Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature

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Objectives: To evaluate the fertility results, obstetric outcomes, and the management of infertility in patients submitted to fertility-sparing surgery (FSS) for invasive cervical cancer.
Design: Systematic review.
Setting: Not applicable.
Patient(s): Patients submitted to FSS for invasive cervical cancer (stage IB).
Intervention(s): Five different FSS procedures were studied.
Main Outcomes Measure(s): Fertility, pregnancy outcomes, and management of infertility.
Result(s): A total of 2,777 patients submitted to FSS and 944 ensuing pregnancies were included in this review. Five different surgical procedures were performed and studied. The overall fertility, live birth, and prematurity rates after these procedures were, respectively, 55%, 70%, and 38%. The pregnancy rate was higher in patients submitted to a vaginal or minimally invasive radical trachelectomy compared with a laparotomic radical trachelectomy. The live birth rate was similar, whatever the FSS procedure. The prematurity rate was significantly lower in patients who had undergone a simple trachelectomy/cone resection and neoadjuvant chemotherapy followed by FSS compared with conservative surgery. A majority of second trimester fetal losses and premature deliveries were related to premature rupture of membranes.
Conclusion(s): The choice between the different FSS procedures depends first and foremost on the oncologic characteristics of the tumor. Nevertheless, when several options seem to offer the same oncologic results (for example, stage IB1 disease >2 cm), fertility results should then be taken into consideration to select the best choice acceptable to the patient/couple. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Cerclage, conization, conservative treatment, early-stage cervical cancer, fertility, neoadjuvant chemotherapy, preterm delivery, trachelectomy

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During the last 3 decades, the use of fertility-sparing surgery (FSS) has gained momentum in the management of cervical cancer, whereas standard surgery in early-stage disease is based on a radical hysterectomy (and lymph node dissection), thereby depriving patients of subsequent fertility (1–3). The "cornerstone" of conservative surgery is the radical trachelectomy (RT), first introduced 3 decades ago by Daniel Dargent (using a laparoscopic approach to remove the lymph nodes and a vaginal approach to remove the upper part of the vagina, the cervix, and proximal part of parametria) (1). Other treatment modalities or approaches were defined during that period, and at present five different FSS procedures are now available for cervical cancer: conization or a simple trachelectomy, a vaginal RT, an abdominal RT (a laparotomic or a minimally invasive procedure using a pure laparoscopic or a robot-assisted laparoscopic RT), and neoadjuvant chemotherapy (NACT) followed by FSS (conizzation/simple trachelectomy or RT).

The oncologic issues raised by these different techniques were recently covered extensively in a systematic review of the literature and will not be

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mentioned in this article (4). Nevertheless, when two or three surgical strategies offer the same oncologic results in a subgroup of patients with the same prognostic factors, the fertility results and the obstetric outcomes need to be appraised comprehensively, to present a complete overview of the results of each technique and to then propose objective data to the patient/couple to decide which is the most adequate FSS procedure.

The aim of this systematic review of the literature concerning different FSS procedures in stage I cervical cancer was therefore to analyze the fertility results, obstetric outcomes, and the management of infertility in the light of recent publications.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

The design of this systematic review of the literature was in accordance with PRISMA guidelines. Data were identified from searches of MEDLINE, Current Contents, PubMed, and from references in relevant articles from 1987 (date of the first Dargent procedure) to March 15, 2016, using the following search terms: "early-stage cervical cancer," "conservative surgery," "conservative treatment," "fertility-sparing surgery," "trachelectomy," "radical trachelectomy," "laparoscop* trachelectomy," "laparot* trachelectomy," "robot* trachelectomy," "abdominal trachelectomy," "neoadjuvant chemotherapy," "conization" and "cone resection," "fertility." Only articles published in English were included. For series exclusively published in abstract form, only English abstracts with new data were analyzed. For repeated publications by the same team on a similar topic, the series comprising the largest number of patients (or the most complete data) was retained. We excluded the specific management of pediatric tumors and the recently published study on the conservative strategy for cervical cancer during pregnancy (5). We excluded series exclusively focused on stage IA disease, except when the results of new innovative management procedures were presented (particularly minimally invasive modalities). We excluded series only devoted to technical aspects and/or with results specifically focused on oncologic results without any information (or updated data) on fertility outcomes. Pure reviews of the literature were not included in the analysis, except when the authors incorporated new personal unpublished/updated data. Case reports presenting two or fewer cases were not included in this review. Series addressing RT using several approaches but without specifically distinguishing each of them in their results were not included. The flowchart details the selection and exclusion criteria in the articles extracted from the literature (Supplemental Fig. 1, available online). According to local regulation, no institutional review board agreement was required for this type of report.

Data Extraction and Analysis

The corresponding author and the first author extracted all the series on these topics. The analysis comprises patient characteristics (age, previous parity, previous infertility if specified), specific surgical aspects (approach, morbidities that could exert an impact on subsequent fertility, preservation or not of the uterine artery, cerclage), fertility outcomes, and infertility after FSS and the management thereof. This analysis was done according to the five FSS procedures. Patients who had received NACT followed by FSS may have undergone a conization/simple trachelectomy after initial chemotherapy or a RT. Nevertheless, because the initial treatment of these patients could have exerted an impact on fertility (ovarian function), it was not classified according to the type of cervical surgery performed (simple or radical trachelectomy) but rather in a specific category where the potential impact of the radicality of the dissection on fertility could then be examined specifically. The pregnancy rate was defined as the ratio of patients who had at least one pregnancy and the total number of patients wishing to become pregnant (this was then determined exclusively in series with both types of data). The live birth rate was defined as the ratio of live-birth deliveries to the total number of pregnancies achieved (in series in which both figures were reported). This rate could not be determined per pregnant patient because very few series reported such specific results. A premature delivery was defined as a delivery $<$36 weeks' gestation (WG). When the data were available, these deliveries were classified into three categories of prematurity: 22–28 WG, 28–32 WG, and 32–36 WG. The pregnancy rate was defined as the ratio of patients who had premature delivery to the total number of pregnancies resulting in live births.

RESULTS

A total of 2,777 patients submitted to FSS, and 944 ensuing pregnancies were analysed. One hundred six recurrences were reported: 4 after conization or a simple trachelectomy, 52 after a vaginal RT, 28 after an abdominal RT by laparotomy, 15 after a RT by minimally invasive procedure, and 7 after NACT (Table 1). The numbers of surgeries and pregnancies according to the five different FSS procedures are detailed in Table 1. The overall fertility, live birth, and prematurity rates for these procedures were, respectively, 55%, 70%, and 38% (Table 1). There was no difference between life birth rates according to the five FSS procedures (P=.17), but pregnancy rates and prematurity rates were significantly different (P<.001 for both rates).

Vaginal RT

Because this was the first procedure ever described, nearly half of the FSS modalities reported were performed using this modality (Table 1) (1,6–43). The fertility results of 1,355 cases were reported. The FSS procedure was abandoned or not retained for oncologic reasons in 150 patients (nodal involvement, involvement of the upper part of the trachelectomy specimen, inadequate margins, other histologic poor prognostic factors) (Table 2).

All but two teams used a prophylactic cerclage at the end of the procedure (Table 2). This information was not mentioned by three teams. The most common complications likely to impact fertility were cervical stenoses (91 cases; 8%) or cervical erosion (7 cases).

Nearly 500 pregnancies were reported, and 90 patients had undergone specific management for infertility after the surgical procedure (at least 40 having a pregnancy). The