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CLINICAL ARTICLE

Proportion of cervical excision for cervical intraepithelial neoplasia as a predictor of pregnancy outcomes

Maria Kyrgiou [a,b,*], George Valasoulis [c,d], Sofia-Melina Stasinou [c,e], Christina Founta [c,f], Antonios Athanasiou [c], Phillip Bennett [a,b], Evangelos Paraskevadis [c]

[a] Department of Surgery and Cancer, Faculty of Medicine, Imperial College, London, UK
[b] West London Gynecological Cancer Center, Queen Charlotte's and Chelsea–Hammersmith Hospital, Imperial Healthcare NHS Trust, London, UK
[c] Department of Obstetrics and Gynecology–Gynecological Oncology, University Hospital of Ioannina, Ioannina, Greece
[d] Department of Obstetrics and Gynaecology, Worthing Hospital, Western Sussex Hospitals NHS Foundation Trust, Worthing, UK
[e] IVF Unit, Queen Charlotte's and Chelsea–Hammersmith Hospital, Imperial Healthcare NHS Trust, London, UK
[f] Northern Gynecological Oncology Center, QE Gateshead NHS Trust, Gateshead, UK

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ABSTRACT

Objective: To assess how the proportion of the cervical volume/length removed during treatment for cervical intraepithelial neoplasia (CIN) varies and whether this correlates to the pregnancy duration at delivery. *Methods:* The present prospective observational study included 142 women undergoing CIN treatment at a university hospital during 2009–2013. The pretreatment and post-treatment cervical dimensions and cone size were measured with magnetic resonance imaging, three-dimensional transvaginal ultrasonography, or two-dimensional transvaginal ultrasonography, and the correlation between pregnancy outcomes and the relative proportion of the cervix excised was assessed. *Results:* Pretreatment cervical volumes and cone volumes varied substantially (range 11–40 cm^3 and 0.6–8 cm^3, respectively). The proportion of the volume excised ranged from 2.2% to 39.4%. Sixteen (11%) women conceived following treatment; 12 had a live birth (seven at term, three preterm). The pregnancy duration at delivery was significantly correlated with the proportion of the cervical volume ($r = -0.9$; $P < 0.001$) and length ($r = -0.7$; $P = 0.01$) excised and the cone volume ($r = -0.6$; $P = 0.04$). *Conclusion:* The pretreatment cervical dimensions and the proportions of the volume/length excised vary substantially, and the latter correlates with the pregnancy duration. Assessment of the proportion excised might help to stratify women at risk who need intensive surveillance when pregnant.

1. Introduction

Intraoperative and postoperative short- and long-term complications of treatment techniques for cervical intraepithelial neoplasia (CIN) have generally been thought to be uncommon and relatively mild. However, meta-analyses of cohorts [1,2] and large linkage studies [3–10] have demonstrated that particular excisional techniques may be associated with an increased risk of prematurity and perinatal morbidity in a future pregnancy (1.5-fold to two-fold increase over the background population).

The amount of tissue excised or destroyed at treatment is likely to be an important risk factor for prematurity and its influence might be greater than that of the actual method used. Evidence from retrospective studies [1,11–13] indicates a "dose–effect" relationship, and the cone length appears to be a predictor for subsequent prematurity.

It is biologically plausible that because cervical volumes/dimensions vary between individuals [14], the proportion of the volume excised may more accurately reflect the extent of cervical damage than the absolute dimensions of the excised tissue; there might in fact be a cutoff for the proportion of excision that signifies women at risk [15,16]. Prospective data indicate that cervical regeneration and, as a result, the deficit 6 months post treatment correlates with the proportion of the cervical volume excised [14,17].

Our hypothesis is that the proportion of the cervical tissue removed is likely to influence both cervical healing and the cervical volume following surgery and as a result the risk of prematurity in subsequent pregnancies. The present prospective study investigated the variation in the proportion of the cervix removed during excisional treatment and provides pilot data on pregnancy outcomes in a sample population for which the dimensions and proportions of the cervical tissue excised were assessed at the time of treatment.

* Corresponding author at: West London Gynecological Cancer Center, 2nd Floor, Hamm House, Queen Charlotte's & Chelsea–Hammersmith Hospital, Imperial Healthcare NHS Trust, Du Cane Road, London, W12 0HS, UK. Tel.: +44 2083833268; fax: +44 2033138065.
E-mail address: m.kyrgiou@imperial.ac.uk (M. Kyrgiou).

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2. Materials and methods

The present study was a prospective observational feasibility study conducted at the University Hospital of Ioannina (Ioannina, Greece). The recruitment commenced on January 1, 2009, and was completed for the purposes of the present preliminary analysis on January 1, 2013.

The study included all women of reproductive age (21–45 years) planned for excisional treatment for CIN who wished to have future pregnancies. Women were included irrespective of their parity, previous obstetric history, and CIN grade.

Women with a history of previous cervical treatment and those who had completed their family were excluded, as were women planned for ablative treatment, and carrying multiple pregnancies. Women who relocated with no identifiable pregnancy outcome data and women who delivered elsewhere were also excluded.

All included participants provided their consent. Ethics approval was granted by the Ethics Committee of the Department of Research and Development at the University of Ioannina.

The dimensions and volume of the cervix before treatment were calculated by magnetic resonance imaging (MRI), three-dimensional transvaginal sonography (3D-TVS), or two-dimensional transvaginal sonography (2D-TVS). A validation study tested all imaging modalities in a sample population and revealed similar measurements with the three imaging techniques (unpublished data).

The first part of the population underwent MRI using transverse T1-weighted and transverse and sagittal T2-weighted images (Supplementary Material S1). The second part of the population underwent 3D-TVS. Good view of the sagittal plane of the cervix was obtained, with a clear view of the endocervical canal. A three-/four-dimensional transvaginal probe (RIC5-9-RS series) and a Voluson (GE Healthcare, Zipf, Austria) ultrasound machine were used (Supplementary Material S1). The third group of the population was submitted to two-dimensional gray-scale ultrasonography (Supplementary Material S1). For both sonographic techniques, three separate images and datasets were obtained for each participant and stored. The image of the best quality was chosen for analysis.

The scans with either technique were performed with an empty bladder and without exerting any pressure on the cervix for those having an ultrasound; the settings were adapted to minimize artifacts and optimize reproducibility. The following parameters were measured: cervical length, anteroposterior diameter of the cervix, and transverse diameter of the cervix. The cervical length was defined as the distance between the external and internal cervical os. The edge of the bladder wall was used as a marker for the internal os to ensure reproducible results. The midpoint of the cervical length was defined as the center of the endocervical canal and used for the measurement of the transverse and anteroposterior diameters. The cervical volume for the MRI and two-dimensional sonography was computed based on the volume formula for cylinders: volume $= \pi$ [(anteroposterior diameter + transverse diameter)/4]^2 $\times$ length] (Supplementary Material S1) [14]. In patients who underwent three-dimensional ultrasound, the images were processed and the volume was calculated off-line using 4D View version 10.5 (GE Healthcare, Zipf, Austria) (Supplementary Material S2).

After imaging, the patients underwent excisional treatment by a single experienced colposcopist. The dimensions of the cone were measured with a measuring tape and a ruler before formalin fixation. The measurements included the length/depth, and the anteroposterior, transverse, and lateral diameters (Supplementary Material S2). A fluid-filled volumetric cylindrical vial (tube) was subsequently used to measure the cone volume with the fluid displacement technique [14,17]. The cone was submerged in the fluid-filled tube and the difference in

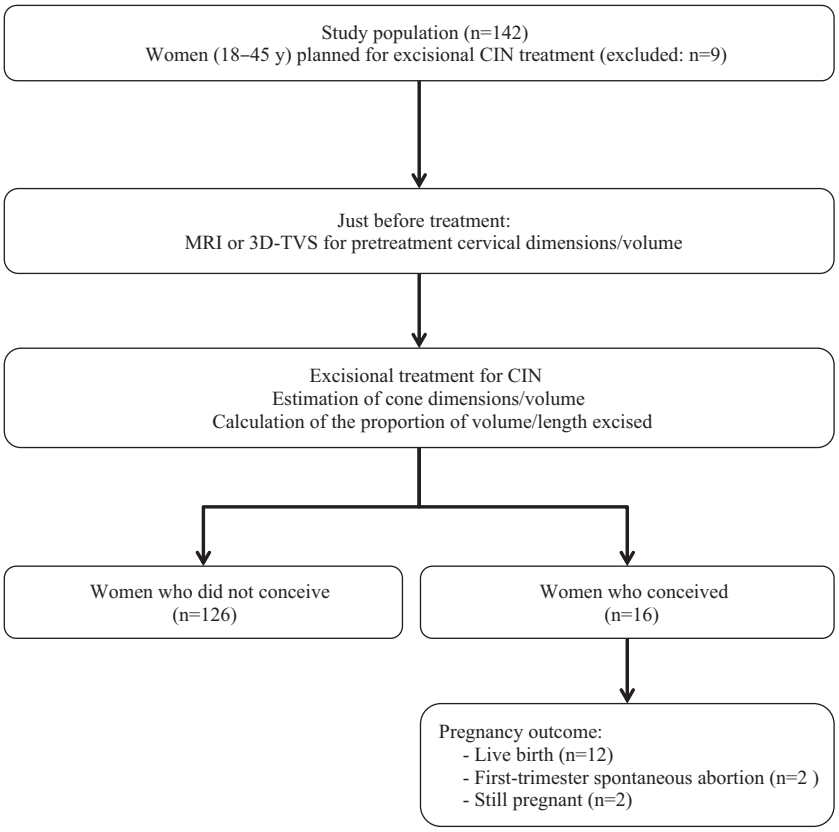

Fig. 1. Study flow chart. Abbreviations: CIN, cervical intraepithelial neoplasia; MRI, magnetic resonance imaging; 3D-TVS, three-dimensional transvaginal sonography.