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What is the impact of preconception abdominal cerclage on fertility: evidence from a randomized-controlled trial

Running Headline: Fertility and preconception abdominal cerclage

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Abstract

Introduction: There is documented concern that cerclage may cause cervical stenosis or changes to the cervical mucus, which may reduce fertility. The aim of this study is to determine whether placement of a preconception abdominal cerclage affects fertility.

Material and methods: This was a planned subgroup analysis of a randomized controlled trial comparing abdominal cerclage, high vaginal or low vaginal cerclage. Women with a history of previous second trimester miscarriage or preterm birth despite having a low vaginal cerclage, presenting to specialist preterm birth services in the UK, were eligible for inclusion. Only women randomized prior to conception were included in this analysis. Women randomized to abdominal cerclage had the surgery performed prior to conception (abdominal group). Women randomized to high or low transvaginal cerclage received it in the subsequent pregnancy (control group). *Results:* Abdominal cerclage was performed in 19 women and transvaginal cerclage in 48 women. Overall there was no statistically significant difference between time to conception between the two groups (hazard ratio 1.34 (95% CI 0.72-2.50), $p=0.35$). Rates of conception at 6, 12 and 18 months were similar (37% in abdominal group vs. 35% in control group at 6 months (RR 1.04; CI 0.52 – 2.10; $p=0.91$); 58% in abdominal group vs. 42% in control group at 12 months (RR 1.39; CI 0.84 – 2.31, $p=0.21$); 74% in abdominal group vs. 56% in control group at 18 months; (RR 1.31; CI 0.91 – 1.89; $p=0.15$)).

Conclusion: This subgroup analysis of randomized data indicates that abdominal cerclage does not affect fertility rates.

Keywords

Abdominal cerclage, cervical cerclage, fertility, randomized controlled trial

Abbreviations

preterm birth (PTB),

relative risk (RR),

confidence interval (CI),

body mass index (BMI)

Key message

Abdominal cerclage is a suture placed at the cervico-isthmic junction with the aim of preventing preterm birth. In this randomized cohort, placement prior to conception does not reduce fertility.

Introduction

Cervical cerclage has been identified as one of the most promising interventions for reducing global preterm birth (PTB) rates (1). Cerclage can be classified according to placement and indication. A transvaginal cerclage can be placed at the cervico-vaginal junction either without mobilization of the bladder (known as low vaginal), or with mobilization of the bladder (known as high vaginal). An abdominal cerclage can be performed via a transverse abdominal incision or laparoscopy and placed at the level of the cervico-isthmic junction.

Current recommendations are for a cerclage to be placed prophylactically in asymptomatic women with singleton pregnancies and a history of three or more previous second-trimester losses or spontaneous PTB (2). Transvaginal cerclages are usually placed after conception between 12 to 14 weeks of gestation, following assessment of viability and chromosomal risk, or later with cervical shortening. In women with a previous failed transvaginal cerclage or extensive cervical surgery, insertion of a transabdominal cerclage may be considered. Abdominal cerclages can be placed prior to conception or early in pregnancy. The advantage of placement prior to conception is avoiding perioperative risk to the pregnancy. However, the main disadvantage is the difficulty managing first trimester pregnancy complications with the suture in situ.

Although there is little published evidence, there is documented concern that cerclage may cause cervical stenosis or changes to the cervical mucus which may in turn reduce fertility (3,4). However, in a systematic review of 1547 patients, those that received a cervical cerclage at the time of radical trachelectomy had an increased risk of cervical stenosis compared to those that did not (8.6%; 104/1215 compared to 3.0%; 2/44; $p=>0.05$) (5). It is concluded that this may be a result of increased erosion and activation of inflammatory pathways and infection (6,7). There are currently no published randomized studies comparing

the effectiveness of preconception transabdominal cerclage with that of expectant management or transvaginal cerclage, and therefore none comparing their effect on fertility.

This study aims to determine whether placement of abdominal cerclage prior to conception affects rates of fertility.

Material and methods

This is a planned subgroup analysis of all women presenting pre-conceptually in a registered randomized controlled trial of abdominal cerclage compared to high or low transvaginal cerclage that is now complete (MAVRIC study; ISCTRN: 33404560). Institutional Review Board approval for project ref: 07/H1102/13 was given by the South East Research Ethics Committee on 20/11/2007. This was a multicenter study, which accepted referrals from across the UK, and recruited in four National Health Service hospitals in the UK. Eligible women had a previous second trimester miscarriage or PTB before 28 weeks' despite having a low vaginal cerclage in place. Women giving informed consent were included in this trial. Those registered prior to conception were eligible for this analysis but the main trial also included those pregnant but <14 weeks' gestation. Women unwilling or unable to give informed consent or <16 years of age were excluded. Recruitment occurred from 01/12/2007 to 30/09/2014.

In the whole trial cohort women were randomized and minimized according to their current pregnancy status, as well as gestational age (<24 weeks) of prior pregnancy outcome. Due to the nature of the intervention blinding was not possible. For the purpose of this analysis only women that were randomized preconception were included. Women randomized to receive transabdominal cerclage had it inserted prior to conception (abdominal group). Women randomized to receive a high or low transvaginal cerclage had it inserted after conception and thus for the purpose of this study represent the control group (control group). As this is a subgroup analysis of ability to conceive, and not pre term birth, the main analysis was per protocol limited to the women who had an abdominal stitch before conception. Therefore, those who conceived prior to abdominal cerclage were excluded from the analysis, as were those who did not receive a cerclage. Crossovers were also excluded. An intention to treat

analysis was also performed for comparison. All women in the trial were instructed to inform the trial staff of any pregnancies. All women randomized were systematically contacted for outcome data before 30/09/2015.

The outcomes of this analysis are time from randomization to conception, regardless of intervention. In addition to overall conception rates at 6, 12 and 18 and 24 months' post-randomization in the abdominal group (i.e. those with a cerclage in situ) compared to control group (i.e. those without a cerclage in situ). Statistical analysis was performed using Stata version 14 (StataCorp, College Station, TX, USA). Survival analysis using Cox's regression was used to compare the overall groups. Differences in event rates at each time point was determined, ignoring censored data, using risk ratios by binomial regression with a log link.

Results

Demographics were similar between groups suggesting the randomization and minimization were valid in the preconceptual women, as shown in Table 1. The most represented ethnic group of women recruited to this study was black (49%) and the average body mass index (BMI) was 30. More women in the control group had had a previous PTB but the number of women with a previous late miscarriage was similar.

In the abdominal group, 19 women were randomized and received an abdominal cerclage prior to conception. Five women randomized pre-conceptually were excluded (two had not received cerclage by time of analysis, and three received cerclage after conception). In the control group 48 women were randomized prior to conception and analyzed. One pre-conceptual woman randomized to transvaginal opted out of the trial and received a transabdominal cerclage prior to pregnancy. Therefore, we compared 19 women that received a pre-conceptual abdominal cerclage with 48 who received a transvaginal cerclage following conception.

The median time from randomization to conception was similar between groups (abdominal group: 332 days vs. control group: 447 days). Overall there was no statistically significant difference between times to conception between the two groups (Hazard Ratio 1.34 [95% confidence interval (CI) 0.72-2.50], $p=0.35$). This is shown in Figure 1. Analysis by intention to treat was similar (Hazard Ratio 1.30 [95% CI 0.72-2.33], $p=0.38$). Rates of conception between the two groups at 6, 12 and 18 months were similar (37% in abdominal group vs.

35% in control group at 6 months (relative risk (RR) 1.04; CI 0.52 – 2.10; p=0.91); 58% in abdominal group vs. 42% in control group at 12 months (RR 1.39; CI 0.84 – 2.31, p=0.21); 74% in abdominal group vs. 56% in control group at 18 months; (RR 1.31; CI 0.91 – 1.89; p=0.15)). Rates of conception at 24 months were 82% (n=14/17) in the abdominal group and 60% (n=28/47) in the control group (RR 1.38; CI 1.00 – 1.91; p=0.049).

Discussion

Overall there was no significant difference in the time taken to conceive following transabdominal cerclage compared to controls. Rates of conception were also similar between the groups. Therefore, this study indicates that women can be reassured that placement of a transabdominal cerclage prior to conception does not negatively affect fertility. Whilst this analysis is limited by its small sample size it offers unique data from the first randomized trial of abdominal cerclage compared to transvaginal cerclage in a high risk population for which the national recruitment took over six years. Formal power calculations for the MAVRIC study were based on preterm delivery rates prior to 32 weeks'. Time to delivery was selected as a continuous variable to be able to detect clinically important differences. However, a limitation is that no formal power calculation was performed on this end point.

The demographics of this group may in part reflect the population of the lead recruiting centre and its referrals in London (73% booked pregnancy within Greater London). However, women of black ethnicity are at higher risk of PTB than women of white ethnicity (13.3% versus 9% respectively(8)). This study was undertaken in women at very high-risk of PTB and this could explain the ethnic demographic. Since there is no substantial difference in ethnicity between groups this does not effect the conclusions that can be drawn. 57% of the UK's female population are overweight or obese with a high proportion having a BMI of well over 30 therefore this demographic is representative of the trial population (9). There is a trend towards greater BMI in the abdominal group compared to the control group (32 versus 28). As obesity is associated with reduced fertility (10), this finding would favor fertility in the control group yet the abdominal group showed a shorter time to conception.

No previous studies have assessed the effect of cerclage on fertility. Reported rates of conception with abdominal cerclage vary within the literature from 71% to 100% following placement prior to conception(11). Overall rates of conception in this data were lower than expected, but our analysis was curtailed at 24 months. Reasons for this may include intentional delay following either psychological distress or clinical recommendation to delay

pregnancy until after cerclage following multiple pregnancy losses. There was also a trend towards improved rates of conception at 24 months in the abdominal group. This is hard to explain (if real) as it is likely that the majority of women in this group will have delayed attempting conception whilst waiting for or recovering from surgery. Physiological reasons seem unlikely and further qualitative work determining patients' intentions to conceive, in addition to collection of data on previous history of subfertility/assisted conception may be valuable. However, given the randomized design, and that women only took part if they intended to conceive, these differences are likely to be matched.

One group, in a series only published in abstract form, has suggested that preterm outcome following pre-conception abdominal sutures maybe better, rates of conception were not reported. Our data is evidence that pre-conception sutures do not adversely affect fertility and given the theoretical advantages of avoiding surgery during pregnancy, may be preferable. Other concerns, such as managing early or even late miscarriage occurring with a cerclage in place, have all been successfully dealt with when using pre-conceptual abdominal sutures (12,13).

Overall, analysis of this randomized data indicates no significant difference in fertility rates following placement of a preconception abdominal cerclage. This is an emotive area for patients with very poor obstetric histories. It is important that this evidence is utilized to reassure women regarding their fertility so that informed decisions can be made regarding risk of surgery and future family planning.

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Legend

Figure 1: Time to conception. The time to conception in months in women receiving an abdominal cerclage prior to conception (abdominal) compared to women randomized to receive transvaginal cerclage in the subsequent pregnancy (vaginal, representing control group).

Table 1: Sociodemographic data of women included in study, stratified by group.

Characteristic		Abdominal Group (n=19)	Control Group (n=48)
Maternal Age (mean(SD))		31 (3.9)	32(4.2)
Body Mass Index (mean(SD))		32 (5.2)	28 (5.0)
Ethnicity	White (%)	7 (37%)	21 (44%)
	Black (%)	8 (42%)	25 (52%)
	Asian (%)	1 (5%)	4 (8%)
	Other (%)	3 (16%)	5 (10%)
Smoking	Current (%)	2 (11%)	3 (6%)
	Non-smoker (%)	17 (89%)	45 (94%)
Gestational age of prior pregnancy (mean(SD))		21 (2.3)	21.8 (2.7)
Past Obstetric History	Early Pregnancy Loss	9 (47%)	25 (52%)
	Late Miscarriage (14 ⁺⁰ -23 ⁺⁶)	18 (95%)	45 (94%)
	Preterm Birth (24 ⁺⁰ -36 ⁺⁶)	6 (32%)	30 (63%)
	Term Birth ($\geq 37^{+0}$)	5 (26%)	7 (15%)
	Second Trimester Surgical Management of Miscarriage or Termination	0 (0%)	1 (2%)

