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Original Research

Morbidity of radical hysterectomy combined with caesarean section in pregnant patients with cervical cancer

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Objectives: In pregnant patients with early stage cervical cancer, the preferred mode of delivery is a caesarean section (CS), which can be combined with a radical hysterectomy and pelvic lymphadenectomy (RHLD). The aim of this study was to compare this group of patients with non-pregnant cervical cancer patients treated by RHLD alone with regard to perioperative morbidity, oncological outcomes, and perinatal outcomes. *Methods*: We retrospectively reviewed all consecutive patients diagnosed with early stage cervical cancer during pregnancy who were treated by CS and RHLD at our institution. Non-pregnant counterparts served as controls and were matched on a 1 : 2 ratio. Key outcomes were perioperative complications, cancer outcome and perinatal outcome. *Results*: Nineteen pregnant women treated with a CS and RHLD were matched with 38 non-pregnant control patients with cervical cancer who underwent a RHLD. The only difference in morbidity was a higher estimated perioperative blood loss in the pregnant group (1600 mL) compared to the control group (800 mL; $P = 0.001$), resulting in seven (36.8%) and eight (21.1%) blood transfusions ($P = 0.22$; OR 2.19; 95% CI 0.65 to 7.38), respectively. *Conclusion*: Oncological outcomes were similar with 5-year overall survival rates of 94% in the pregnant group and 95% in the non-pregnant group. The neonatal survival rate was 100%. Complication rates and oncological outcomes after treatment with RHLD were comparable for pregnant and non-pregnant patients with early stage cervical cancer. Therefore we feel that it is safe to combine a CS with a RHLD in pregnant patients with early stage cervical cancer.

Keywords

Uterine cervical cancer; Postoperative complications; Caesarean section; Radical hysterectomy; Pregnancy; Survival; Perinatal mortality

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide, most frequently diagnosed in women between the ages of 35 and 44 years [1]. Approximately 1–3% of cervical cancers are diagnosed in pregnant patients, during delivery or shortly thereafter [2]. Over the past years the mean age at which women have their first child has increased in developed countries [3]. As a consequence of the increasing maternal age, the incidence of cancer during pregnancy in the developed world is expected to rise. Standard treatment for early stage cervical cancer in non-pregnant patients is a radical hysterectomy with pelvic lymphadenectomy (RHLD). Similar management can be offered during pregnancy. However, delay of local definitive treatment, with or without neoadjuvant chemotherapy, is an option in response to maternal request in order to improve neonatal outcomes [4]. The preferred mode of delivery is a caesarean section (CS) with a classical incision in the uterus to avoid surgical tumour spread. This procedure can be combined with local definitive treatment: a RHLD [4, 5]. During pregnancy, the uterus is enlarged and well vascularized, which might impede operative treatment and potentially result in an increased risk of perioperative complications [6].

In a recently published population based, retrospective study, the perioperative morbidity in pregnant cervical cancer patients treated by CS combined with radical hysterectomy was found to be higher compared to a non-pregnant control group treated by radical hysterectomy alone [7]. The authors of this study therefore, advised to consider performing the radical hysterectomy four to six weeks after the CS. Delayed surgery, however, carries a potential risk of progression of the cervical cancer. In addition, patients have to be scheduled for a second operation after the CS. In this population based study, no data were available on the extent of the radical hysterectomy, stage of disease, pathological characteristics and oncological outcome. As this information is essential to guide treatment decisions, more studies are needed on this subject. Currently, there are limited additional data in larger patient sets reporting on complication rates, morbidity, and perinatal and oncological outcomes in pregnant patients with cervical cancer. For that reason, the aim of this study was to evaluate these outcomes in cervical cancer patients, in whom a caesarean delivery was combined with a RHLD. These patients were matched with non-pregnant cervical cancer patients who underwent only a RHLD.

2. Materials and methods

2.1 Design and setting

This was a single centre, retrospective, case-control study. All consecutive patients diagnosed with cervical cancer during pregnancy between 1995 and 2019 who underwent a CS

and RHLD in the same session were identified and included in the pregnancy group. Patients were all treated at a tertiary referral centre for gynaecological cancer and obstetrics in the Netherlands. All radical hysterectomies were open procedures and performed according to the Okabayashi method (Querleu type C2 radical hysterectomy) [8]. Controls were non-pregnant cervical cancer patients treated with RHLD, matched on a 1 : 2 ratio for year of treatment, age (both with a 5 year interval), International Federation of Gynaecology and Obstetrics (FIGO) 2009 stage and clinical tumour size ($<$ 2 cm, 2–4 cm and $>$ 4 cm) measured by physical exam or imaging, all at time of diagnosis. Year of treatment was one of the criteria in matching to correct for the potential influence of changes in treatment (techniques) over the years. Statistical Package for the Social Sciences software (BM SPSS Statistics version 25.0), used for all analyses, randomly selected cases who met the matching criteria in the electronic database. All cancer diagnoses were histologically confirmed and staged according to the FIGO staging system of 2009. Conversion to the latest FIGO (2018) staging system, which is based on clinical, imaging and pathological data, was not feasible due to lack of imaging results in patients analysed in the early years of this retrospective study [9, 10]. Some pregnant patients received neo-adjuvant chemotherapy in order to postpone delivery and definitive treatment. Cases and controls, regardless of pregnancy, received adjuvant radiotherapy, when pathological examination after surgery showed positive lymph nodes, parametrial invasion or close resection margins. Radiotherapy was combined with chemotherapy in the presence of a combination of unfavourable prognostic factors, i.e., positive lymph nodes, parametrial invasion and/or non-squamous histology.

2.2 Data collection

All information was extracted from the electronic patient records. Information was collected regarding preoperative haemoglobin level, American Society of Anaesthesiologists (ASA) classification, body mass index, smoking status, histopathological tumour type, tumour grade, lymphovascular space invasion, invasion depth, parametrial invasion, lymph nodes, resection margin (pathological close tumour margin was defined as $<$ 1 mm), (neo-) adjuvant radio- and chemotherapy, and diagnosis-treatment interval (time between date of diagnosis and radical hysterectomy). We collected information on operation time, estimated blood loss and duration of hospital admission. A complication was defined as blood loss requiring transfusion, intraoperative injuries (i.e., bowel, bladder and ureteral injury), thromboembolic events, infections, intensive care admission and ileus during or within 30 days after surgery. The Clavien-Dindo grading system was used for the classification of surgical complications [11]. Furthermore, the location and date of recurrence, last follow-up date, date of death and cause of death were recorded. Patients who did not experience recurrence or who were alive at the end of their follow-up were censored at the last known date of follow-up. Information concerning perinatal outcomes included gestational age, severe pregnancy complications, birth weight and percentiles, presence of congenital defects and duration of neonatal intensive care unit admission. Small for gestational age was defined as any birth weight $<$ 10th percentile, corrected for gestational age and sex [12]. For the purpose of this paper, we defined severe pregnancy complications as pregnancy related events that required delivery earlier than initially planned. Ethical approval for the study was obtained from the Medical Ethics Review Committee of the Academic Medical Centre (reference number W20_265#).

2.3 Statistical analysis

Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed data were compared with the use of the independent samples *t*-test, whereas data with non-normal distribution with the Mann-Whitney U-test. Discrete variables were compared using the Chi-square independence or the Fisher's exact test. Survival analysis were performed with a Kaplan-Meier-curve using the log rank to statistically test for differences. Furthermore, cox and logistic regression analysis were used for calculating hazard ratios (HR) or odds ratios (OR) with 95% confidence intervals (CI). We considered a *P*-value below 0.05 as indicating a statistically significant difference.

3. Results

3.1 Clinical characteristics

Nineteen pregnant women met the inclusion criteria and were matched with 38 non-pregnant control patients. Clinical and pathological characteristics of the patients are summarized in Table 1. Since matching was based on age, year of treatment, FIGO stage and tumour size, these characteristics did not differ between both groups. In the pregnant group, the ASA classification was higher (P = 0.001) and the preoperative haemoglobin was lower ($P < 0.001$) than in the control group. The diagnosis-treatment interval was 16 days longer in the pregnant group compared to the non-pregnant group, but this difference did not reach statistical significance. The mean gestational age was 27 weeks at diagnosis and 35 weeks at caesarean delivery. Neo-adjuvant chemotherapy was administered in 10 patients, including one non-pregnant patient, who received neo-adjuvant treatment in the context of a study. Chemotherapy consisted of cisplatin monotherapy (early years until 1999) or carboplatin and paclitaxel for two to five cycles. Only one patient out of nine in the pregnant group did not respond, corresponding with response rates of 88.9% in the pregnancy and 100% in the control group. Adjuvant therapy, either consisting of radiotherapy or chemoradiation, was administered to 26% in the pregnant group and 34% in the control group (P = 0.55). The median follow-up was 56 months (range 7–186 months) and 61 months (range 12–261 months), respectively.

Table 1. Characteristics of pregnant patients (caesarean section, radical hysterectomy with pelvic lymphadenectomy) and matched controls (radical hysterectomy with pelvic lymphadenectomy).

	Pregnant group n = 19	Control group n = 38	*P*-value
Characteristics			
Age (mean)	34 ± 3.8	35 ± 4.9	0.23
Body mass index (kg/m^2)	26 (19–34)	23 (16–41)	0.18
American Society of Anaesthesiologists classification			0.001
American Society of Anaesthesiologists 1	8 (42.1%)	32 (84.2%)	
American Society of Anaesthesiologists 2	11 (57.9%)	6 (15.8%)	
Year of treatment	2013 (2001–2019)	2008 (1996–2017)	0.053
Smoking			0.57
Yes	4 (21.0%)	13 (34.2%)	
Former smoker	3 (15.8%)	6 (15.8%)	
No	12 (63.2%)	19 (50.0%)	
Preoperative haemoglobin (mmol/L)	6.8 ± 0.8	8.0 ± 0.8	< 0.001
Mean gestational age at diagnosis (weeks)	26 ± 7.3	-	-
Median gestational age at radical hysterectomy (weeks)	35 (21–37)	-	-
Diagnosis-treatment interval (median days)	46 (6–158)	30 (3–84)	0.22
Median follow-up (months)	56 (7–186)	61 (12–261)	0.28
Tumour stage (FIGO[a] 2009)			1.00
FIGO stadium IB1	13 (68.4%)	26 (68.4%)	
FIGO stadium IB2	5 (26.3%)	10 (26.3%)	
FIGO stadium IIA	1 (5.3%)	2 (5.3%)	
Tumour size			0.42
< 2 cm	3 (15.8%)	10 (26.3%)	
2–4 cm	12 (63.2%)	17 (44.7%)	
> 4 cm	4 (21.1%)	11 (28.9%)	
Histologic type			0.40
Squamous cell carcinoma	10 (52.6%)	24 (63.1%)	
Adenocarcinoma	6 (31.6%)	12 (31.6%)	
Adenosquamous carcinoma	3 (15.8%)	2 (5.3%)	
Invasion depth (mean mm)	9.7 ± 7.6	11.7 ± 6.8	0.34
lympho-vascular space invasion	11 (57.9%)	19 (51.4%)	0.64
Positive lymph nodes	3 (15.8%)	9 (23.7%)	0.73
Close resection margin	1 (5.3%)	4 (10.5%)	0.51
Parametrial invasion	1 (5.3%)	5 (13.2%)	0.65
Neo-adjuvant therapy	9 (47.4%)	1 (2.6%)	< 0.001
Cycles (number of)	3 (2–5)	5	0.20
Response rate	8 (88.9%)	1 (100%)	1.00
Adjuvant therapy (any)	5 (26.3%)	13 (34.2%)	0.55
Radiation	2 (10.5%)	6 (15.8%)	0.71
Chemoradiation	3 (15.8%)	7 (18.4%)	1.00

[a] International Federation of Gynaecology and Obstetrics (FIGO); Data are *n* or % per patient group.

3.2 Operation and complications

Two out of 19 cases underwent a sectio parva, immature surgical termination of pregnancy, at the gestational age of 21 and 23 weeks. One out of 19 cases was treated by a laparoscopic pelvic lymphadenectomy at the gestational age of 15 weeks, before definitive treatment at 32 weeks. In all other pregnant patients, the radical hysterectomy was combined with a lymphadenectomy. The complication rate in both groups was almost 50%, mostly caused by urinary tract infections and blood loss requiring transfusions grade II (Table 2). Pregnant patients receiving combined treatment had more excessive perioperative blood loss compared to non-pregnant patients receiving RHLD alone (blood loss 1000–2000 mL; OR 20.63; 95% CI 4.38 to 97.03 and blood loss > 2000 mL; OR 7.50; 95% CI 1.32 to 42.50). The median amount of perioperative blood loss in the pregnant group was 1600 mL (range 250–3000 mL). Although this was twice the median compared to the control group (800 mL; range 150–3500 mL; $P < 0.001$), it did not result in more blood transfusions (7 (36.8%) vs 8 (21.1%), respectively; $P = 0.22$; OR 2.19; 95% CI 0.65 to 7.38). Perioperative injuries and postoperative mortality did not occur within our study population. Only one complication was classified as grade III. This concerned a patient with a urosepsis after CS and RHLD, who

Table 2. Peri- and postoperative morbidity of pregnant patients (caesarean section, radical hysterectomy with pelvic lymphadenectomy) and matched controls (radical hysterectomy with pelvic lymphadenectomy).

Operation and complications	Pregnant group n = 19	Control group n = 38	*P*-value
Operation time (min)	349 (210–998)	317 (208–525)	0.24
Estimated blood loss (mL)	1600 (250–3000 mL)	800 (150–3500 mL)	0.001
Complications	10 (52.6%)	16 (42.1%)	0.45
Blood loss requiring transfusion (grade II[a])	7 (36.8%)	8 (21.1%)	0.22
Intraoperative injury	0 (0%)	0 (0%)	-
Infections	3 (15.8%)	12 (31.6%)	0.34
Wound infection	0 (0%)	0 (0%)	-
Urinary tract infection (grade II)	3 (15.8%)	11 (28.9%)	0.34
Sepsis (grade III)	0 (0.0%)	1 (2.6%)	-
Pneumonia	0 (0%)	0 (0%)	-
Intensive-care admission	0 (0%)	0 (0%)	-
Ileus (grade I)	0 (0%)	2 (5.3%)	0.55
Thromboembolic events[b]	2 (10.5%)	0 (0%)	0.11
Pulmonary embolism (grade II)	1 (5.3%)	0 (0%)	-
Deep vein thrombosis	0 (0%)	0 (0%)	-
Thrombophlebitis (grade II)	1 (5.3%)	0 (0%)	-
Duration of hospital admission (days)	11 (6–22)	11 (6–22)	0.61

[a]Grading by Clavien-Dindo scale; [b]Both thromboembolic events occurred in the same patient.

required a nephrostomy catheter. The duration of hospital admission was the same for both groups with a median of 11 days (range 6 to 22 days).

3.3 Oncological outcomes

With a median follow-up of 56 months, one patient in the pregnant group died of recurrent cervical cancer. The median follow-up in the control group was 61 months and three patients in this group died due to recurrence. The 5-years overall survival rate was 94% for the pregnant group and 95% for the non-pregnant group ($P = 0.92$; HR 0.88; 95% CI 0.08 to 9.75) (Fig. 1). Characteristics that might affect oncological outcomes like lympho-vascular space invasion, parametrial invasion, tumour size, FIGO stage, histopathological type, tumour grade, invasion depth and lymph node metastases were equally distributed in both groups. Seven patients suffered from cancer recurrence, three (15.8%) in the pregnant and four (10.5%) in the control group ($P = 0.68$). There was no difference in 5-years progression-free survival rates between both groups ($P = 0.33$; HR 0.46; 95% CI 0.09 to 2.29) (Fig. 2). One pregnant patient had a locoregional recurrence, and she was treated successfully with chemoradiation. All other recurrences were distant metastases. Five patients with a distant recurrence received palliative chemotherapy and one control patient refused life-prolonging therapy.

3.4 Neonatal outcomes

In two out of 19 a CS was performed before the gestational age of 24 weeks. In the remaining 17 patients, pregnancy was continued beyond the threshold for neonatal viability and all of their 18 neonates, including one set of twins, survived (Table 3). The caesarean delivery in two patients were carried out a week ahead of schedule, because of severe pregnancy complications due to severe vaginal bleeding and persistent contractions. The median gestational age at birth was 35 weeks with a mean birth weight of 2708 gram and corresponding percentile of 61%, including one small for gestational age neonate with a birth percentile below 1%. No congenital defects were observed. Two-thirds (66.7%) of the neonates were admitted to the neonatal intensive care unit for a median duration of seven days (range 1 to 25 days).

Table 3. Neonatal outcomes.

Neonatal outcomes	n = 18
Twin pregnancies	1/17 (5.9%)
Severe pregnancy complications	2/17 (11.8%)
Median gestational age at birth (weeks)	35 (31–37)
Survival rate	18 (100%)
Birth weight (gram)	2708 (± 623)
Birth weight percentile (%)	61 (± 29)
Small for gestational age	1 (5.6%)
Congenital defects	0 (0%)
Neonatal intensive care unit admission	12 (66.7%)
Time of neonatal intensive care unit admission (days)	7 (1–25)

4. Discussion

In this case-control study, we found increased perioperative blood loss, but no more need for blood transfusions, after RHLD combined with a CS compared to RHLD alone. We found no other differences between both study groups in terms of perioperative morbidity or any of the predefined oncological outcomes.

In our series, we found a median blood loss of 1600 mL in RHLD combined with a CS, which is comparable with the 1500–2000 mL found in literature in combined (CS and RHLD) per laparotomy [13–16]. The observed blood loss

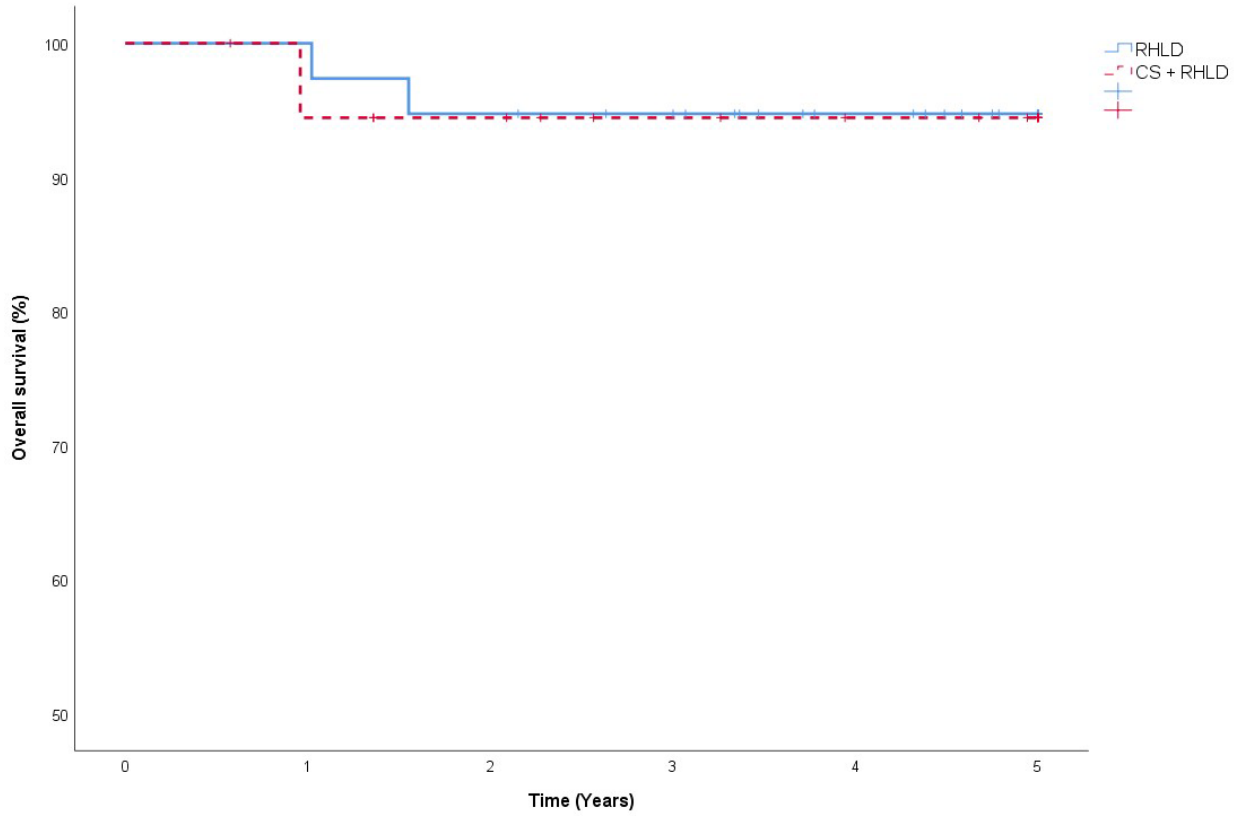

Fig. 1. Oncological outcomes presented by Kaplan-Meier estimates of overall survival for 5 years. Radical hysterectomy and pelvic lymphadenectomy (RHLD) group, caesarean section with radical hysterectomy and pelvic lymphadenectomy (CS + RHLD) group.

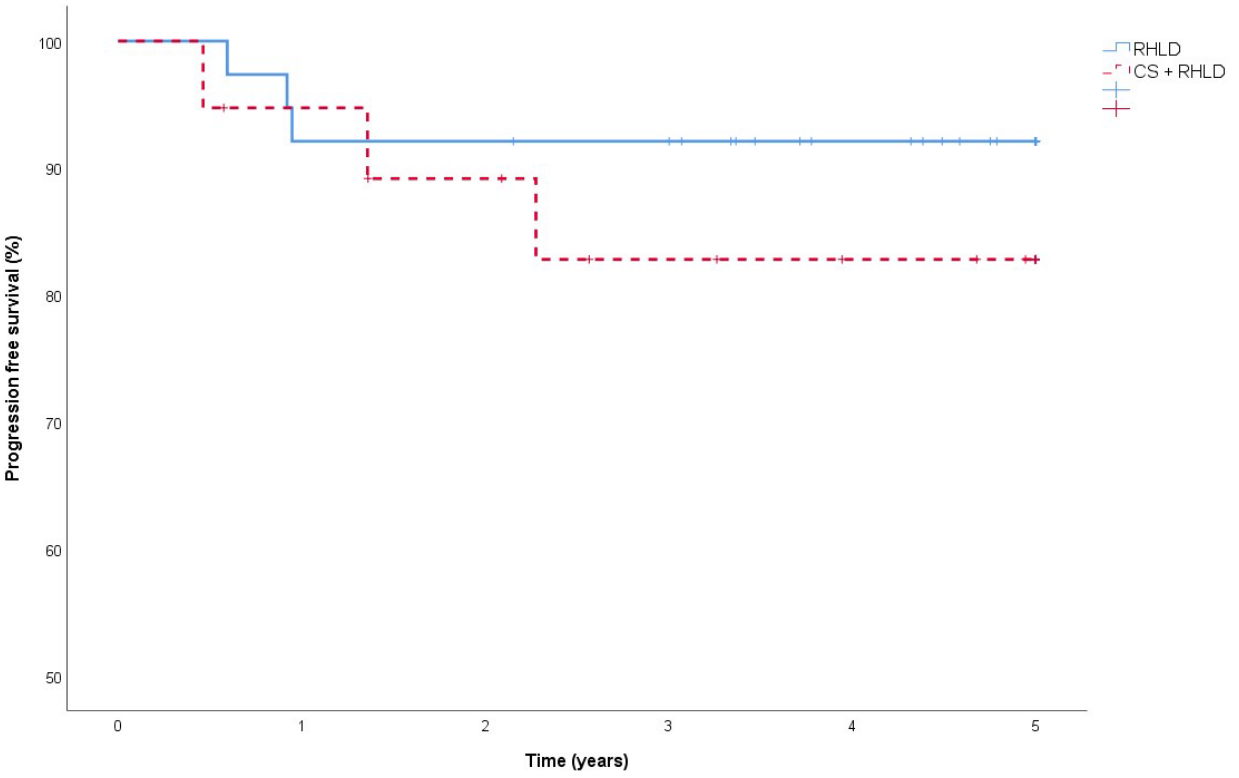

Fig. 2. Oncological outcomes presented by Kaplan-Meier estimates of progression-free survival for 5 years. Radical hysterectomy and pelvic lymphadenectomy (RHLD) group, caesarean section with radical hysterectomy and pelvic lymphadenectomy (CS + RHLD) group.

could be an overestimation, because it may have included amniotic fluid. Although we objectified more blood loss in the pregnant group and a lower preoperative haemoglobin level, the number of blood transfusions did not differ between both groups. Therefore, the difference in blood loss may not have been clinically relevant. In approximately half of our patients a complication occurred, regardless of the patient group. However, only one complication was classified as grade III and the majority of these complications consisted of blood loss requiring blood transfusion and urinary tract infections. The urinary tract infections were possibly due to the prolonged presence of the urinary catheter after radical hysterectomy.

Our finding of increased blood loss, but otherwise no increase in morbidity when a CS is combined with a radical hysterectomy, is supported by others [14–16]. Bigelow *et al.* compared the operative outcome of pregnant patients with cervical cancer based on the timing of radical hysterectomy [16]. Six women who had a CS combined with a radical hysterectomy had statistically significantly higher estimated blood loss compared to eight women who had a postpartum radical hysterectomy (2033 vs 425 mL; $P = 0.0064$), although there was no difference in blood transfusions or surgical complications. On the contrary, a recently published population-based study by Matsuo *et al.* found an increase in total perioperative morbidity in 257 patients with a combined procedure compared to 15,420 patients who underwent an open radical hysterectomy [7]. The increased total perioperative morbidity for the combined group in this study was mainly caused by an increase in perioperative blood loss with an incidence of 27.1% vs 13.8% in the control group. Our study and Bigelow *et al.* found more haemorrhage in the combined group too, but without an increase in blood transfusions, although this might be the result of an insufficient sample size to detect a difference [16]. Because the variable blood transfusion was lacking in the Matsuo study, the clinical impact of the increased blood loss as found in their study, was not evaluated. Comparing morbidity in one surgical group versus another demands matching for variables impacting on morbidity, such as radicality of the procedure, tumour size and stage of disease. Unfortunately, this was not done in both previous mentioned studies [7, 16].

In our study, there was no difference in oncological outcomes between pregnant and non-pregnant women with early stage cervical cancer. These data should be interpreted with caution due to the small sample size. Potentially, combining RHLD with a CS could have a negative impact on maternal survival due to the fact that surgical treatment is often delayed in the interest of the fetus. In addition, technical difficulties, either caused by insufficient access to the deeper pelvis due to the increased size of the uterus, or caused by increased blood loss, can potentially result in less radical surgery and consequently inferior oncological outcome.

There are few studies reporting on survival in patients treated by CS combined with radical hysterectomy. Bigelow *et al.* reported a 5-years survival rate of 100% (6/6), after combined treatment, which was similar to the survival rate after postpartum radical hysterectomy [16]. In a study by Monk *et al*, both the disease free and overall survival in 21 pregnant cervical cancer patients was 95%, with a mean follow-up of 40 months [14]. There was no control group in this study. In a case-control study, oncological outcomes of 30 pregnant women with early stage cervical cancer were found to be comparable with non-pregnant cervical cancer patients [15]. Twenty-nine of the pregnant patients (97%) were alive after 148 months of follow-up versus 27 control patients (90%) after 145 months of follow-up. Lee *et al.* described the effect of delayed treatment on survival in patients with pregnancy associated cervical cancer [17]. Twenty-one pregnant patients with stage IB cervical cancer treated by surgery (RHLD combined with caesarean delivery) were matched with 63 non-pregnant patients. The 5-year survival rates of both groups did not differ with 75% and 89%, respectively. Overall, it is likely that similar oncological safety can be achieved by combining CS and RHLD in the same operative session.

In our series of 19 pregnant patients with cervical cancer, two underwent a sectio parva and 17 continued their pregnancy. All 18 neonates, including one set of twins, survived. The mean birth weight in this series was 2708 gram, which is an adequate birth weight for the median gestational age of 35 weeks at delivery [12]. Administration of chemotherapy after the first trimester appears to be safe in terms of congenital anomalies, this was already shown by others [13, 18]. The vast majority of children in our series was born preterm. This explains the high number of neonatal intensive care unit admission for respiratory support because of lung immaturity. In our study, preterm delivery was induced to prevent a prolonged delay in the mothers' definitive oncological treatment. Despite the prematurity, our neonatal survival rate was 100%. Nevertheless, preterm birth is associated with an increased risk for adverse neurodevelopmental outcomes [19]. Therefore, considerations on fetal maturity and a delay of a potentially curative maternal treatment should be carefully made in a multidisciplinary team.

The strength of this study is that it is a relatively large single centre study, in which we were able to match pregnant patients with controls, and therefore compare outcomes regarding morbidity and oncological outcome. A study cohort of 19 patients within this research field is relatively large compared to available literature and considering the low incidence of cervical cancer in pregnancy. Studies on this topic often lack a control group of non-pregnant patients. Limitations of our study include the ones that are associated with a retrospective design. Although pregnant patients were matched with controls, and no major differences were observed between both treatment groups, heterogeneity is still a potential bias.

5. Conclusions

With the increasing age at which women become pregnant in the developed world, expecting to result in more women diagnosed with cancer in pregnancy, there is a growing need for knowledge on how to adequately treat these patients. Information on the safety of surgical procedures is important to guide treatment decisions. Our findings indicate that combining CS with RHLD is likely to achieve similar oncological safety, without a substantial additional burden of perioperative complications. Therefore, we recommend to consider combining these procedures in pregnant patients with early stage cervical cancer.

Author contributions

JvdV and CHM designed the research study. EPO performed the research by collecting and analysing the data. JvdV, CHM, EPO and RCP wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval for the study was obtained from the Medical Ethics Review Committee of the Academic Medical Centre (reference number W20_265#).

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Conflict of interest

The authors declare no conflict of interest.

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