Cervical Occlusion in women with cervical insufficiency:

Protocol\(^1\) for a randomised, controlled trial with cerclage,
with and without cervical occlusion

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Study protocol\(^1\)
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\(^1\) Please note: This protocol is meant to be a working document that is being revised according to the progress and experiences during the Trial, and recommendations from an external trial monitoring committee.
Objective: To evaluate the effect of double cerclage compared with a single cerclage

Design: Randomised, controlled multicenter trial

Setting: Ten different countries are participating with both secondary and tertiary centres. The countries participating are Denmark, Sweden, Germany, United Kingdom, Spain, South Africa, Australia and India. This gives both a broad spectrum of diversity global and local. We expect a total of 242 women enrolled per year.

Population:  
Prophylactic study:  
1) History of cervical incompetence / insufficiency. (Delivery 15 - < 36 weeks)  
2) Congenital short cervix (secondary to maternal administration of diethyl stilbestrol, DES) or traumatic/surgical damage rendering the vaginal approach difficult (e.g. conisation)  
3) Cervical suture applied in previous pregnancy, successful outcome  
4) Previous failed cerclage  

Therapeutic study:  
5) Secondary cerclage: Short cervix, without the membranes being exposed to the vagina.  
6) Tertiary cerclage: Short cervix, membranes exposed to the vagina  

Observational study: Eligible women who refuse to be randomised will participate in an observational study.  
7) Repeat / Requested Cervical Occlusion

Methods: The women will be randomised between a single (vaginal or abdominal) and a double cerclage. The cervical cerclage (Mc Donald or Shirodkar) as well as the abdominal suture will be done with the same material and technique normally used by the participating department. Those randomised to the double cerclage will have their external os closed with a continuous nylon 2-0 / 3-0 suture, in addition to the standard single cerclage. Local guidelines concerning antibiotics, Heparin, bed rest, tocolytics etc. are followed and recorded in the follow-up form.

Main Outcome measures:  
Primary endpoints: Take-home baby rate  
Secondary endpoints: Gestational age at delivery. Incidence of preterm birth (< 34+0 days); Number of days in neonatal unit.

Funding sources: The study has been supported by the Elsass Foundation with 215.000 Dkk (29.000 EUR). We will apply for further funding.

Estimated completion date: The study started in June 2006, with around 20 participating centres caring for a total of 60,000 deliveries per year. With these numbers, it will take approximately 2½ years to complete the study.

INTRODUCTION

Preterm birth is the single most important cause of neonatal mortality, morbidity and later, neurological handicap. The birth of a preterm baby carries substantial cost in human and socio-economic terms (1). Previous studies have indicated that intrauterine infection caused by ascending infection from the vagina, leads to preterm delivery as well as to cerebral palsy (2, 3). In recent years the importance of the cervical mucus plug as a gate-keeper protecting the feto-placental unit against ascending infection from the vagina, has been demonstrated (4).

There is little worldwide data on the prevalence of preterm birth, but estimates range from 5 % in some developed countries, to 25 % in some developing countries. Rates of preterm birth have been stable at around 5-10 % for the last 30 years in most developed countries (5, 6). The main precipitating factor is probably infection, but other causes include multiple pregnancy, intrauterine growth restriction, excessive stress, heavy manual work, low socio-economic status, and smoking. One third of preterm births are associated with PPROM (Preterm, prelabour rupture of membranes), one-third with a medical indication (such as maternal hypertension) for delivery (induced labour or elective caesarean section) and one third because of spontaneous onset of labour. Preterm birth is normally defined as a delivery at less than 37 completed weeks (WHO, 7) but clinically the transition in terms of need for neonatal special or intensive care is between 34 and 37 weeks.

Infants born preterm are at increased risk of a range of adverse neonatal outcomes, including chronic lung disease, severe brain injury, retinopathy of prematurity, necrotising enterocolitis, and neonatal sepsis. In later life, preterm infants are at increased risk of motor and sensory impairment, learning difficulties and behavioural problems. (8)

It is possible that as many as 40 % of the survivors of preterm birth will not be able to become fully independent adults (9). The costs of preterm birth are substantial, are inversely proportional to gestational age at birth, and persist into mid-childhood.

Thus, the cumulative direct cost of hospital care up to the age of 5 years in infants born at less than 31 weeks is about £14,000, in addition to other indirect costs born by the Health Services (1). Preterm birth also imposes an economic burden on other sectors and on individuals.

In preterm labour, the high frequency of finding organisms in the amniotic fluid that are also present in the vagina is strongly supportive of ascending infection having a significant causal association. The organisms most often associated with chorioamnionitis, neonatal sepsis, and meningitis after membrane rupture are group B streptococcus and Escherichia coli.

The high risk of developmental disabilities with motor problems, and also cognitive limitations, may be at least partly due to white matter damage caused by the inflammation or infection that is associated with preterm labour (10, 11, 12, 13, 14, 2). It is possible that the early loss of the protective cervical mucus plug could predispose to intrauterine infections and consequently preterm delivery.

There are convincing data showing that increased intrauterine cytokine production in the amniotic fluid is not only associated with preterm labour, but also contributes to the mechanism of cervical incompetence. (15)

In one Swedish study, bacterial invasion was found in the amniotic fluid in 13 % of women with spontaneous preterm labour, and 34 % with preterm prelabour rupture of the amniotic membranes (PPROM) (3). The levels of the cytokines IL-8 and IL-6 were increased in the amniotic fluid, if delivery occurred in up to 7 days after PPROM, compared to delivery after 7 days. In a recent study, the diagnosis of intra-amniotic infection by proteomic profiling methods was reported to be a promising method of detecting preterm birth (16).
Cervical incompetence / insufficiency:
A strong risk factor for preterm birth is a prior history of cervical insufficiency / incompetence, based on a history of repeated, painless, mid-trimester losses or preterm delivery. Some workers have defined cervical incompetence as a history of painless dilatation of the cervix, resulting in ruptured membranes and second or early third trimester delivery (12-24 weeks) and the passage without resistance of size 9 Hegar dilators. Another suggested definition is recurrent second or early third trimester losses, caused by the inability of the cervix to retain a pregnancy until term. The cause can be a weak cervix, either due to congenital causes, or previous cervical trauma (conisation, abortion and delivery). Premature dilatation can be followed by infection, but in some cases ascending infection from the vagina seems to be the primary cause of such dilatation. Measuring the cervical length by ultrasound has been directly correlated with the duration of pregnancy. In a recent study of 2567 singletons pregnancies, a cervical length of 5 mm, 15 mm and 50 mm at 23 week of gestation, decreased the risk of labour from $\leq 34$ weeks from 78 % to 4 % and 0.5 % respectively (17).

The incidence of diagnosed cervical insufficiency varies widely between departments and countries. Part of the variation in incidence rates is due to difficulties in diagnosis and registration of cervical insufficiency. In Denmark between 1980 – 1990, cervical insufficiency was diagnosed in 4.6 /1000 women. In such women, the actual miscarriage/pregnancy loss rate was 17.6 % (18).

"The cervical plug factor"
The cervical mucus plug is a well-characterised structure that fills the cervical canal during pregnancy. The mucus plug can be seen on ultrasound examination of the cervix. The plug presents a local defence mechanism, and is an extremely dense and compact structure, which not only acts as an effective mechanical barrier between the vagina and uterus, but also protects the feto-maternal unit from ascending infection during a pregnancy. When micro-organisms enter the cervical canal, they encounter the innate immune system with neutrophils, granulocytes and macrophages being the most important cells involved (19). Lactoferritin, lysozymes, secretory leukocyte protease inhibitors, and calprotectin and defensins are important antibacterial, antifungal and antiviral products of the cervical mucus plug. The high immunoglobulin levels and phagocytes in the cervical mucus plug suggest a considerable potential for adaptive immune protection (20, 21). Thus the mucus plug is a ‘gate-keeper’ protecting the feto-placental unit against ascending infections from the vagina. Cervical occlusion logically keeps a mucus plug ‘in-situ’ This might otherwise be lost due to cervical damage or malformation. Occlusion allows a reaccumulation of mucus in situations where the plug has already started to dissipate.

Cerclage
A transvaginal cervical cerclage may be inserted prophylactically before pregnancy, during the first trimester, or therapeutically, later in pregnancy, after detection of cervical changes. A prophylactic cerclage is considered a primary prevention and is called a primary cerclage. A therapeutic cerclage is called a secondary cerclage, unless the membranes are exposed to the vagina, when it is called a tertiary cerclage (22).

The largest study so far reported was of 1290 women randomised to a circumferential McDonald suture (MRC/RCOG study 1993). It reported a lower rate of preterm deliveries before 33 weeks gestation, 13 % when cervical sutures were inserted, compared with 17 % in the control group. This meant that 24 sutures had to be inserted to prevent one delivery before 33 weeks (23). Meta analyses of other trials of cervical cerclage for prevention of preterm delivery have failed to show a lower rate of preterm delivery before 28 and 34 weeks in women assigned to cervical cerclage (22, 24, 25, 26, 27). However, there is some evidence of a positive role for cerclage in women considered to be at very high risk, with more than one second trimester loss. (28).
In a recent study the cervical length was measured in 47123 women in week 22-24. The cervix was 15 mm or less in 470 and of these 253 (54%) were randomised to cervical cerclage or to expectant management. Primary outcome was the frequency of delivery before 33 complete weeks of pregnancy. No benefits of cervical cerclage were found in the prevention of preterm delivery in these women with short cervices (15 mm or less), relative risk = 0.84 (0.54 - 1.31) (27). It could be speculated that the reason for the lack of benefit in this study, is, that the cerclage is placed too late, and that bacteria from an ascending infection already has affected the fetal membranes and the cervical tissue because of the short cervix. The disruption of the uterine cervix, as documented by funnelling, is a significant risk factor for adverse perinatal outcomes (i.e., preterm labour and chorio-amnionitis) (29). However, a combination of poor obstetric history and progressive shortening of the cervix in a small study of Althuisius 2002, showed that all 19 women with a cervical suture, delivered after 34 weeks, in contrast to only 7 out of 16 without a suture. Tertiary cerclage with bed rest reduces preterm birth before 34 weeks of gestation, while bed rest alone does not (22).

The transabdominal placement of a cervical suture was first proposed as an alternative, if transvaginal placement was difficult. Now the most common indication for its use is in cases with previous failed transvaginal cerclages (30, 31).

In a study of abdominal (117 women) versus vaginal cerclage (40 women) after a failed transvaginal cerclage, Zaveri (31) found that the likelihood of perinatal death caused by delivery before 24 weeks was 6% (3.8 – 8.2) after transabdominal cerclage and 12.5% (2.7 – 22.7) after transvaginal cerclage.

If there are no benefits from cerclage, it could be because:

1) They do not work,
2) Incorrect insertion techniques are used,
3) Selection of patients is incorrect.
4) The cervix is so weak that it cannot be corrected with a suture
5) Failure of the protective mechanism of the cervical plug, possibly due to ascending genital infections.

**Double cerclage / cervical occlusion**

In most cases, it is impossible to determine whether weakness of the cervix or ascending infection is the primary cause in cases with a previous history of an apparently incompetent cervix. Theoretically the double cerclage deals with both problems.

The cervical resistance is increased by placing a circumferential cervical suture (e.g. McDonald, Shirodkar or transabdominal) and the cervical plug is retained by occlusion of the cervical canal.

Preliminary studies from King Faisal Specialist Hospital, Saudi Arabia have indicated that the combination of a cervical cerclage against insufficiency, and occlusion of the external cervical os (to retain the mucus plug) protects against extreme preterm labour, and improve pregnancy outcomes. Women with a previous poor obstetric history and at least one failed single cerclage, where offered a double cerclage. By applying a double cerclage the abortion rate is reduced from 66 % to 17%, and the take home baby rate is raised from 20% to 83% (McCormack, unpublished data).

**PROPOSED TRIAL**

**Aim of the trial / primary objectives**

The primary objectives are to evaluate the effect of double cerclage compared with single cerclage on the incidence of live born infants as well as the gestational age, in women
with a history of cervical insufficiency or short cervix with or without a previously failed cerclage.

The investigation

Design
Randomisation will be centralised and provided by the telephone randomisation service at the Perinatal Epidemiological Research Unit at Aarhus University.

The data will be entered into a spreadsheet on a computer during the telephone call using block randomisation, stratified on major prognostic variables such as history of cervical incompetence, shortening of the cervix in high risk pregnancies, and previous failed cerclage. The study will be discussed with the eligible women and their partners (if appropriate) and an information sheet will be given. A consent form will be signed before the woman will be included in the study.

The allocation will not be made before all details have been given by telephone, and the woman is determined to be eligible.

The women will be randomised in two groups:

I) **Prophylactic trial – primary cerclage**
   1) History of cervical incompetence / insufficiency. (Delivery 15 - < 36 weeks)
   2) Congenital short cervix (secondary to maternal administration of diethyl stilbestrol, DES) or traumatic/surgical damage rendering the vaginal approach difficult (e.g. conisation)
   3) Cervical suture applied in previous pregnancy, successful outcome
   4) Previous failed cerclage

II) **Therapeutic trial**
   5) Secondary cerclage: Short cervix, without the membranes being exposed to the vagina.
   6) Tertiary cerclage: Short cervix, membranes exposed to the vagina

Observational 7) Repeat / Requested Cervical Occlusion**
   ** If only a few women participate in the randomisation, the external validity of the study could be decreased. Therefore, women eligible for the study who refuse to participate, as they wish to choose the operation method themselves, will participate in an observational study.

Flow chart for The Cerclage Trial

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<tr>
<th>Women eligible for inclusion in the trial</th>
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<tr>
<td>Appropriate trial arm for the patient</td>
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<td>The therapeutical trial arm</td>
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<td>The prophylactic trial arm</td>
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<td>Randomisation regime</td>
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<td>Cervical cerclage with occlusion vs</td>
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<td>Cervical cerclage without occlusion</td>
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<td>Abdominal cerclage with occlusion vs</td>
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<td>Abdominal cerclage without occlusion</td>
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<td>Abdominal cerclage vs Cervical cerclage with occlusion</td>
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Stratification of randomisation
In order to avoid the possibility of chance allocation of all women at a single centre to either a single or a double suture (which could introduce bias if the techniques used at different centres are significantly different), random allocation will be stratified by centre, using randomly varying block sizes (6/4/2). Within the centre, (where they might for example use McDonald, Shirodkar and abdominal sutures according to clinical indication), to avoid the possibility that by chance all the McDonald sutures might be double and all the Shirodkars single (which would introduce bias), random allocation will be stratified by type of primary suture (i.e McDonald, Shirodkar or abdominal), in blocks of ten. This will ensure that within each block of ten, there will be five double and five single sutures.

After delivery, a follow-up form is to be completed after discharge of both mother and child, or six weeks after delivery, if the mother and child are still in hospital.

Steering Committee
The trial will be supervised by the Trial Steering Committee, This consists of the Project Management Group and one chairman from each of the participating centres.

The specific tasks of the Steering Committee are:
1) To approve the core protocol.
2) To approve necessary changes in the protocol based on considerations of feasibility and practicality.
3) To receive the report from the Data Monitoring Committee.
4) To resolve any problems brought to it by the coordinating centres.
5) To approve study reports and papers for publication.

The Data Monitoring and Safety Committee
To maintain confidentiality, a Data Monitoring Committee consisting of an obstetrician, a paediatrician and a statistician/data manager (Professor Philip Steer, London, assistant professor Tine Brink Henriksen, Denmark, data manager Jakob Hjort, Denmark) has been set up. This committee is independent of the trial organizers. During the period of recruitment, the interim results of the trial will be assessed after every hundred patients recruited.

If the interim results show that there is evidence beyond reasonable doubt (p<0.01) that double cerclage is clearly indicated or contraindicated, or if it is evident that no clear outcome will be obtained, the Data Monitoring and Safety Committee will advise the Steering Committee of this and the Steering Committee will stop the trial. Otherwise, the Data Monitoring and Safety Committee will advise that the trial should continue. The interim results will not be revealed to anyone outside the Data Monitoring and Safety Committee.

INCLUSION CRITERIA:

a) The physician in charge considers that a cerclage is indicated.
b) Gestational age between 12 and 27 completed weeks
c) Previous late mid-trimester miscarriage, or spontaneous preterm labour and delivery before 28 weeks with or without previous cerclages.
d) Previous cerclage because of short cervix
e) Confirmed gestational age defined as: Gestational age estimated by ultrasound at less than or equal to 22+0 weeks, and / or certain LMP.
f) Vaginal infection treated before cerclage
g) Ability to read and understand the relevant national language
h) Consent obtained in accordance with specifications of the local research ethics committee
i) ≥ 18 years of age and legally competent

Exclusion criteria:
1) Demonstrated cervical infection.
2) Obstetrical complications in the current pregnancy
2) Multiple pregnancies
3) History of a significant abruptio placenta in a previous pregnancy

MEASUREMENT OF OUTCOMES:

Primary endpoints:
Infants discharged alive from the hospital = take-home baby rate

Secondary endpoints:
Gestational age at delivery
Incidence of preterm birth (< 34+0 week’s gestation)

Tertiary endpoints:
Number of days in neonatal unit

Treatment regime
The cervical cerclage (Mc Donald or Shirodkar) as well as the abdominal suture will be done with the same material and technique as normally used by the participating department.
A double cerclage is performed by sewing the anterior cervical lip to the posterior cervical lip, thus closing the external os. The sutures can be interrupted or continuous, and are placed approximately 1 cm deep on each lip, and 0.5 cm apart with a nylon 2-0/3-0 suture.

Local guidelines concerning interventions such as antibiotics, thromboprophylaxis, bed rest, and tocolytics. are followed and carefully recorded in the follow-up form.

Sample size
There is a huge variation in cervical sutures between hospitals and internationally, with a higher "success rate" in departments using cervical sutures frequently. The commonly reported seriously preterm/miscarriage rate with primary suture alone is about 15 % (Roy Farquharson personal communication, 23). With the use of the double suture, we expect that we can halve this failure rate. 604 randomised women are required in total with an $\alpha$ of 0.05 and a power of 80 % to show that outcomes at these rates are significantly different (Fisher exact test). We are aiming for a total sample size of 650 women in order to reduce still further the possibility of a type 2 error. We expect the duration of the study is 2½ years. If needed, the Data Monitoring and Safety Committee will perform conditional sample size calculation.

Ethical implications
Each centre needs the approval of the protocol by the local research ethics committee.
A copy of these approvals will be send to the Data Co-ordinating Centre. The study will be performed according to the guidelines of the current version of the Declaration of Helsinki, and according to the guidelines for the conduct of pragmatic trials (Perinatal Epidemiology Unit, Oxford). The study has been approved by the Central Ethical Committee in Denmark, where the study enrolled the first patients in June 2006.

Patient information and consent
The woman herself and her partner (if appropriate) will be informed about the purpose of the study. The woman will be allowed time to consider the study and consult her primary care providers. The participation in the trial is free and has no influence on the other therapies that the woman will receive. It is the attending obstetrician's responsibility to obtain formal consent. The local research ethics committee will determine how consent is to be recorded in each of the participating centres. Only women more than 18 years old and legally competent will take part in the study.

PROJECT MANAGEMENT STRUCTURE

Organisation of the trial
Department of Obstetrics and Gynaecology, Hvidovre Hospital, Copenhagen, Denmark will be responsible for the overall conduct of the trial, including internal and external
communication. The randomisation and monitoring of the project will be performed in corporation with the randomisation unit in the Perinatal Epidemiological Research Unit at Aarhus University.

Management group
Niels Jørgen Secher, MD, Professor (Principal Investigator) and Tom Weber, MD, ass professor, Department of Obstetrics and Gynecology 537, Hvidovre Hospital, Kettegaard Alle 30, 2650 Hvidovre
Dr. C D McCormack, FRANZCOG Women’s and Children’s Hospital., Adelaide, Australia
Merete Hein, MD, Ph.D, Aarhus University Hospital, Skejby, Denmark, and Rikke Bek Helmig, MD, Ph.D, Aarhus University Hospital, Skejby Denmark.

Data Co-ordinating Centre
The Department of Obstetrics and Gynecology, Hvidovre Hospital, Copenhagen, Denmark will be responsible for the day to day running of the trial. The functions include:
1) Recruitment of participating centres
2) Data collection and management
3) Data entry and cleaning
4) Data analysis
5) Collection of adverse event data and submission to the Project Management Group
6) Organising and servicing the Data Monitoring Committee
7) To represent the collaborators’ views at the Steering Committee meetings

Time table
The study started in June 2006, with around 20 participating centres caring for a total of 60,000 deliveries per year. With these numbers, it will take about 2½ years to complete the study.

Publication Policy
A writing committee comprised of members of the project management group and the Steering Committee will be responsible for the final report of the trial.

To safeguard the scientific integrity of the trial, data from the final report should not be presented in public, either in whole or in part, by any member of the Advisory Group, Steering Committee, DMC or by any collaborator, without the written agreement of the trial Steering Committee.

The success of the trial depends on the collaboration of a large number of doctors, midwives and nurses. For this reason, chief credit for the main results will be given not to the committees or central organisers, but to all who have wholeheartedly collaborated in the study.

Funding
The study has been supported by the Elsass Foundation with 215.000 Dkk (29.000 EUR). We will apply for further funding.

2) Jacobsson B. Infectious and inflammatory mechanism in preterm birth and cerebral palsy. EJOGRB 2004;115:159-60


PARTICIPATING DEPARTMENTS
Country: Clinical centres, contact-obstetrician (number of women expected to be enrolled):

SWEDEN: Universitetssjukhuset MAS in Malmö, Per Olofsson (15). GERMANY: Womens Hospital - University of Marburg, Stephan Schmidt (5).