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Title: MRI measurement of residual cervical length after radical trachelectomy for cervical cancer and the risk of adverse pregnancy outcomes: a blinded imaging analysis.

Authors: Rosa M Alvarez[1,2], Ioannis Biliatis[1], Andrea Rockall[3], Eleni Papadakou[1], S Aslam Sohaib[3], Nandita M deSouza[3], John Butler[1], Marielle Nobbenhuis[1], Desmond JP Barton[1,4], John H Shepherd[1], Thomas EJ Ind[1,4]

Affiliations:

1. Department of Gynaecological Oncology, The Royal Marsden Hospital NHS Trust, London, UK

2. Department of Gynaecology and Gynaecological Oncology, Santa Cristina University Hospital, Madrid, Spain

3. Department of Radiology, The Royal Marsden Hospital NHS Trust, London, UK

4. St George's University of London, London, UK

Corresponding author: Rosa Maria Alvarez, rm.alvarez.lopez@gmail.com

The Royal Marsden Hospital, 203 Fulham Rd, Chelsea, London SW3 6JJ, UK

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Shortened running title: MRI measurement of residual cervical length after radical trachelectomy.

Abstract

Objective: To determine the association between the residual cervix measured on post-operative MRI after radical vaginal trachelectomy (RVT) and adverse obstetric outcomes.

Design: Observational study.

Setting: Referral Cancer centre.

Population: Women who conceived after RVT for cervical cancer at the Royal Marsden Hospital, London, between 1995 and 2015.

Methods: Post-operative MRI scans were analysed by three researchers. The agreement between researchers was assessed by Pearson's correlation coefficient and Bland-Altman plot. Patients were divided into two groups (<10mm and ≥10mm residual cervix) for the analysis of adverse obstetric outcomes.

Main outcome Measures: Late miscarriage, premature delivery, premature rupture of membranes (PROM) and chorioamnionitis.

Results: Thirty-one MRI scans were available; 29 of these women had a pregnancy that progressed beyond the first trimester. There was a strong reproducibility of the measurement of residual cervix ($p<0.001$). Nineteen women (65.5%) had <10mm and 10 (34.5%) had ≥10mm residual cervix. Among women with <10mm residual cervix seven (36.8%) experienced PROM and ten (66.7%) had a preterm birth; No women with ≥10mm residual cervix had PROM and 2 (22.2%) had a preterm birth ($p=0.028$ and $p=0.035$, respectively). Overall, there were nine (16.7%) first trimester

miscarriages, six (11.1%) late fetal losses, twelve (31.6%) preterm births and 36 (66.7%) live births. After a mean follow up of 78.1 months 36 patients were disease-free and one patient died.

Conclusions: MRI measurements of the residual cervix are reproducible between observers. The incidence of PROM and premature delivery is higher when the residual cervix after RVT is less than 10mm.

Funding: The authors have not received any funding to support this study.

Keywords: Cervical cancer, trachelectomy, fertility sparing treatment, pregnancy outcomes, obstetric complications.

Tweetable abstract: The risk of prematurity after RVT can be predicted from measurements of residual cervical length on post-operative MRI scan.

Introduction

Cervical cancer is the fourth most common malignancy in women worldwide [1]. In the European Union 20.9% of women with the condition are diagnosed under the age of 40 while the average age of women who give birth been 30.1 years [2]. Consequently, a number of women are diagnosed in their reproductive age. Most of these are early stage tumours that can be treated with fertility-preserving procedures such as trachelectomy or even cone biopsy depending on the size of the tumour. The most studied approach used by most centres worldwide is the radical vaginal trachelectomy (RVT) that has proven efficient in terms of obstetric outcomes with a good oncological safety profile [3].

In recent years there has been discussion about the risk of premature birth and other adverse obstetric outcomes in patients undergoing cervical tissue removal for treatment of invasive or pre-invasive cervical disease [3,4,5]. Despite different opinions in relation to measurements (dimensions, volume) all seem to agree that the larger the excision, the greater the risk for adverse obstetric results. Premature labour has been observed in 12-28% [6]. The shortening of the cervix plays an important role in the risk of premature delivery as shown in patients after cone biopsy [5,7]. However, the measurement on the specimen excised does not correctly reflect the remaining cervical stroma responsible for maintaining the pregnancy to term. This is because the initial length of the cervix from where the excised tissue is subtracted is different between patients and mainly varies with previous operations on the cervix or cervical trauma and previous pregnancies.

MRI is used pre-operatively to determine the dimensions of the tumour, in relation to healthy cervical stroma and indicate involvement of the parametrium [4,8,9,10]. However, it has not been used routinely post-trachelectomy to assess the risk of adverse obstetric outcome. In this study we sought to estimate the risk of adverse obstetric outcomes in patients following a RVT for stage 1B1 cervical cancer by measuring the length of the residual cervix on a 6-month postoperative MRI scan in order to aid future management and counselling of patients post-trachelectomy.

Methods

Women who had a RVT for stage IB1 cervical cancer at the Royal Marsden Hospital, London, UK between January 1995 and December 2015 were identified. Fourteen of the women included had obstetric outcomes reported as part of a previous publication [4]. From this initial population we excluded the patients that never became pregnant or tried for a pregnancy or lost to follow up. We included only women that conceived after a RVT and their pregnancy completed at least 12 weeks gestation. All included patients needed to have a 6-month postoperative MRI scan of the pelvis according to the protocol followed at the institution. The clinico-pathological characteristics are summarised in Table 1.

Adverse obstetric outcomes were classified as late miscarriage after 12 weeks gestation, premature delivery before 37 weeks of gestation, premature rupture of the membranes (PROM) and chorioamnionitis. An elective Caesarian-section at ≥34 weeks was not considered an adverse event, as this was a standard recommendation for a time in some institutions. Obstetric outcomes were recorded from the letters from postoperative appointments in the clinic for the first 10 years, as well as by contacting the patients' General Practitioners when they were lost to follow up or discharged before completing 10 years. These are summarised in Table 2.

The pregnancy rate was defined as the ratio of patients who had at least one pregnancy as a function of the total number of patients attempting pregnancy. The live birth rate was defined as the ratio of live-birth deliveries to the total number of pregnancies achieved. A premature delivery was defined as a delivery <37 weeks' gestation. These deliveries were classified into three categories of prematurity: 24–28 weeks, 29–33 weeks, and 34–36 weeks. The prematurity rate was defined as the ratio of patients who had premature delivery to the total number of pregnancies ending at the second and third trimester.

Method for the measurement of the residual cervical length:

Routine post-operative MRI images performed at 6 months follow-up were digitally stored and available for analysis. MRI images were analysed by three researchers experienced in Gynaecological Oncology imaging. Each individual researcher independently identified the best sagittal cervical image that captured the entire residual cervical canal and measured the residual cervical length. All three were blinded to the pre- and post-operative obstetric outcomes.

The isthmus of the uterus corresponds to the lower uterine segment and in non-pregnant women is about 5 mm length and is less muscular than the corpus. It forms the junction between the corpus and the cervix. The internal os is situated in the lower part of the isthmus (Fig. 1). The isthmus can be identified based on the external anatomy of the uterus, as there is a slight constriction with corresponding “waisting” at the cervico-uterine junction at the location of the internal os (Fig. 1). Moreover, on T2-weighted images, the inner layer of intermediate signal intensity in the cervix, which corresponds to the endocervical mucosa transitions to a more high signal-intensity endometrium. The appearance of the cervical stroma also differs from the myometrium being lower in signal intensity. This change in zonal anatomy between cervix and uterine body is recognizable. Although the internal os can be more difficult to identify accurately post-trachelectomy as the orientation of the longitudinal axis of the cervix is more variable and the anatomy is distorted (Fig. 1), use of anatomical shape and MRI features meant that it was identifiable after trachelectomy with adequate accuracy.

Statistical analysis

Pearson's correlation coefficient (r) and a Bland-Altman plot were used to evaluate the agreement between the researchers measurements of residual cervical length, and regression models were used to test if there were correlations between the mean difference and average.

Values are given as medians and percentages. Differences in patients' characteristics were analysed using Fisher's exact Test. The measurement used for the analysis of adverse obstetric outcomes was the mean of the three measurements. Patients were divided into two groups. Those with less than 10 mm residual cervical length and those with 10 mm residual cervical length or greater. Only the first pregnancy of each patient was considered for statistical analysis. Differences between groups were tested using the Fisher's exact Test. Events defined as adverse obstetric outcomes included late miscarriage after 12 weeks, premature delivery <37 weeks, premature rupture of membranes and chorioamnionitis. An elective C-section at ≥34 weeks was not included in the analysis of adverse obstetric outcomes. Patients having a first trimester miscarriage were excluded from the final analysis. A logistic regression analysis to assess the predictive value of the residual cervical length was not performed, as the number of patients was too low. P-values <0.05 were considered statistically significant. We used the statistical software SPSS 17.0 for Mac for statistical analysis.

Core outcomes measures

The main outcome of the study was the measurement of the residual cervix after RVT for early cervical cancer on the post-operative MRI scan and the reproducibility of the method for the measurement between researchers. Other outcomes described in the study were the pregnancy results on these patients after RVT and the adverse obstetric outcomes, including late miscarriage, premature delivery, PROM and chorioamnionitis. The association between the residual cervical length measured and the adverse obstetric outcomes was analysed.

Patient involvement

Patients were not involved in the design, development or interpretation of this study; patients facilitated data about their pregnancy in their follow up appointments.

Funding

The authors have not received any funding to support this study.

Results

A total of 140 RVT were performed over the period of study. All patients underwent a RVT and laparoscopic bilateral pelvic lymph node dissection with preservation of the ovaries as treatment for stage IB1 cervical cancer with a cervical cerclage inserted previous to the cervico-vaginal anastomosis. All patients were disease-free at the time of conception. The clinico-pathological characteristics of the patients are described in Table 1. Of the 64 patients who attempted a pregnancy, 37 (57.8%) were identified as having achieved a pregnancy. There were 54 pregnancies from the 37 women in total.

Impacting on subsequent fertility, thirteen of the 64 patients trying to conceive (20.3%) were found to have cervical stenosis. Of the women who achieved a pregnancy, eleven (29.7%) achieved a pregnancy with the help of assisted reproductive techniques. Nine of the 27 patients that were not able to conceive naturally also had unsuccessful IVF. The fertility results are reported in Table 2. There were nine (16.7%) first trimester miscarriages and six (11.1%) late fetal losses. There were twelve cases of preterm birth, with a prematurity rate of 31.6% and a live birth rate of 66.7%. The details of the pregnancy outcomes in each patient are described in Table 3.

Of the 37 pregnant patients, the 6-month follow-up images were missing in six cases. Therefore, 31 MRI scans were analysed. The Pearson correlation coefficient (r) showed a strong positive linear relationship between researcher's observations (r^1=0.851, r^2=0.906, r^3=0.901, p<0.001) indicating the reasonableness of assuming a reproducibility of the method. The Bland-Altman plot analysis showed agreement between researchers. The estimated mean difference (MD) and standard deviation (SD) between the paired measurements and the Bland Altman limits of agreement and the linear regression coefficient (R) are detailed as follow: Researcher 1 and 2 comparison: MD=-0,09, SD=3,11, IC 95%=(5,99)-(-6,18), R=0,258; p=0,019; Researcher 1 and 3 comparison: MD=1,86, SD=2,79, IC 95%=(7,34)-(-3,62), R=0,794; p=0,030; Researcher 2 and 3 comparison: MD=1,51, SD=2,90, IC 95%=(7,18)-(-4,17), R=-0,288; p=0,020.

Of the 31 patients with post-operative MRI scans available, two had a first trimester miscarriage and were therefore excluded from the analysis resulting in 29 patients included in the final assessment of cervical length. Patients were divided into two groups with residual cervical length <10 mm (n=19) or ≥10 mm (n=10). There were seven (36.8%) cases of PROM in the group with <10 mm residual cervix compared to no cases in the group of patients with ≥10 mm residual cervix (7/19 (36.84%) vs. 0/10 (0%) respectively, p=0.032).

For the premature delivery analysis 24 patients with pregnancies over 22 weeks gestation were included. In the group of patients with <10 mm residual cervix, ten (66.7%) had a preterm birth compared to two (22.2%) in patients with ≥10 mm residual cervix (10/15, 66.7%, versus 2/9, 22.2%, respectively, p=0.045). There were no differences for late miscarriage and chorioamnionitis between the two groups (Table 4).

A total of 36 live births and two fetal deaths occurred. The mean follow-up at the time of analysis was 78.1 months (SD 42.4 months, range 17-177 months). At this time 36

patients were alive and disease-free and one patient experienced a recurrence seven years after diagnosis and died of the disease 56 months after recurrence.

Discussion

Main findings

We have demonstrated that shortening of the cervix following RVT plays an important role in the risk of premature delivery. Although this has been shown in pregnant patients following cone biopsy [5], its relevance following trachelectomy has not been documented. Importantly, this means that the risk of preterm birth after RVT may be assessed before pregnancy, which has not previously been described.

Strengths and limitations

There are few studies investigating the roll of the cervical length in patients after radical tracheleclomy. In these studies the measurements of the residual cervix were done during pregnancy and performed by ultrasound scan [11,12]. The present study is the first reporting data on residual cervix before pregnancy. No other articles analysing postoperative MRI scans on trachelectomy patients have been reported in the literature until now.

For many patients included in the last part of the study period, the follow-up time was relatively short and therefore most of them had not tried for a pregnancy at the time of the analysis. Few years more would give more time for these patients to become pregnant and subsequently even more useful data.

Patients were included over a period of 20 years, and over that time the store of the imaging has changed and some of the old MRI imaging were not available for the

analysis. The number of patients was not enough for a multivariable analysis. More cases are needed in order to assess the predictive value of the residual cervical length prior to pregnancy.

Interpretation

The role of residual cervical length in patients after LLETZ on ultrasound done in the second trimester of pregnancy has been described [11]. Kasuga et al [12] investigated the association between mid-trimester residual cervical length and gestational age at delivery after abdominal radical trachelectomy by ultrasound assessment of the residual cervix between 21 and 23 weeks' gestation. They concluded that women with a residual cervix shorter than 13 mm had a higher risk of birth before 34 weeks. Pils et al [13] further reported the results of a screening program for the prediction of preterm delivery in pregnancies after LLETZ, concluding that women with preterm birth had lower cervical lengths than those without. Our data not only shows that adverse obstetric outcomes can be predicted on measurements made 6 months after RVT, but also uses the more robust and repeatable imaging modality of MRI and demonstrates the reproducibility of the measurement of residual cervical length between observers.

RVT has been proven to be a good fertility-sparing treatment for patients with early stage cervical cancer with low recurrence rate [3]. Shepherd et al [4] reported a 5-year cumulative pregnancy rate of 52.8%. The pregnancy rate in the present study was 57.8%. The most important obstetric complication after RVT is preterm birth. In a recent metanalysis performed by Zhabg et al [3] the miscarriage rate reported was 18.8%-29.6% and the preterm delivery rate 19.6%-34.2%. Data from our study are comparable. The 61.5% incidence of PROM reported by Ebisawa et al [14] was associated with cervical granulocyte elastase and bacterial vaginosis. We do not have

information about vaginal infection during pregnancy in our series. Whether routine check-ups of vaginal infection in first and second trimester in trachelectomy patients for treatment with appropriate antibiotics for the prevention of ascending infection is not clear, as other authors have reported that the treatment of bacterial vaginosis in asymptomatic pregnant patients does not decrease the incidence of preterm birth [15]. No cases of bleeding from the residual cervix in the third trimester or endometritis postpartum were reported in our series.

In addition to the risk of ascending infection, other factors could increase the risk of late miscarriage, PROM and preterm birth after trachelectomy. These include insufficient mechanical support and the loss of cervical mucus production [16,17]. In these patients, the value of preventive cerclage is an unresolved question. Some centres prefer to place a preventative cerclage during oncological surgery [18,19,20], as cervical cerclage may prevent dilatation of the residual cervix and the subsequent PROM and chorioamnionitis [20], whereas other centres prefer that placement to be done during pregnancy [21].

RVT may also be associated with fertility problems [22,23]. In the present study, 27 patients were found to be infertile; eleven of them were able to conceive with IVF, nine patients underwent no successful IVF procedure. There were thirteen cases of cervical stenosis. Plante el at [24] reported fertility problems in 13.5% of the patients that tried to conceive, 40% due to cervical factor. It is uncertain how many of these cases had fertility problems before trachelectomy.

Conclusion

This study reveals that the risk of prematurity after RVT can be predicted from MRI measurements of residual cervical length on a 6 month post-operative scan and that the measurements are reproducible. This is invaluable information for counselling

patients that want to conceive after this operation. The incidence of PROM and premature delivery is higher when the residual cervix after a RVT is less than 10 mm. Surgeons therefore should try to preserve at least 1 cm of the upper cervix when it is possible to obtain at least 1 cm clearance of normal tissue surrounding the cervical carcinoma in order to allow better obstetric outcomes.

Disclosure of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

RM Alvarez performed the study design. TEJ Ind and JH Shepherd directly performed the surgical treatment. TEJ Ind, JH Shepherd, J Butler, M Nobbenhuis and DJP Barton were involved in the clinical management of the patients. RM Alvarez, I Biliatis and E Papadakou performed the data collection. RM Alvarez, I Biliatis and A Rockall performed the MRI readings. N deSouza and A Sohaib performed the imaging studies. RM Alvarez performed statistical analysis, the literature review and preparation of the initial manuscript. RM Alvarez, I Biliatis and TEJ Ind completed critical revision of the manuscript and support to all drafts. All authors revised and approved the final version of the manuscript as submitted.

Details of ethics approval

The study was approved for ethics by the Service Evaluation and Clinical Audit Committee of the Royal Marsden NHS Foundation Trust (reference number SE538) on June 2016.

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Figure legends

Figure 1. A: Pre-trachelectomy MRI scan. The internal os can be identified as the transition point between the mucosa of the endocervical canal and the endometrial cavity. B, C and D: Post trachelectomy MRI scans.

Table legends

Table 1. Clinico-pathological characteristics.

Table 2. Details of fertility results.

Table 3. Description of pregnant patients and pregnancy outcomes.

Table 4. Association between the residual cervical length and subsequent obstetrical complications and preterm birth.

Table 1. Clinico-pathological characteristics

Total number of women included	37
Age at diagnosis, mean (range)	30.2 (24-43)
Histology • Adenocarcinoma • Squamous carcinoma • Adenosquamous	 15 (40.5%) 21 (56.8%) 1 (2.7%)
Grade of differentiation • Well • Moderate • Severe • Unspecified	 10 (27%) 13 (35.1%) 12 (32.4%) 2 (5.4%)
LVSI • Present • Absent	 10 (27%) 27 (73%)
Preoperative LLETZ • Yes • No	 36 1
Hospital stay (days), mean (range)	6.53 (0-13)
Follow up (months), mean (range)	78.08 (17-177)

Table 2. Details of fertility results.

	N
Total trachelectomy patients	140
Patients attempting pregnancy	
Yes	64
No	74
Unknown	2
Pregnant patients	37
Natural pregnancy	26
IVF	11
Infertile patients	27
Complications impacting subsequent fertility	
Cervical stenosis	13
Hematometra	2
Cerclage problems	1
Secondary amenorrhoea	1
Total number of pregnancies	54
Fetal loss 1T	9
Fetal loss 2T	5
Fetal loss 3T	1
Termination of pregnancy	2
Ectopic pregnancy	0
Preterm delivery	12
Between 22 and 28 weeks	3
Between 29 and 33 weeks	5
Between 34 and 36 weeks	4*
Pregnancy rate	57.8%**
Live birth rate	66.7%***
Prematurity rate	31.6%****
Total fetal death	2
Total live birth	36

*Cases with elective Caesarean section at ≥34 weeks were not considered premature birth.

**Ratio of patients who had at least one pregnancy and the total number of patients attempting pregnancy.

***Ratio of live-birth deliveries to the total number of pregnancies achieved.

****Ratio of premature delivery to the total number of births (n=38).

Table 3. Description of pregnancy outcomes.

	Age	Conception	Pregnancies after RVT (n)	Type of delivery	WG 1st preg	WG 2nd preg	Complications/comments
1	35	natural	6	Elective CS	37	37	CS at 37 WG in 3 pregnancies. Three 1T miscarriages later
2	43	natural	1	-	1T		1T miscarriage
3	31	natural	2	Elective CS	35	37	-
4	27	IVF	2	1st Emergency CS 2nd Elective CS	34	38	PROM at 34 WG
5	36	natural	1	Elective CS	37		-
6	34	natural	1	Elective CS	36		-
7	27	IVF	3	1st elective CS 2nd Emergency CS	39	33	Preterm birth in 2nd preg. Termination due to trisomy 21 in 3rd at 21 WG.
8	38	IVF	1	-	35		PROM, corioamnionitis, fetal death
9	30	natural	1	Emergency CS	34		Preterm birth
10	35	natural	1	-	1T		7 WG miscarriage
11	32	natural	2	1st Emergency CS 2nd Elective CS	34	38	PROM at 33 WG, CS at 34 WG
12	30	natural	2	Elective CS	37	37	-
13	29	natural	3	Elective CS	37		Two 1T miscarriage after baby
14	31	natural	2	1st Emergency CS 2nd Elective CS	33	34	PROM in 1st preg
15	29	natural	1	Elective CS	37		-
16	31	natural	1	Emergency CS	19		PROM at 17 WG, chorioamnionitis and cord prolapse at 18 WG, late miscarriage one week later
17	26	IVF	1	Vaginal delivery	24		Preterm birth, fetal death
18	29	IVF	1	Elective CS	35		-
19	34	natural	3	Elective CS	37+1	1T	11 WG miscarriage in 2nd, termination due to malformation in 3rd
20	30	IVF	1	Emergency CS	27		Preterm birth
21	35	IVF	1		1T		1T miscarriage
22	26	natural	1		12		Late miscarriage
23	27	natural	1	Vaginal delivery	27		PROM. Preterm birth
24	37	IVF	2	Elective CS	38	37	-

25	28	IVF	1		21		Late miscarriage
26	27	natural	1	Elective CS	38		-
27	26	natural	1		16		Late miscarriage
28	26	natural	1	Emergency CS	33		Preterm birth
29	24	IVF	1	NVD twins	36		-
30	30	natural	1	Elective CS	36		-
31	30	IVF	1	Emergency CS	32+4		Fetal distress
32	25	natural	1	Elective CS	34		-
33	33	natural	1	Elective CS	38		-
34	25	natural	1	Elective CS	39		-
35	28	natural	1	Emergency CS	32		PROM at 26 WG, got 32 WG
36	25	natural	1	Elective CS	35		-
37	28	natural	1		14		Late miscarriage

Preg: Pregnancy

CS: Caesarean section

PROM: Premature rupture of membranes

WG: weeks' gestation

1T: first trimester

IVF: In vitro fertilization

Table 4. Association between the residual cervical length and subsequent obstetrical complications and preterm birth.

	<10 mm length (n=19)	≥10 mm length (n=10)	p
Late miscarriage	4/19 (21.05%)	1/10 (10%)	0.424[a]
PROM	7/19 (36.84%)	0/10	0.032[a]
Premature delivery[*]	10/15 (66.7%)	2/9 (22.2%)	0.045[a]
Chorioamnionitis	2/19 (10.53%)	0/10	0.421[a]
Any pregnancy complication	14/19 (73.68%)	3/10 (30%)	0.030[a]

[a]Fisher's exact Test

For this analysis patients with 1T miscarriage have been excluded (included n=29).

[*]For the premature delivery analysis patients with pregnancies over 22 WG have been included only (included n=24).