

Review article

Abdominal radical trachelectomy versus chemotherapy followed by vaginal radical trachelectomy in stage 1B2 (FIGO 2018) cervical cancer. A systematic review on fertility and recurrence rates



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HIGHLIGHTS

- More pregnant women in the NACT followed by VRT group than in the ART group, 21% and 7% respectively.
- More women attempt to conceive and succeeded after NACT followed by VRT than after ART, 70% and 21% respectively.
- Higher chance on a life birth in women treated with NACT followed by VRT in comparison with ART, 63% and 43% respectively.
- Equal number of recurrences and the mortality rate between NACT followed by VRT and the ART group.

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ABSTRACT

Introduction: There is currently no standard of care for women with cervical cancer stage IB2 (FIGO 2018, ≥ 2 cm and < 4 cm in greatest dimension) who wish to preserve their fertility. Generally, two approaches are offered. Option 1: neoadjuvant platinum-based chemotherapy (NACT) to reduce the tumor size to ≤ 2 cm, followed by Vaginal Radical Trachelectomy (VRT) with Pelvic Lymph Node Dissection (PLND) either before chemotherapy or at the time of VRT. Option 2: Abdominal Radical Trachelectomy (ART) with PLND.

Objective: To compare rates of fertility, pregnancy, life births as well as recurrence for women with cervical cancer stage IB2 treated with either NACT followed by VRT, or ART.

Methods: A systematic review was performed using the PubMed database. Articles reporting the search term 'trachelectomy' as text word or as Medical Subject Headings (MeSH) were identified.

Results: Ten studies were identified with a total of 338 patients. After NACT followed by VRT 39% of the women tried to conceive, 70% of these women got pregnant, of which 63% resulted in a life birth. The overall recurrence and death rate were 10% and 2.9% respectively. After ART 40% of the women tried to conceive, 21% of these women got pregnant, which resulted in a life birth rate of 42%. Recurrence and death rate after ART were 6.9%, and 3.4% respectively.

Conclusion: Women with cervical cancer stage IB2 and a wish to preserve fertility treated with NACT followed by VRT have a significantly higher chance of pregnancy than women treated with ART, with comparative oncological results.

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1. Introduction

Cervical cancer is the fourth most common malignancy in women worldwide with an estimated 570 000 new cases in 2018 representing 6.6% of all female malignancies [1]. Since the introduction of screening programs for cervical cancer, the number of women diagnosed with cervical cancer at an early stage has increased. At the same time, more women in western countries delay their first pregnancy to their late twenties, resulting in more women diagnosed with an early stage cervical cancer within their reproductive lifespan [2]. It is estimated that 40% of the women with early stage cervical cancer are diagnosed within their reproductive age [3].

Radical hysterectomy with pelvic lymph node dissection (PLND) is the recommended treatment for women with FIGO stage 1B2 cervical cancer (FIGO 2018, ≥ 2 cm and < 4 cm in greatest dimension) and completed families [4,5]. Radical trachelectomy (RT) with PLND is the treatment of choice for women with stage 1B1 cervical cancer measuring ≤ 2 cm who wish to preserve their fertility. RT may be performed vaginally, abdominally, or laparoscopically/robotically. For patients with cervical cancer ≤ 2 cm, vaginal radical trachelectomy (VRT) is a safe option. Reviews have shown that 80% of the women are able to conceive after VRT, and recurrence rates are less than 5% [6]. However, VRT is usually not performed in women with cervical cancer measuring ≥ 2 cm because of the higher risk of recurrence of up to 20.8% [7].

Currently there is no standard of care for women with stage 1B2 cervical cancer who wish to preserve fertility. There are two approaches offered to these women. Option 1: neoadjuvant platinum based chemotherapy (NACT) to reduce the tumor size to ≤ 2 cm, followed by VRT with PLND either before chemotherapy or at the time of VRT [8–12]. Option 2: abdominal radical trachelectomy (ART) with PLND [13–17].

Presently it remains unknown which of these procedures has the best oncologic and fertility outcomes, and whether oncologic outcomes are comparable to radical hysterectomy. The aim of this review is to compare the rates of fertility, pregnancy, life births as well as recurrence rate for women with early stage cervical cancer stage 1B2 treated with either NACT followed by VRT, or treated with ART.

2. Methods

A systematic review was performed investigating women with early stage cervical cancer with a tumor diameter of ≥ 2 cm and < 4 cm in greatest dimension who wish to preserve their fertility. The PubMed database was searched for articles published from April 1985 to June 2019, using the search term 'trachelectomy' as text word or as Medical Subject Headings (MeSH). All titles and abstracts were examined by two independent researchers (KvK, TV). Any discrepancies between the two reviewers were resolved by a third researcher (RB).

Articles were included if reported patients had early stage cervical cancer with a tumor of ≥ 2 cm and < 4 cm in greatest dimension and treated with a fertility preserving method. The full text

inclusion criteria were; articles published in English, including information about age, histology, tumor diameter, fertility outcomes, pregnancy rates, follow-up period and recurrence. Reviews of literature, case reports, and letters to the editors were excluded. Series exclusively focusing on tumors ≤ 2 cm, and procedures for cervical cancers during pregnancy and conization procedures were excluded. Of articles with duplicate patient information and articles updating prior published series, the most recent data was retained. Reference lists of all included articles were analysed in search of missed articles.

Finally, only articles describing $> 80\%$ of the patients with early stage cervical cancer with a tumor diameter of ≥ 2 cm and < 4 cm in greatest dimension, or articles in which this group of patients was described separately, were used in this review. The quality of the included articles was assessed using the Newcastle-Ottawa scale.

Statistical analysis was performed using the chi-square test or the Fisher exact test. Statistical significance was set at $p < 0.05$.

3. Results

The PubMed search revealed 667 articles. After screening titles and abstracts, 17 relevant articles were evaluated for full text and 10 articles met the selection criteria of this systematic review. No additional studies were identified by checking the reference lists. Fig. 1 shows the flow diagram of the selection process.

3.1. Characteristics of included studies

The 10 included articles consisted of 5 retrospective cohort studies and 5 prospective cohort studies. Results of the studies are summarized in Tables 1 and 2

In 2012 Vercellino et al. performed a prospective cohort study which included 18 women who underwent laparoscopic PLND including paraaortic lymphadenectomy followed by NACT and VRT. Cao et al. compared the surgical and pathologic characteristics, the prognosis and fertility outcomes of 150 patients treated with VRT or ART in a prospective cohort study in 2013. In 2013 Lintner et al. reported the oncological and fertility outcomes of 45 patients after ART. Wethington et al. assessed the oncological outcomes after RT in 29 patients with cervical cancer with a tumor diameter of 2–4 cm retrospectively in 2013. In 2014 Lu et al. examined the feasibility and safety of neoadjuvant intra-uterine arterial chemotherapy followed by total laparoscopic RT in stage 1B2 cervical cancer in 7 women. Robova et al. performed a prospective cohort study in 2014 and reported the oncological and fertility results of 28 women after laparoscopic PLND and vaginal simple trachelectomy after NACT. Lanowska et al. assessed the oncological and fertility results in 22 women after laparoscopic PLND followed by NACT and VRT in 2014. In 2016 Deng et al. evaluated the safety of sentinel lymph node biopsy guided ART in 49 patients with stage 1B2 cervical cancer of whom they observed the surgical, oncologic and fertility outcomes. Guo et al. compared in 2018 the oncologic outcomes between ART and radical hysterectomy for 329 patients with stage 1A2–1B1 cervical cancer (tumor diameter 2–4 cm). Marchiole et al. (2018) performed a retrospective cohort study and reported

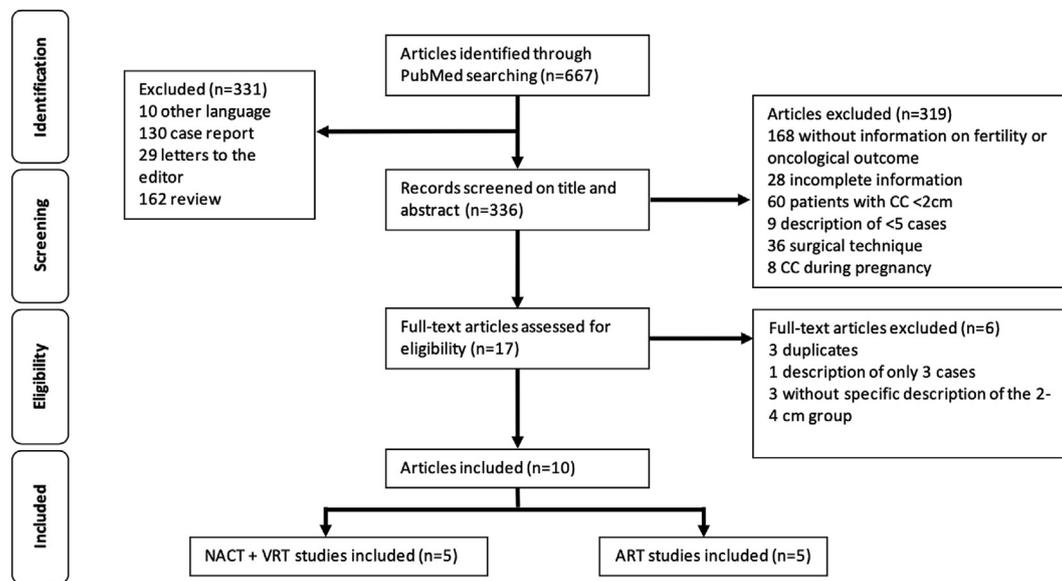


Fig. 1. Flowchart of the selection procedure for systematic review.

the oncological results and survival rates of 19 patients with cervical cancer with a tumor diameter of 2–5 cm stage IB1-2 and IIA1, treated with NACT followed by radical laparoscopic-assisted vaginal radical trachelectomy and investigated the rate of successful pregnancy after the treatment.

3.2. Newcastle-Ottawa Scale

All included studies were assessed as good according to the Newcastle-Ottawa Scale for cohort studies (Table 3).

3.3. Analysis

The 5 articles describing NACT followed by VRT had a total of 92 patients (Table 1A and 1B). The fertility sparing procedure was successfully completed in 69 patients (75%). Twenty-seven women attempted to conceive after the fertility sparing procedure (39%). A total of 27 pregnancies occurred in 19 different women, which is 70% of the women who tried to conceive. Seventeen pregnancies succeeded in a life birth (63% of all pregnancies). The mean follow-up period was 48.0 months. Overall, 7 patients developed a recurrence (10%) and 2 patients died because of their disease (2.9%), 29% of the patients that developed a recurrence died because of the

recurrence. Overall, regarding the initial 92 patients, 19 women (21%) got pregnant, and 17 babies were born (18%).

The 5 articles describing ART had a total of 246 patients (see Table 2A and 2B). The fertility sparing procedure was successfully completed in 204 patients (83%). Eighty-two women attempted to conceive after the fertility preserving procedure (40%). A total of 21 pregnancies occurred in 17 different women, which is 21% of all the women who attempted to conceive. Nine pregnancies succeeded in a life birth (42% of all pregnancies). The mean follow-up period was 59.8 months. Overall, 14 women developed a recurrence (6.9%) and 7 women died because of their disease (3.4%), 50% of the patients that developed a recurrence died because of the recurrence. Overall regarding the initial 246 patients, 17 women (7%) got pregnant, and nine babies were born (4%).

3.4. Statistics

There is no significant difference between the number of women that completed the fertility-sparing surgery (FSS) procedures in both groups (χ^2 2.709, $p = 0.100$). There are significantly more women pregnant in the initial NACT followed by VRT group in comparison with the initial ART group (χ^2 16.608, $p = 0.000$). The number of patients that tried to conceive after the completing the FSS in both groups are not significant different (χ^2 2.858, $p = 0.091$).

Table 1A

Characteristics, oncologic, and fertility outcomes after NACT followed by VRT in patients with cervical cancer stage IB2.

	N	Age (median)	NACT FSS	Attempt to conceive	N = pregnant women	Pregnancy	Miscarriage	Live birth	Follow-up (months)	Recurrence	Deaths
Marchiole (2018)	19	28,3	19 ^a	18 5	3	8	5	3	Median 79	2	0
Robova H (2014)	28	28,3	28 ^b	20 10	8	11	3	8	Median 42	4	2
Lanowska (2014)	20	32,1	20 ^c	18 7	5	5	1	4	Mean 23	1	0
Lu Q (2014)	7	28	7 ^d	7 4	2	2	1	1	Median 66	0	0
Vercellino GF (2012)	18	31,5	6 ^e	6 1	1	1	0	1	Mean 30	0	0
Total	92	29,6		69 27	19	27	10	17		7	2

VRT = vaginal radical trachelectomy, NACT = neoadjuvant chemotherapy, FSS = fertility-sparing procedure, N = number, TIP = Paclitaxel, ifosfamide and cisplatin
TEP = paclitaxel, epirubicin and cisplatin TP = paclitaxel with cisplatin, SCC = squamous cell cancer, AC = adenocarcinoma, ASC = adenosquamous carcinoma.

^a TIP = 11 in 8 patients with SCC and 3 patients with AC, TEP = 5 in AC, and TP = 3 in 2 patients with SCC and 1 with AC.

^b 15 cisplatin plus ifosfamide in SCC and 13 cisplatin plus doxorubicin in AC.

^c TIP = 19 in 11 SCC and 8 AC patients, TP = 1 ASC.

^d TP = 7 in SCC.

^e TIP = 5 in 3 AC and 2 SCC patients, TP = 1 ASC.

Table 1B
Percentages of the oncological and fertility outcomes after NACT followed by VRT for patients with cervical cancer stage IB2.

	N	% of total	% of FSS	% attempt to conceive	% pregnancies	% of recurrence
Stage IB2 cervical cancer	92	100%				
FSS	69	75%	100%			
Attempt to conceive	27	29%	39%	100%		
Pregnant women	19	21%	28%	70%		
Pregnancy	27				100%	
Miscarriage	10				37%	
Live birth	17	18%	25%		63%	
Recurrence	7		10%			100%
Death	2		2.9%			29%

NACT = neoadjuvant chemotherapy, FSS = fertility-sparing procedure, N = number.

There are significantly more women pregnant that tried to conceive after completing NACT followed by VRT in comparison with completing ART (χ^2 22.627, $p = 0.000$). There are significantly more live births after completing the FSS with NACT followed by VRT than when women are treated with ART (χ^2 24.479, $p = 0.000$). There is no significant difference between the numbers of live birth after pregnancy between both groups (χ^2 1.923, $p = 0.165$). There is no significant difference between the number of recurrences between both groups (χ^2 0.782, $p = 0.376$) and the mortality rate (Fisher exact = 1).

4. Discussion

This study shows that women with FIGO stage 1B2 cervical cancer (FIGO 2018, tumor diameter ≥ 2 cm and < 4 cm in greatest dimension) and a wish to preserve fertility treated with NACT followed by VRT have a significantly higher chance of pregnancy (21%) than women treated with ART (7%), with comparative oncological outcomes (mortality rate 2.9% versus 3.4% respectively).

The oncological and obstetrical results in our systematic review for patients with stage IB2 treated with NACT followed by VRT compare well to the results of women with early stage cervical cancer ≤ 2 cm treated with VRT. Plante et al. assessed the oncologic, fertility and obstetrical outcomes for 125 patients treated with VRT

in a systematic review, of which 89% of patients had cervical cancer ≤ 2 cm. They reported a life birth rate of 73%, with an overall recurrence rate of 4.8% and a mortality rate of 1.6% [6].

The oncological and obstetrical results in our systematic review for patients with stage IB2 treated with ART are worse in comparison with patients with early stage cervical cancer ≤ 2 cm treated with ART. Pareja et al. assessed the fertility and obstetrical results for 298 patients with cervical cancer ≤ 2 cm after treatment with ART in a systematic review. They reported that 38% of the women attempted to conceive after ART, with a pregnancy rate of 59.3%. This resulted in a life birth rate of 73%. The recurrence rate and mortality rate were 3.8% and 0.4% respectively [18]. The largest series on ART was reported by Li et al. [19]. They reported on 333 patients with tumors till 4 cm in greatest dimension (132 patients with tumors ≥ 2 cm and < 4 cm), with 6.6% pregnant women (22/333) and 4.5% live birth rate (15/333), with an overall recurrence rate of 3.3% and an overall mortality rate of 1.5%. They reported a recurrence rate of 5.3 for women with tumors ≥ 2 cm and < 4 cm.

Of the 7 recurrences in the NACT followed by VRT group, 4 occurred in the study of Robova et al. (2014) who performed a simple trachelectomy instead of a radical trachelectomy after NACT. Of these 4 women 2 had adenocarcinoma (AC) and 2 had squamous cell cancer (SCC) stage IB2 with lymph vascular space invasion (LVSI), which both died because of their disease. The optimal

Table 2A
Characteristics, oncologic, and fertility outcomes after ART in patients with cervical cancer stage IB2.

	N	Age (median)	FSS	Attempt to conceive	Pregnant women	Pregnancy	Miscarriage	Live birth	follow-up (months)	Recurrence	Death
Guo J (2018)	75	ART 31	71	29	5	8	6	2	Mean 75,5	2	2
Deng X (2016)	49	ART 28,5	45	19	5	5	4	1	Mean 61	2	1
Cao DY (2013)	48	RT ^a 30	48	24	3	3	0	3	Mean 24,5	5	2
Lintner B (2013)	45	ART 32	31	8	3	4	1	3	Median 90	4	2
Wethington SL (2013)	29	RT ^b 31	9	2	1	1	1	0	Median 44	1	0
Total	246	30,5	204	82	17	21	12	9		14	7

ART = abdominal radical trachelectomy, N = number, FSS = fertility-sparing procedure, RT = radical trachelectomy, VRT = vaginal radical trachelectomy.

^a 24 ART and 24 VRT, all 5 recurrences occurred in the VRT group, pregnancies not specified.

^b 22 ART, 6 VRT and 1 robotic, 1 recurrence occurred in the robotic case, pregnancies not specified.

Table 2B
Percentages of the oncological and fertility outcomes after ART in patients with cervical cancer stage IB2.

	N	% of total	% of FSS	% attempt to conceive	% pregnancies	% of recurrence
Stage IB2 cervical cancer	246	100%				
FSS	204	83%	100%			
Attempt to conceive	82	33%	40%	100%		
Pregnant women	17	7%	8%	21%		
Pregnancy	21		10%		100%	
Miscarriage	12				57%	
Live birth	9	4%	4.4%		43%	
Recurrence	14		6.9%			100%
Death	7		3.4%			50%

ART = abdominal radical trachelectomy, N = number, FSS = fertility-sparing procedure.

Table 3

Newcastle-Ottawa quality assessment scale for included cohort studies.

Article	Selection				Comparability of cohorts	Outcome			Quality
	Representativeness of the exposed cohort ^a	Selection cohorts' same source	Ascertainment of exposure	Outcome of interest was not present at start of study		Assessment of outcome ^b	Follow-up ^c	Adequacy of follow-up	
Marchiole (2018)	★	NA	★	★	NA	★	Median 79 months ★	No lost to follow-up ★	Good
Robova H (2014)	★	NA	★	★	NA	★	Median 43 months ★	No statement about lost to follow-up	Good
Lanowska (2014)	★	NA	★	★	NA	★	Mean 23 months	No lost to follow-up ★	Good
Lu Q (2014)	★	Na	★	★	NA	★	Median 66 months ★	No statement about lost to follow-up	Good
Vercellino GF (2012)	★	Na	★	★	NA	★	Mean 30,6 months ★	No statement about lost to follow-up	Good
Guo J (2018)	★	NA	★	★	NA	★	Mean 75,5 months ★	Follow-up rate 96,5% ★	Good
Deng X (2016)	★	NA	★	★	NA	★	Mean 61 months ★	Follow-up rate 93% ★	Good
Cao DY (2013)	★	NA	★	★	NA	★	Mean 24,5 months ★	Follow-up rate 75%. Patients that were lost to follow-up were not included in database ★	Good
Lintner B (2013)	★	NA	★	★	NA	★	>5 years ★	No lost to follow-up ★	Good
Wethington SL (2013)	★	NA	★	★	NA	★	Median 44 months ★	No statement about lost to follow-up	Good

NA = not applicable.

★ fulfilled all criteria of the Newcastle Ottawa Scale for this item.

^a Representativeness of the exposed cohort: all included studies representative for women with cervical cancer tumor diameter 2–4 cm and a wish to preserve fertility.^b Assessment of outcome: all with medical records.^c Follow-up period ≥ 24 months was assessed as long enough for outcomes to occur.

response rate to NACT was 60.7% in this study, which is less than the 78.8% after NACT used in IB bulky tumors followed by radical hysterectomy. So, it remains unsure whether suboptimal response to chemo, or simple trachelectomy caused these recurrences [20]. Two of the 7 recurrences occurred in the study of Marchiole et al. (2018). Both patients had SCC stage IB2 with LVSI. The woman diagnosed with a recurrence in the study of Lanowska et al. was diagnosed with an AC stage IB2. Some authors report on the results of patients treated with NACT followed by conization, however with the data of Robova et al. in mind, caution is warranted with this policy.

Of the 14 recurrences in de ART group 4 occurred in the studies of Guo et al. and Deng et al. They both reported 2 patients with recurrence with SCC and 1 of those patients with LVSI. Both women died in the study of Guo et al. because of the recurrence. In the study of Deng et al., the women with LVSI died. Linter et al. reported 4 recurrences, 2 patients died, 1 patient had an IB2 glassy cell tumor and 1 patient with a stage IB1 AC. Wethington et al. reported 1 recurrence with SCC without LVSI.

The tumor characteristics of the group women with recurrences are unfavorable. Patients with AC are associated with poorer prognosis than patients with SCC. AC has a significantly lower survival rate compared to SCC [21,22]. LVSI have been identified as a factor to influence the survival of patients with SCC. LVSI is an independent predictor of pelvic nodal metastases and the quantity of LVSI is an independent prognostic factor for time to recurrence in patients with early stage SCC [23,24].

Not all the women included in this study who successfully completed the fertility-preserving treatment tried to get pregnant

after successfully completing the treatment. Studies have found that experience of cancer did not decrease the desire to have children, it increased the value on parenthood [25]. There are different reasons that could affect why women didn't try to get pregnant after the fertility preserving treatment. Women could have lost their chance of pregnancy because of the chemoradiation treatment after recurrence. Some women did not desire pregnancy during the follow-up period of the studies. Of course, there can be other reasons for not pursuing a pregnancy such as relationship problems, being single, or worries concerning having sexual intercourse or recurrence. Some patients have unrelated problems which could interfere with conception like age, male partner infertility, endometriosis or premature ovarian failure [8,9,13,15].

There is some heterogeneity between included studies. Not all included women are treated the same way. There is some difference in the neoadjuvant chemotherapy regimens, not all women with the same histological type are treated with the same chemotherapy regime: Paclitaxel, ifosfamide and cisplatin (TIP), paclitaxel, epirubicin and cisplatin (TEP), and paclitaxel with cisplatin (TP) are used in the studies. TIP chemotherapy is one of the most active NACT regimen. Studies suggest that it might be better to treat patients with AC with TEP instead of TIP [26]. Alkylating agents such as ifosfamide and cisplatin are detrimental to the ovarian follicles and are associated with ovarian fibrosis and can lead to premature ovarian failure. Avoiding regimen like ifosfamide would make the chemotherapy less gonadotoxic [27]. A combination of carboplatin and paclitaxel might be more tolerable. Women treated with a fertility preserving procedure including NACT, might benefit from a lower toxic dose like TP regimen [28]. Despite the

fact that NACT may have negative effects on ovarian function, we showed in this study higher fertility rates after NACT with VRT, than after ART. This indicates that NACT seems a safe option.

Not all patients that are included in this study are treated with ART, 2 studies included patients after radical trachelectomy. Cao DY et al. (2013) included 24 patients who underwent ART and 24 patients who underwent VRT. Wethington SL et al. (2013) included 22 patients who underwent ART, 6 patients who underwent VRT and 1 robotic.

To our knowledge this is the first systematic review that reported the oncological, fertility and pregnancy rates for women with stage IB2 cervical cancer (FIGO 2018, tumor diameter ≥ 2 cm and < 4 cm in greatest dimension) treated with either NACT followed by VRT or treated with ART. It describes a large scale of patients and we didn't include any case reports or studies with a number of patients ≤ 5 . The following limitations need to be addressed: there is no information about the fertility state of the women before the fertility preserving treatment. The surgeries in the studies were performed by different gynecologists and the NACT had not been standardized in this study. Most of these limitation factors can be eliminated in a randomized controlled trial, but this may be hard to complete due to the very different treatment arms. Further investigation among NACT followed by VRT and ART is necessary. Ongoing research will provide more concrete guidelines in the treatment for women with stage IB2 cervical cancer who wish to preserve their fertility. The FIGO 2018 Stage IB2 (2–4 cm) Cervical cancer treated with Neoadjuvant chemotherapy followed by fertility Sparing Surgery (CONTESSA); the Neoadjuvant Chemotherapy and Conservative Surgery in Cervical Cancer to Preserve Fertility (NEOCON-F) is an ongoing multicenter study [29]. Until results of this study is available, this systematic review provides women and physicians with information on the potential impact of NACT followed by VRT, or ART on fertility and oncological outcomes.

In conclusion, this systematic review showed that women with stage IB2 cervical cancer (FIGO 2018, tumor diameter ≥ 2 cm and < 4 cm in greatest dimension) and a wish to preserve fertility treated with NACT followed by VRT have a significantly higher chance of pregnancy than women treated with ART, with comparative oncological results.

Authors' contribution to the manuscript

K.G.G van Kol: search, study selection, data collection, interpretation of results, manuscript writing T.F.M. Vergeldt: search, study selection, manuscript writing R.L.M. Bekkers: protocol development, interpretation of results, manuscript writing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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