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Fertility-sparing surgery and fertility preservation in cervical cancer: The desire for parenthood, reproductive and obstetric outcomes

R.C.J. van der Plas [a,b,*], A.M.E. Bos [a], I.M. Jürgenliemk-Schulz [c], C.G. Gerestein [b], R.P. Zweemer [b]

[a] Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, the Netherlands
[b] Department of Gynecological Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, the Netherlands
[c] Department of Radiology and Radiotherapy, University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, the Netherlands

HIGHLIGHTS

- The majority of cervical cancer survivors desiring fertility-sparing treatment, maintain their desire for parenthood after cancer treatment.
- For patients with early-stage disease, vaginal radical trachelectomy shows good reproductive outcomes.
- For patients requiring (chemo)radiotherapy, fertility preservation is successful in the majority of patients.
- Gestational surrogacy with frozen-thawed material enables those without a (functional) uterus to have a genetic offspring.

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ABSTRACT

Objective. To evaluate the desire for parenthood and reproductive outcomes of young cervical cancer survivors who underwent fertility-sparing surgery or fertility preservation procedures for invasive cervical cancer.

Methods. All women <45 years who underwent fertility-sparing treatment for invasive cervical cancer in a tertiary referral center in the Netherlands between January 2009 and January 2020 were identified. Fertility-sparing treatment options included Vaginal Radical Trachelectomy (VRT) for patients with early-stage disease and fertility preservation techniques (FP) when requiring Radical Hysterectomy (RH) or chemoradiotherapy. Data on reproductive intentions – and outcomes were retrieved from medical files and questionnaires.

Results. 75 patients were identified of whom 34 underwent VRT, 9 RH and 32 had (chemo)radiotherapy. 26 patients started FP of whom 23 (88.5%) successfully preserved fertility through cryopreservation of embryos, oocytes and ovarian tissue. After a median follow-up of 49 months, 5 patients developed recurrent disease and died. Reproductive outcomes were retrieved in 58 patients. 89.6% maintained their desire for parenthood after cancer treatment. Following VRT, we report a pregnancy rate of 61.9% among the patients attempting conception ($n = 24$). 15 patients conceived 21 pregnancies which resulted in 15 live-births, yielding a live-birth rate of 75.0%. Following RH or (chemo)radiotherapy, 3 surrogate pregnancies were established (21.4%) using frozen-thawed material with good neonatal outcomes.

Conclusion. Many cervical cancer survivors maintain the desire to become parents eventually. In early-stage disease, VRT shows good reproductive outcomes without compromising oncological safety. For those requiring gonadotoxic treatment fertility preservation and gestational surrogacy provides a promising alternative for achieving a biological offspring.

1. Introduction

Cervical cancer is the fourth most common cancer among women worldwide and affects women at a significantly younger age than most other malignancies. Approximately 42% of the women diagnosed with cervical cancer is ≤45 years [1,2]. Combined with a trend towards delayed childbearing, many of these women may desire to preserve their fertility at time of cancer diagnosis. Recent studies on the effects of treatment-associated infertility among young cancer survivors have quantified the impact of treatment-induced infertility which results in long-lasting emotional and physical distress [3,4]. Combined with the improved survival rates for cervical cancer, which are now exceeding

* Corresponding author at: UMC Utrecht Cancer Center, Department of Gynecological Oncology, University Medical Center Utrecht, PO Box 85500, 3584CX Utrecht, the Netherlands.
E-mail address: R.C.J.vanderplas-4@umcutrecht.nl (R.C.J. van der Plas).

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90% for early-stage disease, the desire for fertility-sparing treatment modalities rises [5].

Standard treatment options for invasive cervical cancer include radical hysterectomy (RH) with pelvic lymphadenectomy for early-stage disease and chemoradiotherapy for advanced stage-disease [6]. Both with obvious implications for fertility [7]. The past two decades, fertility-sparing treatment options have been introduced in the management of invasive cervical cancer including Vaginal Radical Trachelectomy (VRT) and fertility preservation (FP) procedures. VRT was first reported on by *Dargent* et al. [8] in 1994, and has proven to be an oncologically safe treatment option in carefully selected patients with favorable obstetric outcomes [9,10]. Pregnancy and live-birth rates following VRT range between 41 and 67% and 50.9–73.0 respectively [11,12].

For those patients ineligible for radical trachelectomy, biological parenthood is only feasible through assisted reproduction technologies (ART)and gestational surrogacy. Recognized FP options include cryopreservation of embryos, oocytes and recently, ovarian tissue cryopreservation (OTC) has emerged as promising treatment modality [13,14].

Despite the variety of fertility-sparing treatment options for young cervical cancer patients, very few studies have been found which report on the desire for parenthood and reproductive outcomes following fertility-sparing treatment for invasive cervical cancer.

The aim of this study is to evaluate fertility-sparing treatment for invasive cervical cancer as a whole, addressing both fertility-sparing surgery and fertility preservation procedures. These data will provide both patients and clinicians with realistic expectations regarding reproductive outcomes for all-stages of disease and therefore improve counseling in newly diagnosed cervical cancer patients.

2. Materials and methods

2.1. Study design and participants

This retrospective cohort study reports reproductive intentions and outcomes of women who underwent fertility-sparing surgery or fertility preservation procedures for invasive cervical cancer in a tertiary referral clinic for gynecological oncology in the Netherlands. Using a computerized database, patients ≤45 years old, diagnosed with invasive cervical cancer stage IA2 to IVA and who desired to maintain reproductive potential between January 2009 and January 2020 were identified. Patient, tumor and treatment data were retrieved from medical files. Data on reproductive intentions and pregnancy outcomes were derived from medical files and postal questionnaires.

2.2. Setting & treatment

In our hospital, fertility-sparing treatment options for cervical cancer include 1) VRT with Sentinel Node Procedure (SNP) and Pelvic Lymph Node Dissection (PLND), 2) radical hysterectomy (RH) with preservation of the ovaries and 3) fertility preservation (FP) prior to (chemo)-radiotherapy.

After standardized diagnostic workup including medical history, physical examination, laboratory tests, MR-imaging and histopathological analysis, an individualized treatment plan was made after discussion in the multidisciplinary team. Staging was done according to the International Federation of Obstetrics and Gynecology 2018 classification [7]. Available treatment options included:

1) VRT with laparoscopic or robotic SNP and PLND was indicated in IA2-IB1 tumors measuring ≤2 cm as recommended by international guidelines [7,15]. Our surgical technique was previously described by *Zusterzeel* et al. [16] and included SNP with frozen section (FS) analyses, complete PLND and VRT. The sentinel node is dissected into small tissue fragments, one tissue fragment is used for FS analysis leaving the remaining fragments for complete histopathological analysis (i.e. microstaging). A 2-step procedure consisting of a separate laparoscopic or robotic SNP and PLND with serial sectioning was performed in patients with an estimated risk of lymph node (LN) positivity of >10%. In absence of LN metastases, a VRT was performed in a second session. In these cases the FS was not performed and final histopathology determines whether or not the VRT was performed or chemoradiotherapy was required. A complementary radical hysterectomy was performed in presence of positive surgical margins and adjuvant chemoradiation was recommended in case of LN positivity.
2) Robot-assisted radical hysterectomy with SNP and PLND was indicated in FIGO stage IB2 and IIA1 disease [7]. As previously described, first the SNP was performed and sent for FS analyses before the PLND was completed using the da Vinci robot [17]. In absence of lymph node metastases, a RH was performed. Adjuvant radiotherapy was indicated in patients with intermediate-risk disease according to the criteria stated by *Sedlis* et al. [18]. Adjuvant chemoradiotherapy was indicated for patients with high – risk disease, including LN metastases or (microscopic) parametrial involvement as described by *Peters* et al. [19].
3) For patients with stage IB3 to IVA stage disease, primary treatment consisted of concurrent external beam chemoradiotherapy followed by MRI guided brachytherapy performed by a radiation oncologist [20].

Routine follow-up visits were performed every 3 months for the first year, every 4 months for the second year and biannually for the last three years.

2.3. Fertility preservation counseling

Pre-treatment fertility counseling was offered to all patients primarily treated with RH or chemoradiotherapy. When adjuvant treatment was indicated upon surgery, emergency fertility counseling was performed within one week to prevent any delay in starting (chemo)radiotherapy.

Fertility counseling was performed by a reproductive specialist and consisted of a 1,5 h consultation addressing treatment-induced infertility and information provision on FP procedures. FP procedures included ovarian transposition, cryopreservation of embryos and/or oocytes and ovarian tissue cryopreservation (OTC). The FP procedure of choice was carefully selected upon shared-decision making, in consensus with patient, gynecologic oncologist and radiation oncologist.

2.4. Postal questionnaires

Data from medical files were supplemented with data from postal questionnaires assessing the desire for parenthood and reproductive outcomes following cancer treatment. All patients received an invitation letter and informed consent form before participating in the questionnaire. The questionnaire addressed several topics including the desire for parenthood, attempts to conceive, fertility problems, obstetric and neonatal outcomes. Three and four weeks after sending the initial invitation, respondents received a reminder asking them to participate. Deceased or severely ill patients were excluded from receiving the questionnaire.

2.5. Statistical analyses

A data-management plan was constructed in order to improve the reproducibility of our study. Data was anonymously collected using Castor Electronic Data Capture [21]. Due to the size of the study population, we were limited to descriptive and basic statistics in SPSS statistics (version 25) only.

3. Results

3.1. Patient and treatment characteristics

Between January 2009 and January 2020 a total of 219 patients ≤45 years were treated for cervical cancer at our hospital of whom 75 desired to maintain reproductive potential. Of these, 34 patients were treated with vaginal radical trachelectomy, 9 with radical hysterectomy and 32 patients with (chemo)radiotherapy. An overview of patient and tumor characteristics per treatment is presented in Table 1. A flow-chart describing the intention to treat, performed treatment and reproductive outcomes treatments is presented in Fig. 1.

3.2. Intention to treat and treatment performed

Thirty-eight patients were planned for VRT with SNP and PLND, but the procedure was actually performed in 35 patients. VRT was abandoned in 3 patients because of LN positivity upon serial sectioning. All 3 cases had separate SNP/PLND procedures prior to VRT.

A complementary radical hysterectomy was performed in 1 patient due to positive resection margins upon final pathology. Therefore, a total of 34 patients had VRT as definitive treatment. One patient received neoadjuvant chemotherapy prior to VRT due to a tumor size >2 cm. This treatment plan was performed upon individualized shared decision making basis.

RH with SNP and PLND was initially recommended in 17 patients, and complementary treatment after VRT in 1 patient. RH was abandoned intraoperatively in 4 patients because of sentinel node positivity after FS analysis. Subsequently those patients were treated with chemoradiotherapy. RH was completed in 14 patients. A total of 5 patients received adjuvant treatment following RH. 3 patients received adjuvant radiotherapy because of positive resection margins ($n = 1$) or parametrical involvement ($n = 2$). 2 patients received adjuvant chemoradiotherapy because of LN metastases upon final pathology.

Chemoradiotherapy was primarily indicated in 20 patients and additionally indicated in 9 patients upon pathologic risk factors as previously described. As adjuvant radiotherapy was indicated upon final pathology in another 3 patients, a total of 32 (42.7%) patients were treated with (chemo)radiotherapy.

3.3. Fertility preservation

All 32 patients treated with (chemo) radiotherapy received pretreatment fertility counseling. An overview of patient decisions and treatment flow regarding FP procedures is presented in Fig. 2. After counseling, 26 patients (81.3%) started FP procedures whereas 5 patients (15.6%) decided to not preserve fertility and 1 patient (3.1%) with neuroendocrine tumor was advised to not start FP due to oncologic reasons. Personal reasons for not pursuing FP after counseling included fear of postponing cancer treatment or the complexity of gestational carrier procedures.

While 26 patients started FP procedures, oocyte cryopreservation failed in 5 patients due to poor ovarian response. 2 of them underwent emergency ovarian tissue cryopreservation (OTC) and 3 decided to not start alternative FP procedures. Fertility was successfully preserved in 23 (88.5%) of the 26 patients who started FP procedures.

9 patients underwent more than one procedure; i.e. a combination of the aforementioned. Ovarian transposition was performed to retain hormonal function in 5 patients or for fertility preservation purposes in 2 patients. Vaginal oocyte pickup procedures and laparoscopic retrieval of ovarian tissue were performed succesfully in all patients. FP procedures were all performed within 6 weeks after diagnosis, therefore it did not interfere with cancer treatment.

3.4. Follow-up study cohort

By May 2020, the mean follow-up (FU) time was 55 months (1−132) in the VRT group, 25 months in the RH group (8–64) and 49 months

Table 1
Clinical and histopathological characteristics of study cohort[a].

	Vaginal Radical Trachelectomy ($n = 34$)	Radical Hysterectomy ($n = 9$)	(Chemo)radiotherapy ($n = 32$)	Total ($n = 75$)
Age, median (range)	31 (25–37)	30 (25–37)	29 (24–36)	31 (24–37)
BMI, median (range)	22.5 (18.0–36.7)	21.2 (17.3–36.7)	22.0 (18–33.3)	22.1 (17.3–36.7)
Parity				
Nulliparous	27 (79.4%)	7 (77.8%)	28 (87.5)	62 (82.7%)
Parous	7 (20.6%)	2 (22.2%)	4 (12.5%)	13 (17.3%)
Stage				
IA2		1 (11.1%)		1 (1.3%)
IB1	30 (88.2%)	3 (33.3%)		33 (44.0%)
IB2	3 (8.8%)	4 (44.4%)	2 (6.3%)	9 (12.0%)
IB3	1 (2.9%)		3 (9.4%)	4 (5.3%)
≥ II		1 (11.1%)	27 (84.8%)	28 (37.3%)
Grade				
I	7 (20.6%)	2 (22.2%)	4 (12.5%)	13 (17.3%)
II	18 (52.9%)	5 (55.6%)	16 (50.0%)	39 (52.0%)
III	9 (26.5%)	2 (22.2%)	12 (37.5%)	23 (30.7%)
Histology				
Squamous cell carcinoma	27 (79.4%)	5 (55.6%)	22 (68.0.8%)	54 (71.1%)
Adenocarcinoma	6 (17.6%)	4 (44.4%)	7 (21.9%)	17 (22.7%)
Adenosquamous carcinoma	1 (2.9%)		2 (6.3%)	3 (4.0%)
Neuroendocrine			1 (3.1%)	1 (1.3%)
Median tumor size in mm (range)	9.0 (6.0–40.0)*	20.0 (7.0–35.0)	40.0 (20–73)	20.0 (6.0–73)
LVSI				
No	21 (61.8%)	6 (66.7%)	18 (56.3%)	45 (60.0%)
Yes	13 (38.2%)	3 (33.3%)	13 (40.6%)	30 (40.0%)
Lymph node metastasis				
No	34 (100%)	9 (100%)	9 (28.1%)	52 (69.3%)
Yes	0 (0%)	0 (0%)	23 (71.9%)	23 (30.7%)
Neoadjuvant chemotherapy	1 (2.9%)			2 (2.7%)
Follow-up in months	55 (1–132)	25 (8–64)	37 (12–134)	49 (1–134)
Recurrence	–	–	5 (15.6%)	5 (6.7%)
Deceased	–	–	5 (15.6%)	5 (6.7%)

[a] According to the FIGO 2018 staging

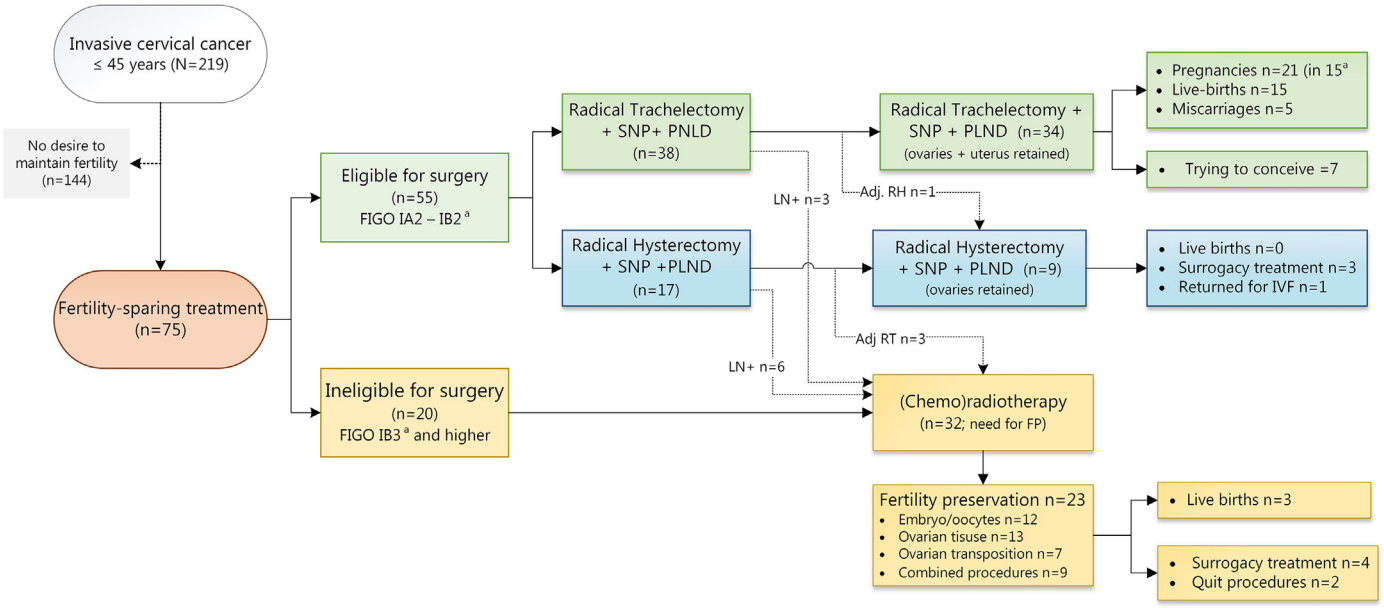

Fig. 1. Flowchart of patients in study cohort. SNP, sentinel node procedure; PLND, pelvic lymph node dissection; LN+, lymph node positivity; RH, radical hysterectomy; RT, radiotherapy.[a] according to the FIGO 2018 classification

in the (chemo)radiotherapy group (1–134). During FU, five patients (6.7%) developed recurrent disease at a median time of 12 months after diagnosis (range 3–24 months) and died following palliative chemotherapy with a median survival time of 17 months (range 13–32 months). All were diagnosed with tumor stage IIB or higher and were treated with chemoradiotherapy.

3.5. Desire for parenthood

As 4 patients died shortly after cancer treatment and follow-up data could not be retrieved in another 13 patients, reproductive outcomes were analyzed in the remaining 58 patients (81.7%).

51 (87.9%) of the 58 patients reported to have a current or future desire for parenthood after cancer treatment. 4 patients (8.6%) reported to be to be uncertain about their desire for parenthood and 2 patients (3.9%) reported to have withdrawn their desire for parenthood. An overview of the desire for parenthood and reproductive outcomes is presented in Supplementary 1.

3.6. Reproductive outcomes - VRT

In the VRT group, data on reproductive outcomes were available for 29 of the 34 patients. Among those, 28 patients reported to have either an active or future desire for parenthood and 24 patients had attempted to conceive.

12 of the 24 patients who attempted conception (50.0%) experienced difficulty conceiving for which they consulted a reproductive specialist. Causes for difficulties conceiving included cervical stenosis in 4 (33.3%) patients, male factor in 2 (16.7%) patients, tubal pathology in 1 (8.3%) patient or unknown fertility problems in 5 (41.7%) patients. Among the patients with cervical stenosis, 2 patients presented with dysmenorrhea and hematometra whereas 2 patients were asymptomatic. All underwent isthmic dilatation procedures for reproductive purposes which succeeded in 2 patients. The remaining 2 patients experienced persistent stenosis of the cervical ostium and ultimately received experimental transmyometral embryotransfers resulting in an ongoing pregnancy in 1 patient. To date, 5 patients (41.7%) who

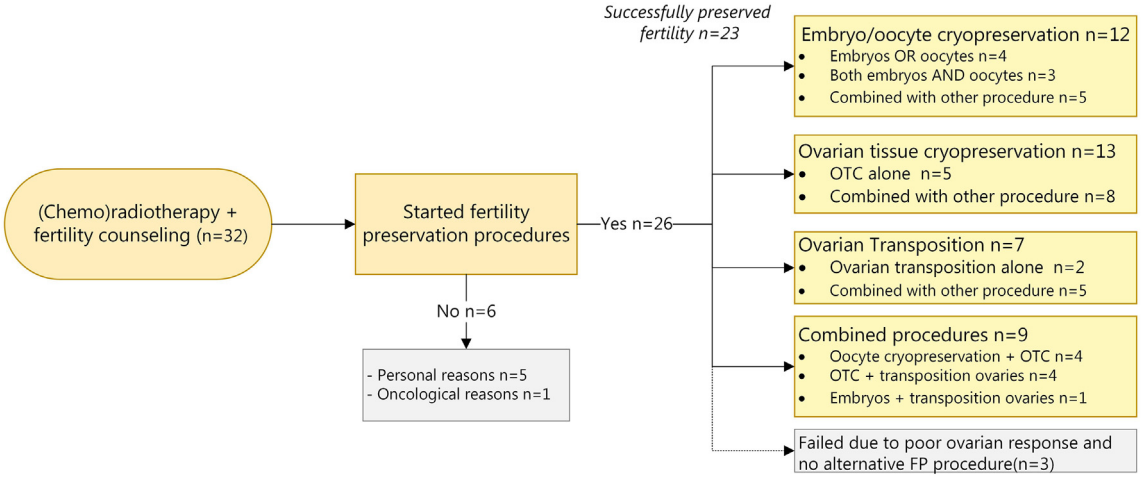

Fig. 2. overview of patients decisions after fertility counseling. OTC, ovarian tissue cryopreservation.

experienced difficulties conceiving and consulted a reproductive specialist, have ultimately conceived through ART while 7 patients (58.3%) are still attempting conception via ART or naturally.

So far, a total of 15 patients conceived a total of 21 pregnancies following VRT, yielding a pregnancy rate of 62.5%. Reproductive, obstetric and neonatal outcomes are presented in Tables 2 and 3 respectively. A total of 15 pregnancies reached the third trimester (75.0%) and resulted in 15 healthy babies. All women delivered via cesarean sections, which were scheduled between 38 and 39 + 0 weeks. There were no fetal losses or neonatal complications identified in our study cohort.

3.7. Reproductive outcomes following RH-CRT

Among the patients treated with hysterectomy or (chemo)radiotherapy and thus requiring a gestational carrier, reproductive outcomes were available for 29/41 patients. 23 of the 29 patients (79.3%) desired to have children after cancer treatment, and 14 of these 23 (60.1%) were referred for gestational surrogacy treatments. This resulted in 3 ongoing gestational surrogacy pregnancies (21.4%), while 7 patients (50.0%) are still searching for a suitable gestational carrier and 2 patients (14.3%) discontinued gestational surrogacy treatments. One of these patients adopted a child. Two pregnancies were established using frozen-thawed oocytes and one pregnancy was established through orthotropic auto-transplantation of ovarian tissue and ovarian stimulation. There were no obstetric or neonatal complications and all gestational carriers delivered at term.

4. Discussion

We present our 10-year experience with fertility-sparing management for cervical cancer in a tertiary referral hospital in The Netherlands, including both fertility-sparing surgery and fertility preservation procedures.

4.1. Desire for parenthood

One of the objectives of this study was to investigate whether patients maintain their desire for parenthood after cancer treatment.

Table 2
Reproductive outcomes VRT.

Pregnancies ($n = 21$)	
Way of conception	
Naturally	13 (61.9%)
IUI	5 (23.8%)
IVF/ICSI	2 (9.5%)
TMET	1 (4.8%)
Pregnancy outcome ($n = 20$)	
1st trimester miscarriage	4 (20.0%)
2nd trimester miscarriage	1 (5.0%)
Preterm delivery 32–37 WOG	1 (5.0%)
At terme delivery ≥37 WOG	14 (70.0%)
Ongoing pregnancies	1
Complications pregnancy[a]	
PROM	1 (5,0%)
PPROM	1 (5,0%)
1st trim vaginal bleeding	2 (10,0%)
2nd trim vaginal bleeding	3 (15.0%)
Cervical insufficiency	2 (10,0%)
Cerclage erosion	1 (5,0%)
Chorioamnionitis	1 (5,0%)
Pregnancy rate[b]	62,5% (15/24)
Live-birth rate[c]	75.0% (15/20)

IUI, intra-uterine insemination; IVF, in vitro fertilization; ICSI, intracytoplasmatic sperm injection; TMET, transmyometral embryotransfer; WOG, weeks of gestation; PROM, prelabour rupture of membranes.

[a] n = 20 ongoing pregnancies.

[b] Pregnancy rate: total number of patients attempting to conceive to patients who succeeded.

[c] Live-birth rate: total amount of pregnancies/live births.

Although results from previous studies suggest that not all patients maintain their desire for parenthood after cancer treatment (27.7–71.8%), we found that nearly 90% does [22,23]. Possible explanations may be that we specifically selected the subset of women desiring to maintain reproductive potential and that the majority of women was nulliparous at time of diagnosis. As treatment-induced infertility significantly impairs the quality-of-life in cancer survivors, these results stress the importance of fertility-sparing treatment options in this population [3,4].

4.2. Vaginal radical trachelectomy

Over the past two decades, VRT with pelvic lymphadenectomy has been accepted as an oncologically safe fertility-sparing alternative to RH in carefully selected patients with early-stage disease. In accordance with previous studies, we found that 4 patients (10.8%) were found to have more extensive disease or LN metastases when attempting fertility-sparing surgery [11,12]. In our cohort, no VRTs were abandoned intraoperatively as all patients with LN metastases were identified during separate SNP/PLND procedures. Fertility-sparing surgery in cervical cancer warrants careful risk stratification. Apart from routine preoperative MR-imaging and physical examination, we feel that SN assessment prior to VRT contributes in proper patient selection by detection of (micro) LN metastases. This two-step procedure prevents not only for undertreatment but also for delay in starting chemoradiotherapy due to surgical morbidity after VRT or RH.

No recurrences occurred after a median FU of 52 months, which is favorable when compared with previous literature reporting rates of 2.7–7.1% [11,12,24]. Given that our findings are based on a limited number of cases, the results are encouraging but should be interpreted with considerable caution.

Although many uncomplicated live-births have been reported after VRT, well-known complications include infertility and prematurity. We report a pregnancy rate of 62.5% and a live-birth rate of 75.0%, which is comparable to previously reported rates ranging from 41 to 67% and 51–73% respectively [11,12,25]. Although 5 of the 12 (41.7%) patients experiencing difficulty conceiving ultimately conceived through ART, we report a relatively high number of patients experiencing fertility issues. As most of our patients were nulliparous, it is difficult to establish whether fertility problems were related to VRT or due to intrinsic factors. As reported by others, cervical stenosis is a well-known cause of subfertility after VRT, presenting in approximately 8.1% of the patients [26,27]. Cervical stenosis may cause significant morbidity due to dysmenorrhea, haematometra and difficulties when performing assisted reproduction technologies. As all patients in our cohort required surgical dilatation of the cervical ostium due to either haematometra or the inability of performing ART, we feel that clinicians should make an effort to timely recognize and treat cervical stenosis to improve fertility outcomes.

The rates for first- (19.0%) and second term miscarriages (4.8%) were both in line with those reported in previous studies and not higher than in the general population [12,25]. We report only 1 (5.0%) preterm delivery which is low when compared with the prematurity rate of 25% as reported in a review concerning 200 pregnancies [28]. There were no severe obstetric or neonatal complications in our study cohort. Our data confirm the earlier described favorable obstetric and neonatal outcomes after VRT in most patients.

4.3. Radical hysterectomy and chemoradiotherapy

For patients requiring radical hysterectomy or (chemo)radiotherapy, biological parenthood is only feasible through ART and surrogacy. Pre-treatment fertility preservation requires close collaboration of both gynecological-oncologists, reproductive specialists and radiation specialists to minimize delay in starting cancer treatment. In our cohort, all patients requiring (chemo)radiotherapy received pre-treatment

Table 3
Obstetric and neonatal outcomes study cohort.

Patient no.	Treatment	Pregnancy	Way of conception	Time to conception (months)	Outcome	Gestational weeks	Fetal weight (g)	Obstetric and neonatal complications
1	VRT	1	IUI	13	Live birth	39 + 0	U	
		2	Naturally	29	Miscarriage 1st trim	8		
		3	Naturally	32	Live birth	38 + 0	U	
2	VRT	4	IUI	19	Ongoing pregnancy	24+	U	
3	VRT	5	Naturally	21	Live birth	39 + 0	2806	
		6	IUI	58	Live birth	38 + 5	3480	
4	VRT	7	TMET	71	Ongoing pregnancy	38 + 0	3440	
5	VRT	8	Naturally	39	Live birth	37 + 2	2340	spontaneous rupture of membranes, dysmaturity
6	VRT	9	Naturally	11	Miscarriage 1st trim	7		
7	VRT	10	Naturally	20	Live birth	37 + 5	U	
		11	Naturally	28	Live birth	38 + 3	U	gestational diabetes
8	VRT	12	Naturally	1	Live birth	37 + 6	U	conceived within one month after VRT, 1st and 2nd trimester hemorrhage
9	VRT	13	Naturally	22	Miscarriage 2nd trim	17 + 0	U	PROM, chorioamnionitis, placenta previa
10	VRT	14	ICSI		Live birth	38 + 0	U	
11	VRT	15	Naturally	10	Live birth	37 + 5	3385	spontaneous rupture of membranes
12	VRT	16	ICSI	53	Live birth	38 + 0	2745	2nd trimester iatrogene hemorrhage for which admission
13	VRT	17	IUI	39	Live birth	39 + 0	2858	cervical insufficiency
		18	IUI		Live birth	39 + 0	U	
14	VRT	19	Naturally	7	Live birth	36 + 3	U	PROM, 2nd trim blood loss
15	VRT	20	Naturally	59	Miscarriage 1st trim	7		uterine myomas
		21	Naturally	41	Miscarriage 1st trim	6		
16	CRT	22	ET + surrogacy	U	Live-birth	38 + 0	U	
17	CRT	23	ET + surrogacy	U	Live-birth	U	U	
18	CRT	24	Ovarian tissue autotransplantation + ICSI + ET + surrogacy	U	Live-birth	39 + 0	U	

IUI, intra-uterine insemintation; TMET, trans-myometral embryo transfer; ICSI, intracytoplasmatic sperm injection; ET, embryotransfer; PROM, prelabor rupture of membranes; VRT, vaginal radical trachelectomy; CRT, chemoradiotherapy.

fertility counseling and fertility was preserved in 23 patients (88.5%), These results suggest that the structural implementation of oncofertility services is feasible in a multidisciplinary oncofertility center. As maintaining fertility potential is of utmost importance in young patients with cervical cancer, we advocate the implementation of a well-integrated oncofertility care program in all centers treating young cancer patients. To minimize delay in cancer treatment, we believe that efforts should be made to perform fertility counseling within one week after diagnosis. Furthermore, we emphasize the importance of weighing in the possible delay of FP in patients with high-risk disease and feel that an individualized risk assessment regarding oncological safety should be carefully evaluated for each patient.

Gestational surrogacy is considered to be a good reproductive option for patients without a (functional) uterus with an ongoing pregnancy rate of 66.7% [29]. We report a live-birth rate of 21.4% among the women who started gestational surrogate treatments. Barriers explaining this discrepancy include the challenge of finding a suitable gestational carrier who is approved by the regulations in centers performing surrogate treatments [29]. The process of finding a gestational carrier is additionally complicated by the Dutch law, that prohibits commercial surrogacy and the public search for a surrogate. Lastly, the chance of achieving a biological genetic offspring may be additionally complicated as some patients may fail to preserve oocytes leaving OTC as only option to preserve fertility. Restoration of ovarian function after frozen-thawed ovarian cortex fragments is achieved in 25–30%, resulting in over 130 live-births worldwide [14,30]. However, this procedure is still considered experimental in the Netherlands. We report only one birth in our cohort after auto-transplantation of frozen-thawed ovarian tissue fragments in an experimental setting. As this may be the only option for patients who cannot delay cancer treatment or fail to preserve oocytes, we do support to continue using this technique.

We expect that the number of surrogate pregnancies in our cohort is likely to increase, as 7 patients are still searching for a gestational carrier and one patient found a gestational carrier for which she currently is within fertility treatments.

4.4. Strengths and limitations

Pregnancy- and live-birth rates may have been underestimated as a result of the experimental nature of novel fertility treatments and retrospective study design. By sending out postal questionnaires we tried to minimize missing data.

5. Conclusion

This study demonstrates that many cervical cancer survivors desire to become parents eventually and that biological parenthood is feasible even in advanced stage disease without compromising oncologic safety. We believe that the findings of this study provide both patients and clinicians with realistic expectations regarding biological parenthood after cervical cancer treatment, which may improve the process of counseling and shared-decision making in newly diagnosed patients. To further improve the chances at biological parenthood in young cancer patients, we advocate the implementation of structural and joined oncofertility care programs in all centers treating young cancer patients.

Author's roles

R.C.J.v.d.P was responsible for data collection, cleaning and analysis, interpretation and discussion and drafting of the article. A.M.E.B., C.G.G. and R.P.Z. initiated the study, contributed to data collection, involved in data interpretation, and critically revised the article. I.M.J-S. contributed to data collection and revised the article. All authors critically reviewed and approved the article.

Details of ethical approval

The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices and was approved by the local Medical Ethical Research Committee on 07-03-2019(document no:19-427).

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No external funding was used for this study.

Declaration of Competing Interest

All authors declare that they have no conflict of interest [31].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.09.003.

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