6 weeks) cervical length measurement to predict PTB <33+0 gestational weeks will be examined in the same manner.

The calculations described above for PTB <33+0 gestational weeks will be made also for spontaneous PTB < 33+0 gestational weeks and for total and spontaneous PTB <28+0, <29+0, <30+0, <31+0, <32+0, <34+0 and< 35+0 gestational weeks.

The prevalence of "short cervix" (using different definitions) will be calculated.

Based on our results it will be possible to estimate if a screening programme for PTB in asymptomatic women with a singleton pregnancy using cervical length measurements is potentially beneficial in Sweden (poor sensitivity and specificity would make it unlikely to be so). If it seems potentially beneficial, our results will be used to calculate the sample size of a randomized placebo controlled trial to investigate the effect on PTB and neonatal outcome of screening asymptomatic women with a singleton pregnancy with ultrasound measurement of cervical length followed by vaginal progesterone treatment if the cervix is "short".

The argument for choosing PTB <33+0 gestational weeks as main outcome variable is that the most severe consequences of PTB occur when birth takes place < 33 or <34 weeks [4, 7, 30, 31].

Time frame:

Recruitment of patients: May 2014 to December 2016. Analysis of data and manuscript writing: January 2017-December 2017.

Project organization and coworkers:

The following *six centers* participate in the study: the Departments of Obstetrics and Gynecology at Skåne University Hospital (Malmö-Lund), Sahlgrenska Universitetssjukhuset (Gothenburg) , Karolinska Hospital (Stockholm), Örebro University Hospital, Falu Hospital and Norra Älvsborgs Länssjukhus (NÄL hospital).

Arguments for the study being multicenter: To recruit 11 000 women with a singleton pregnancy to the study we need to have access to 30-40 000 pregnant women: 27 500 if 40% accept to participate and 37 000 if 30% accept to participate. This explains why this study is multicenter. The number of potentially eligible women per year are 7000 in Malmö-Lund, 13000 in Gothenburg-NÄL, 7500 at Karolinska Hospital in Stockholm, and 6000 in Örebro-Falun, i.e. 33 500 per year. This means that it should be possible to recruit 11000 women within 1.5 to 2 years (this time frame includes time for education and training of the midwives performing the cervical length measurements, the slower recruitment in the beginning of the study before all centers have started to recruit patients, and the slower recruitment during summer holidays, when both staff and patients are on holiday).

The project is led by a *steering committee* with the following members: professor Lil Valentin, the applicant (Skåne University Hospital), professor Henrik Hagberg, professor Bo Jacobsson, docent Ulla-Britt Wennerholm (all three at Sahlgrenska Hospital), Med Dr Peter Lindgren, (Karolinska Hospital), Med Dr Helena Fadl (Örebro University Hospital) and Med Dr Jan Wesström (Falu Hospital). The steering committee is responsible for the study design, the co-ordination between centers, the progress of the study, and for results being statistically analyzed and summarized for publication. The members of the steering committee are also principal investigators, i.e. they are responsible for the project at their own center, for example the quality of the cervical length measurements and data

collection, adherence to the study protocol , recruitment, and any practical problems that may arise within the frame of the project. The registered PhD student Pihla Kuusela will help administer the project during the whole period of data collection. She will do the first statistical analysis of the data and write the first draft of the manuscripts emanating from this study.

Dr Carina Bejlum is the principle investigator at NÄL Hospital, and oversees the progress of the study there. Dr Karina Ljuba helps to run the study at Skåne University Hospital Lund.

The ultrasound examinations are performed by specially trained midwives employed in the project (see above).

Clinical significance

Results of scientific studies performed in countries with a much higher PTB rate than in Sweden and with different distribution of ethnicity/race show that PTB rate and neonatal morbidity-mortality can be reduced by screening asymptomatic women with a singleton pregnancy by measuring cervical length with ultrasound at mid-gestation and by instituting daily treatment with vaginal progesterone if the cervix is short. It is important to explore if these extremely encouraging results are applicable to a Swedish population (they are not necessarily so, see under ”Survey of the field”), because both human suffering and money can be saved if they are. As a first step we need to define what constitutes a “short cervix” in a Swedish population and the ability of “short cervix” to predict PTB in a Swedish population. This is the aim of the current study. Our results will be used to calculate the sample size of a Swedish randomized placebo controlled trial to investigate the effect on PTB and neonatal outcome of screening asymptomatic women with a singleton pregnancy with ultrasound measurement of cervical length followed by vaginal progesterone treatment if the cervix is “short”. The results can also be used as a basis for calculating the sample size of a trial evaluating the effect of any other intervention to prevent PTB in the future, for example the Arabin pessary.

Health economic considerations

Two American analyses have concluded that general screening of asymptomatic pregnant women with a singleton pregnancy by sonographic cervical length measurements and institution of prophylactic progesterone treatment if the cervix is short is cost-effective [32, 33]. For example, Werner et al estimated that 12 million US dollars and 22 cases of neonatal deaths or neurological handicap could be saved per 100 000 screened "low risk" singleton pregnancies [33]. Results from the USA are not directly applicable to Sweden (given the higher rate of PTB in the USA, the different distribution of ethnicity/race, possibly different etiologies of PTB and therefore possibly different effect of prophylactic progesterone treatment), but they do support that it is worth exploring the possibility that introducing the screening policy outlined above could be beneficial and highly cost saving also in Sweden.

Preliminary results

Six midwives at Sahlgrenska University Hospital in Gothenburg, two at Skåne University Hospital Malmö, and three at Falu Hospital have been certified to perform cervical length measurements with ultrasound within the project. Recruitment of women into the study started in Gothenburg and Falun in May 2014 and in August 2014 in Malmö. Recruitment came to a halt during the summer holidays. As per 29th August 2014 a total of 347 women had undergone cervical length measurements within the project, and 257 women had accepted partial participation (i.e. they gave us permission to collect and use medical information but did not consent to cervical length measurement).

National collaboration

This is a Swedish multicentre study involving six Swedish hospitals (Skåne University Hospital, Sahlgrenska hospital, Karolinska Hospital, Örebro University Hospital, Falu Hospital, Norra Älvsborgs Läns sjukhus). For details, see above under project description (project organization and co-workers).

Ethical considerations

Because studies have shown that the shorter the cervix as measured by ultrasound at mid-gestation the higher the risk of PTB [11, 12, 13] our decision to with-hold the results of the cervical length measurements may be questioned. Had this information been made available to medical staff some women might have been offered some kind of prophylactic treatment that potentially might have prevented or delayed a PTB. However, to estimate sensitivity and specificity of "short cervix" and to define the optimal cervical length cutoff, there should be no intervention between the measurement and the outcome, and therefore the measurements results must not be disclosed. We find it justified to withhold the results of the cervical length measurements for the following reasons:

We do not know what is a "too short cervix" in a Swedish population.

Cervical cerclage does not decrease PTB <33 gestational weeks in asymptomatic women with a sonographically short cervix at mid-gestation [28]; the Arabin pessary has been shown to be effective in asymptomatic women with a sonographically short cervix in one randomized controlled trial [24] but not in another [34]; and the positive results of prophylactic progesterone treatment [15, 16, 18] might not be applicable to a Swedish population for the reasons described above under "Survey of the field".

The women included in our observational study are not denied anything, because had they not participated in our study nobody would have known their cervical length.

The women who consent to participate are informed both orally and in writing that the results of the measurements will not be disclosed but that they are participating only for scientific purposes, that participation is completely voluntary, and that their medical care will not be affected if they decline to participate.

Most women with a "short cervix" do not give birth preterm. This is true even if the cervix is <10mm. For example, in the observational study by Heath et al in an unselected population of women with a singleton pregnancy (n =2567), the odds of delivery >32 weeks were 10:8 in women with a cervix 0-10 mm at mid-gestation and 77:3 in women with a cervix 11-20 mm at mid-gestation [11].

The vaginal ultrasound examination is highly unlikely to be harmful either for the woman or for the fetus (for most women it is completely painless, but a few may find it uncomfortable). On the other hand, acting on a "short cervix", without knowing what is "too short", may cause harm, at the very least it is highly likely to cause unnecessary anxiety.

Conducting this study has potential to do a lot of good: it will provide us with the necessary information (prevalence of short cervix, definition of short cervix, how and when to measure cervical length, sensitivity and specificity of "short cervix" to predict PTB) for estimating if screening for PTB with vaginal ultrasound measurement of cervical length has potential to be beneficial in Sweden, and if so to calculate the sample size of a randomized controlled trial to estimate the effect of prophylactic progesterone treatment (or other prophylactic treatment) in Sweden. It is important to explore if the very encouraging results of cervical length screening and prophylactic progesterone treatment reported from countries with a much higher PTB rate than Sweden and with different distribution of race/ethnicity are applicable to a Swedish population, because if they are, both suffering and money can be saved. On the other hand, introducing such a screening program is a huge undertaking, and to do it without having collected evidence that it has potential to be beneficial and economically defensible would be highly unethical.

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