

BMFMS/TAMBA Interim Report June 2018

Study Title: ENCIRCLE Trial (Emergency Cerclage in Twin Pregnancies at Imminent Risk of Preterm Birth: an Open-Label Randomised Controlled Trial

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Professor Asma Khalil (CI)

Dr Rosemary Townsend (Study Coordinator)

Fetal Medicine Unit
St George's University Hospitals NHS Foundation Trust
Blackshaw Road
London
SW17 0QT

SPONSOR: St George's University Hospitals NHS Foundation Trust

Background

Preterm birth is a leading cause of perinatal mortality and morbidity, and twin pregnancies are at particular risk spontaneous preterm birth or preterm birth in the context of the complications of monochorionic placentation.⁽¹⁻⁴⁾ More than half of twin pregnancies deliver before 37 weeks and approximately 15% have preterm birth prior to 34 weeks' gestation.^(1,5) Adverse neonatal outcomes include neonatal death, respiratory and neurological complications, the likelihood of which are related to the gestational age at delivery, ranging from 77% in those born before 28 weeks to less than 2% at term.⁽⁶⁾

Interventions to reduce preterm birth include progesterone, cervical pessary insertion and cervical cerclage. These interventions have been evaluated in singleton pregnancy and found to be of benefit in carefully selected cases, but the existing evidence in multiple pregnancies has so far presented disappointing results.⁽⁷⁻¹⁰⁾

There are two time points at which interventions to prevent preterm birth might be applied. Firstly, prophylactic interventions that could prevent or reduce the incidence of preterm labour might be given to all multiple pregnancies in the first trimester, or to a group identified as high risk of preterm labour by the application of a screening test such as cervical length measurement. One group known to be at extremely high risk of preterm labour are those patients who have been treated by fetoscopic laser ablation for twin-to-twin transfusion syndrome and have been found to have a short cervix after the procedure. While one observational study found a benefit of cerclage insertion where the cervix was <15mm after laser,⁽¹¹⁾ another found none when they used a cervical length of <25mm as inclusion criteria.⁽¹²⁾ There have been no randomised trials investigating the role of cerclage in these pregnancies.

Secondly, 'emergency' or 'rescue' interventions could be applied to women presenting with an already dilated cervix in the second trimester. In twin pregnancies with a dilated cervix, the rate of preterm birth can be as high as 90%. The perinatal benefit of interventions that reduced this by even 10% would be significant, but there are no randomised trials investigating the role of emergency cerclage solely in multiple pregnancies.⁽¹³⁻¹⁷⁾ The existing observational data together with this one small trial suggests that placement of an emergency cerclage might be associated with a longer mean cerclage-to-delivery interval, and lower rates of preterm delivery before 34 weeks and of neonatal morbidity.⁽¹³⁻¹⁷⁾

It must be acknowledged that cerclage is an intervention that in itself carries significant risks including rupture of membranes, cervical trauma, infection and preterm delivery. The existing studies are retrospective, subject to bias as observational studies and small in size. The use of emergency cerclage cannot be recommended based on the existing evidence, but warrants further investigation.

The ENCIRCLE trial has been designed to investigate the role of cervical cerclage in the prevention of perinatal morbidity and mortality in twin pregnancies at imminent risk of preterm delivery.

Research question

The study hypothesis is that the placement of an emergency cervical cerclage prolongs the pregnancy in:

(1) twin pregnancies with a dilated internal cervical os between 14+0 and 26+0 weeks,

and

(2) in monochorionic twin pregnancies complicated by TTTS treated by Laser surgery between 16+0 and 26+0 weeks' gestation in whom a short cervix (<15mm) is identified.

Study design

ENCIRCLE is a pragmatic open-label pilot randomised controlled trial. Recruiting mothers carrying high risk twin pregnancies is challenging because of the relative scarcity of the patient population and because of the complexity of clinical cases and variation in regional protocols for the management of threatened and active preterm labour. Individual units may vary in the use and timing of steroids, magnesium sulphate, indomethacin, tocolytics (including atosiban and nifedipine), antibiotics and bed rest. We also anticipated that many mothers would have strong opinions about the use of cerclage and might not accept randomisation. ENCIRCLE will determine the feasibility of recruiting mothers in these circumstances, assess the frequency of their presentation and capture observational data on pregnancy outcomes from those patients not randomised to explore the effect of clinical and maternal factors on trial recruitment.

There two arms to the trial. In the first group, eligible patients are 14-26 weeks pregnant with a DCDA or MCDA twin pregnancy and present with a dilated cervix <5cm dilated, intact membranes, two living fetuses with no known congenital abnormality and no signs of infection or active labour. In the second group, eligible patients are 16-26 weeks pregnant with an MCDA twin pregnancy affected by TTTS who are identified to have a short (<15mm, <5th centile) cervix after fetoscopic laser treatment of TTTS.

Eligible patients are randomised 2:1 to cerclage or control using a web-based application. Masking is impossible because of the nature of the intervention. No other element of the clinical management is required by the trial protocol and is at the managing clinicians' discretion, but the use of any supplementary interventions (including bed rest, progesterone, antibiotics etc) is recorded.

The primary outcome is time to delivery from randomisation and the secondary outcomes include gestation at delivery, preterm birth before 28, 32 and 34 weeks gestation, birthweight, stillbirth, neonatal death, survival to discharge, days of admission in NICU, days of maternal admission for preterm labour, a composite of maternal morbidity and a composite of adverse perinatal outcomes.

Changes to study protocol since start of trial

In order to recruit sufficient patients, a multi-centre group of international collaborators has been established. Although the trial protocol initially specified that McDonald (low) type cervical

cerclage would be performed, we recognised that a number of our collaborating centres routinely use the Shirodkar (high) approach. Given that recent evidence suggesting little difference in perinatal outcome in singleton pregnancies between high and low vaginal cerclage⁽¹⁸⁾ and in keeping with other trials investigating cerclage⁽¹⁹⁾ we have modified the trial to allow the treating clinician to use the technique they feel is optimal for the patient.

A key concern is that recruitment to this study may be affected by strong patient preference for or against cerclage in addition to the scarcity of the target patient group. It will also be useful to establish the actual incidence of preterm delivery in these high risk groups of patients. Pregnancy outcomes for eligible patients who choose not to participate in the trial are now also collected as supplementary observational data and we therefore seek explicit consent from those women for the collection of their pregnancy outcome data.

Key study milestones:

Date of HRA Approval: 18th April 2017

Planned recruitment: 31 patients (20 in Group 1 and 11 in Group 2)

First patient recruited: 27th October 2017

Current recruitment (as of 26th May): 5 screened, 2 patients recruited

Planned end of recruitment: 31st December 2018

Progress so far

ENCIRCLE requires a large number of collaborating centres and early efforts have been directed at developing relationships with collaborators and obtaining regulatory approval for the trial at individual sites. The study set up process is well advanced at over 20 sites, with 10 open for recruitment. (see Appendix, Table 1)

To date, recruitment has been behind schedule. At the present time the primary cause seems to be that there are few eligible patients, only 5 potentially eligible patients were identified across the participating centres, of which 2 were determined to be ineligible and only 1 declined to participate. At the centre recruiting for the longest time (St George's), 3 eligible patients have been identified over a 9 months period. Inviting additional study sites to participate is expected to address this issue and we expect to see increased recruitment going forwards.

Planned output

There are several planned outputs from the ENCIRCLE trial.

- Publication of the trial protocol
- Publication of trial findings
- Analysis of challenges to recruitment in studies of high-risk multiple pregnancies
- Meta-analysis of the use of emergency cerclage in high-risk twin pregnancies

The findings of this trial will be shared via presentation at appropriate conferences, peer-reviewed publications and also via the BMFMS and TAMBA websites and press release.

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 19. Protocol Cerclage Suture Type for an Insufficient Cervix and its effect on Health outcomes (C-STICH). 2017;

Appendix. Table 1.

Participating Centre	PI	Date opened
St George's Hospital	Asma Khalil	10 th August 2017
University College Hospital	George Attilakos	15 th February 2018
Leicester Royal Infirmary	Penelope McParland	27 th February 2018
St Michaels, Bristol	Melanie Griffin	23 rd March 2018
UNAM, Mexico	Rogelio Cruz Martinez	6 th April 2018
Royal London (Barts)	Joseph Aquilina	9 th April 2018
Royal Preston	Amanda Bellis	10 th April 2018
Edith Wolfson Medical Center	Jakob Bar	4 th May 2018
Fetal Medicine Barcelona	Eduard Gratacos	8 th May 2018
Queen Elizabeth 2 Hospital, Glasgow	Marieanne Ledingham	21 st May 2015
Study set up well advanced		
Royal Jubilee Hospital, Belfast	Carolyn Bailie	
Newham (Barts)	Ferha Saeed/Luxmimalar Velauthar	
Oxford University Hospitals	Lawrence Impey	
The Rosie, Cambridge	Kasia Gajewska-Knapik	
Royal Victoria Infirmary, Newcastle	Paul Ayuk	
KU Leuven, Belgium	Liesbeth Lewi	
Study set up in initial phases		
Whipps Cross (Barts)	TBC	
Frimley Park	Anne Deans	
Sunderland	Kim Hinshaw	
James Cook (South Tees)	Vedrana Caric	
Northwick Park	Hiran Samirage	
Liverpool Women's	Zarko Alfirevic	