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Authors: Anna Dąbrowska, Adrian Perdyan, Bartosz K. Sobocki, Jacek Rutkowski

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Management of cervical cancer during pregnancy – a systematic review

Anna Dąbrowska[1 0000-0002-0026-241X], Adrian Perdyan[2 0000-0002-5098-4357], Bartosz K. Sobocki[1 0000-0002-5074-9701], Jacek Rutkowski[3 0000-0002-7532-9447]

1. *Student Scientific Circle of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland*
2. *3P-Medicine Laboratory, Medical University of Gdansk, Gdansk, Poland*
3. *Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland*

Diagnosis of neoplasms during pregnancy and establishing a treatment schedule that is safe for both mother and fetus is problematic. This review summarizes knowledge about the problems associated with cervical cancer during pregnancy and current recommendations for diagnosis and treatment. The systematic review was performed according to PRISMA guidelines. The search was performed using PubMed, Scopus, Web of Science, and Google Scholar. Seven articles on 317 pregnant women with cervical cancer were included. Stage of disease, gestational age at diagnosis, treatment in pregnancy, type of delivery, gestational age of delivery, treatment after delivery, follow-up and main conclusion were analyzed. The rare phenomenon of neoplasms during pregnancy, as well as a limited research, do not allow for the development of clear guidelines for the treatment of cervical cancer in pregnant women. It is warrant to address discussed problems in future clinical research to provide the best care for pregnant cancer patients.

Key words: pregnancy, cervical cancer, chemotherapy, radiotherapy, surgery

Introduction

The prevalence of cancer during pregnancy is relatively low and reaches about 0.1% of all pregnancies [1, 2]. The most commonly diagnosed malignancies are breast cancer (BC), cervical cancer, melanoma, lymphoma, and leukemia [1]. Moreover, the management of

cervical cancer during pregnancy is highly challenging in the context of reproductive organs involvement and the occurrence of hormonal changes affecting the anatomy of women's pelvis [3]. Additionally, during pregnancy, an increase in vascular permeability and vascularization is observed with simultaneous immune system suppression, which can contribute to delaying cancer detection and rapid tumor progression [1]. Thus, it is warranted to establish a relevant treatment strategy that will be safe for both mother and fetus. In this review, we summarized current knowledge about cervical cancer management during pregnancy in the context of different oncological treatment modalities.

Material and methods

Search strategy

The systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol [4] and the PICO (Population, Intervention, Comparison, Outcome) search tool [5].

Evidence acquisition

To find studies reporting information about management of cervical cancer during pregnancy, on the 4th of April 2023 we performed a data searching using PubMed, Scopus, Web of Science, and Google Scholar. We used the following search queries: "cancer during pregnancy", "chemotherapy during pregnancy" and "gynecologic cancer during pregnancy", "cervical cancer during pregnancy". Additionally, articles were found in the references of included articles. We selected 28 articles for full-text analysis, and 7 of them were further analyzed.

Inclusion and exclusion criteria

We included original articles, reviews, cohort studies, case reports, case studies and guidelines. The included articles covered the diagnosis, treatment, pregnancy termination, and delivery of cervical cancer in pregnant women. Studies in languages other than English were excluded from this review. Studies published as abstracts or letters were excluded. We also excluded articles that focused only on gynecological cancers in pregnancy without considering cervical cancer.

Evidence synthesis

Table I includes the following information: name of the first author, year of the study, number of patients, stage of disease, gestational age at diagnosis, treatment in pregnancy, type of delivery, gestational age of delivery, treatment after delivery, follow-up, and main conclusion.

Results

We included and analyzed 7 original articles. There were 317 pregnant women with cervical cancer, including 1 patient with carcinoma in situ, 213 patients with stage I, 46 patients with stage II, 2 patients with stage III, 1 patient with stage IV, 26 patients with stage II–IV, 7 patients with stage III–IV, and 21 with unknown stages.

Gestational age at diagnosis and delivery

The diagnosis was usually made in the 2nd trimester of pregnancy (5 studies). Then in the 1st trimester (2 studies), the 3rd trimester (2 studies), and postpartum (1 study). The 35th week of pregnancy was the most common time for delivery, according to the analyzed articles (2 studies). In 4 articles these data were not provided.

Treatment in pregnancy

We summarized various treatments before delivery. In the case of as many as 71 patients, pregnancy termination was performed. 50 patients underwent surgery. Combination therapy was used in 68 women. 51 patients received chemotherapy, 2 patients received concurrent chemoradiotherapy, and 2 patients received radiotherapy. One dilatation and curettage were performed. One patient refused treatment. The data for 3 patients was not provided.

Type of delivery

The most common type of delivery was caesarean section (156 patients, including 29 with additional procedures); 29 patients ended their pregnancies by vaginal delivery. In 2 articles these data were not provided.

Treatment after delivery

Across the included studies, 6 patients received radiotherapy alone, 20 patients received radiochemotherapy, and 6 patients received concurrent chemoradiotherapy; 24 women underwent post-delivery surgery; 23 patients received combination therapy. In the case of 9 women, no treatment or unclear treatment was declared. The data for 41 patients was not provided.

Discussion

The incidence of cancer in pregnant women is relatively uncommon. The strictly established guidelines for their management are lacking. Hence, it is important to discuss diagnostic and treatment strategies, especially for less common and difficult-to-manage tumors, such as cervical cancer.

Diagnosis

Although symptoms of cervical cancer may often be masked by hormonal changes, due to routine prenatal screening, the detection rate is above 70% [6]. However, there is still a risk of assigning the symptoms of cervical cancer to normal pregnancy and benign conditions, which ultimately delays the diagnosis [1, 7]. Therefore, pregnant and postpartum women should be cautious about irregular vaginal bleeding or abnormal vaginal discharge (bloody, purulent, or smelly) [7, 8]. Therefore, it should be remembered that a clinical examination and histological verification of cervical cancer in a pregnant patient are obligatory [9].

Cytology and pelvic examinations are useful for the detection of asymptomatic cervical cancer. Therefore, the first visit during pregnancy is crucial, especially for patients who have not participated in screening programs [6, 10]. Cytology is a safe procedure for pregnant women and the fetus. Its specificity and sensitivity are comparable to the results of non-pregnant women [7]. In the case of abnormal cytology results, a colposcopy-directed biopsy should be performed, preferentially during the first two trimesters before the periods of the highest hormonal secretion and increased revascularization [7, 10]. Colposcopy provides high sensitivity and safety, with a complication rate up to 0.6%. The most frequent complications are hemorrhage, premature birth, or miscarriage [2]. Even if the colposcopy

results are abnormal, endocervical curettage is contraindicated as it increases the risk of miscarriage and premature delivery [2, 7, 9].

In general, diagnosis and staging should be performed similarly as in non-pregnant women, with an exception of imaging procedures emitting ionizing radiation (e.g., PET-CT, CT, and X-ray) [11]. Therefore, ultrasound and MRI are the first-choice diagnostic methods [2, 12]. However, in exceptional circumstances, CT or X-ray may be considered. For instance, for patients with invasive cervical cancer in stage IB1 and higher, a chest X-ray to assess lung metastases should be done [13]. A chest CT scan with abdominal shielding can also be used as an alternative to a diffusion-dependent magnetic resonance imaging (WB-DWI/MRI) to evaluate nodal and distant metastases [9]. Although it should be remembered that any exposure of the fetus to ionizing radiation may be associated with negative effects. If performed in the first trimester, the risk of fetal impairment, childhood cancer, and leukemia is significantly increased [1, 14]. Gadolinium, which is commonly used for MRI as a contrast, is not recommended during pregnancy due to an increased risk of stillbirth, neonatal death, rheumatologic and skin diseases [12, 15].

To establish the clinical stage of disease, a lymph node assessment is done, preferably by 24 weeks of pregnancy. This is particularly important due to the prognostic significance and determination of further management [9]. PET-CT, which is commonly used for this purpose, is not recommended during pregnancy. Unfortunately, standard MRI scanning is not specific enough to assess the lymph nodes. Thus, the best approach is to perform a laparoscopic lymphadenectomy and histopathological examination afterward, as it has been proven to be a safe and effective method in women before the 22nd week of pregnancy [2, 12]. On the other side, in the advanced stages of pregnancy, lymphadenectomy should be avoided [12]. An acceptable alternative to PET-CT and lymphadenectomy in these circumstances can be a WB-DWI / MRI, which has no negative effects on the fetus and has higher specificity than standard MRI scanning [6, 15].

Each patient should be consulted by a multidisciplinary team to establish a treatment plan, considering not only tumor stage and gestational age at diagnosis but also patient preferences. Further treatment should only be carried out in gynecology and oncology centers affiliated with perinatal centers [9].

Treatment

Treatment of cervical cancer in pregnant patients can be challenging due to the leverage between positive oncological effects on the mother, protection of the fetus, and preservation of fertility [7, 16]. After fertility-sparing treatment, any pregnancy should be considered a high-risk pregnancy [9]. Moreover, the choice of treatment regimen is highly dependent on the gestational age at the time of diagnosis. Hence, during the first trimester, a standard of care adequate to the FIGO stage and pregnancy termination is preferred [17, 18]. During the second or third trimester, neoadjuvant chemotherapy or definitive treatment delay and induction of delivery are used, respectively. Importantly, tumor size and local extension (FIGO stage) influence cancer management. Small tumors are more often treated surgically, whereas neoadjuvant chemotherapy is used to treat tumors bigger than 2–4 cm [17]. Nevertheless, in case of lymph node involvement, neoadjuvant chemotherapy should be administered as soon as possible [8]. On the other hand, it has been stated that treatment delay during pregnancy should be discouraged due to the risk of underdiagnosis, which occurs more frequently in pregnant than in non-pregnant women [12]. According to the latest guidelines, delaying oncological treatment until fetal maturity should be considered if the term of delivery or fetal maturity is approaching (>34 weeks of age). Then, immediately after the caesarean section, treatment can be started [9]. In conclusion, due to the limited and conflicting data, a safe delay time for treatment cannot be determined. Due to the difficulties associated with the treatment of cervical cancer in pregnant women, it is important to have access to several therapeutic methods and discuss them with the patient [9].

Surgery

In women with early-stage cancer (IA2–IB2 and IIA1), a hysterectomy or trachelectomy is performed, whereas chemoradiotherapy is administered for locally advanced tumors [19], [20]. Conization or simple trachelectomy can remove the tumor if the patient wants to preserve the pregnancy [9]. Radical trachelectomy is not recommended during pregnancy due to the high prevalence of surgical and obstetric complications [15, 21]. After a simple or radical trachelectomy, delivery is possible only by caesarean section [9]. If surgery is decided upon, the best time is between the 15^{th} and 20^{th} week of pregnancy [2, 15]. If there is a residual tumor after surgery that cannot be completely removed, chemotherapy may be

started [9]. Still, surgical treatment seems to be the safest option during pregnancy. However, the condition of the fetus should be checked with ultrasonography before and after the induction of general anesthesia [11]. Interestingly, the negative effects of anesthesia on the fetus are related to complications on the mother's side rather than the direct influence of administered drugs [1, 14, 21]. The condition of the fetus should be constantly monitored and consulted with an obstetrician during the whole treatment period.

Chemotherapy

Neoadjuvant chemotherapy provides the opportunity for regression of not only the primary tumor but also the site of nodal and distant metastases if they are present. However, the main drawback is the loss of ovarian reserve [19, 22]. Hence, pregnancy preservation should be considered before the administration of chemotherapy [16]. Teratogenicity is highly associated with exposure time, applied dose, type of drug, and placental transfer. Thus, most standard regimens are implemented after the 14th week of pregnancy.

The most common neoadjuvant chemotherapy regimen is a combination of cisplatin and paclitaxel as both provide the lowest risk of adverse effects [11, 23]. In case of preeclampsia or renal failure, carboplatin may be considered instead of cisplatin as it is less nephrotoxic, but more hematotoxic [14, 16]. Furthermore, it is possible to combine platinum derivatives with taxanes. It is noteworthy that the use of bevacizumab and immune checkpoint inhibitors is contraindicated [9].

Currently, the main challenge to overcome is the placental transfer of maternally administered drugs. In comparison to taxanes, cisplatin and carboplatin penetrate this barrier easier and increase fetal side effects [8, 23]. For instance, children whose mothers have received cisplatin may have impaired hearing [7, 15]. Further research in this field is needed to find ways of decreasing the placental transfer of teratogenic drugs.

A hardly addressed issue is drugs' pharmacokinetics, which may significantly vary from the 4th week of pregnancy [8]. Specifically, an increase of plasma volume, glomerular filtration rate, and enterohepatic circulation, reduce the concentration of the drug in the body [1, 16]. Additionally, the amniotic fluid serves as a "third space", extending drug exposure [21, 23]. The standard dosing schedule is based on height and current weight, the

same as for non-pregnant women. Thus, it is important to take into account the patient's weight during pregnancy when calculating the dose of chemotherapy in each cycle [8, 14].

Administration of chemotherapy in each trimester increases the prevalence of different complications. As such, in the first trimester, there is an increased risk of malformations and spontaneous miscarriage [2, 11, 24]. On the other side, in the second and third trimesters increase the chance of stillbirth, premature birth, intrauterine growth restriction (IUGR), and low birth weight [1, 2]. To decrease the occurrence of congenital abnormalities, chemotherapy should be delayed until the second trimester, but the consequences of this approach should be considered in the light of maternal health [15]. Despite some negative effects in the second and third trimesters, which need to be monitored, chemotherapy is considered to be quite safe during this period [1, 2].

Each cycle of chemotherapy should be preceded by a clinical examination and transvaginal or transrectal ultrasound to assess the patient’s response to treatment. If there is no response after 2 cycles of chemotherapy, treatment should be evaluated [9].

Importantly, chemotherapy should be stopped 3 weeks before delivery or before the 37^{th} week of pregnancy to regenerate the bone marrow of the mother and the fetus [1, 15]. Intriguingly, there is a lack of consensus about the long-term side effects of children whose mothers have received chemotherapy during pregnancy. However, there are studies reporting negative results [17, 19], including associations with a higher risk of growth restriction, cognitive impairment, ototoxicity and cardiotoxicity [8].

Radiotherapy

Due to the emission of high doses of ionizing radiation, radiotherapy is generally forbidden in pregnant women as it induces spontaneous abortion within one month of completion [21]. Hence, postponing the radiotherapy until delivery is the only option when pregnancy preservation is the primary goal.

Concomitant radiochemotherapy and brachytherapy are applied when the disease stage is defined as FIGO IB and above [25]. When the patient chooses to preserve pregnancy, radiotherapy with chemotherapy is postponed after delivery [6].

Interestingly, postpartum radiotherapy planning might be challenging. The uterus returns to its physiological shape and size within 6 weeks after delivery [26]. Due to these dynamic changes and organ motion, monitoring and eventual modification of the irradiated area during radiotherapy should be applied.

Delivery and breastfeeding

Cancer progression may enforce premature delivery. If possible, delivery after the 37th week of pregnancy is preferred. If early delivery is unavoidable, steroids should be administered to induce fetal lung maturation [7, 15]. Spontaneous delivery is associated with a negative prognosis [9]. Therefore, in the management of invasive cervical cancer, caesarean section is the preferred method of delivery, followed by definitive treatment [7, 14, 18, 27]. This type of schedule may decrease the risk of neoplastic cell implantation in the episiotomy scar and metastasis spreading during vaginal delivery [14, 15]. Finally, as chemotherapy passes into breast milk, breastfeeding is forbidden during treatment. However, it can be reintroduced at least 3 weeks after the last cycle [2, 15, 21].

Pregnancy termination

If the patient wishes to preserve the pregnancy, neoadjuvant chemotherapy should be considered for locally advanced cervical cancer. However, if woman decides not to preserve the pregnancy, the standard of care adapted to the FIGO stage should be the same as for non-pregnant women [2, 6]. In general, pregnancy termination is offered to patients diagnosed with cervical cancer before the 20th week of pregnancy [14]. However, at different stages of pregnancy, the use of specific treatments may carry different risks of complications. Thus, in stages IB3 and higher, the patient may undergo chemoradiotherapy with the fetus present in the uterus in the first trimester. However, in the second trimester, a hysterectomy followed by chemoradiotherapy should be performed, as it reduces the risk of obstetric complications [15].

Future directions

Due to the low incidence of cervical cancer among pregnant women, there are no specific treatment guidelines established [28]. Thus, the current recommendations are based on limited data derived from a small number of retrospective trials [17]. There is a definite need

for true evidence-based data that would define the cancer treatment schedule with adequate and safe drug doses. However, such data may only be obtained from prospective clinical trials, which obviously cannot succeed due to ethical considerations [29]. Moreover, due to the rising rate of cervical cancer in young women, it is necessary to establish fertility-sparing management and guidelines [10]. Furthermore, there is no relevant data assessing the impact of pregnancy on the course of gynecological neoplasms [15]. Recently, Li et al. observed no survival differences between women who preserved their pregnancy and those who terminated it [20]. However, this observation should be further confirmed by others, as physiological changes during pregnancy may accelerate the development of cancer [1, 7, 30].

Conclusions

It is undoubtful that the treatment of pregnant women with cancer represents an outstanding challenge. The lack of experience in the diagnosis and treatment of neoplasms in pregnant women may lead to delayed and inappropriate management. As such, it can harm maternal and fetal health. The analyzed literature does not define uniform treatment methods, as it is based on general recommendations and small sample case studies. Therefore, the care of an experienced board of obstetricians, gynecologists, neonatologists, and oncologists should be guaranteed to the patient. It is warranted to address discussed problems in future clinical research to provide the best care for pregnant cancer patients

Article information and declarations

Author contributions

Anna Dąbrowska – conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, roles/writing – original draft, review and editing.

Adrian Perdyan – data curation, formal analysis, investigation, methodology, resources, validation, visualization, roles/writing – original draft, review and editing.

Bartosz K. Sobocki – investigation, methodology, resources, validation, roles/writing – original draft, review and editing.

Jacek Rutkowski – conceptualization, funding acquisition, investigation, project administration, resources, supervision, validation, roles/writing – original draft, review and editing.

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Conflict of interest

None declared

Anna Dąbrowska
Medical University of Gdansk
Student Scientific Circle of Oncology and Radiotherapy

ul. Marii Skłodowskiej-Curie 3a

80-210 Gdańsk, Poland

e-mail: anna.dabrowska@gumed.edu.pl

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Table I. Summary of analyzed studies

First author,	Stage (n –	Gestational age at	Treatment in	Type of delivery	Gestational age at	Treatment after	Follow-up	Main conclusion

year	patients)	diagnosis in weeks (median [range])	pregnancy		delivery in weeks (median [range])	delivery		
Fukushima, 2009 [10]	IA1 (6) IB1 (13) IB2 (2) IIA (1) IIIB (1) IVB (1)	16 (6–33)*	TAH (1) TOP + sRAH (1) TOP + RAH (9) TOP + ExL + CCRT (1) TOP + RAH + RT (1) DC (1) denied (1)	CD (1) VD (10)	35.4 (22–42)	Cone + TAH (2) RAH (3) ExL + CT (1) CCRT (1) Cone + ExL + CCRT (1)	median follow-up was 50.5 months (9–150)	treatment delay during pregnancy should be discussed due to the risk of underestimated disease severity in pregnant patients (p = 0.016)
Halaska, 2019 [17]	IA (19) IB1 (62) IB2 (25) II–IV (26)	18.4 (7–39)	S (23) TOP (35) NACT (28)	CD (84) VD (12) ND (1)	ND	CT + RT (18) S (17)	median follow-up was 67 months (2–269)	the prognosis of pregnant patients with cervical cancer is similar to non-pregnant women the hazard ratio for progression-free survival was 1.17 (95% CI: 0.64–2.12, p = 0.62)
Li, 2020	IA (7)	TOP: 14.8	RH (23)	CD (34)	ND	RH + CT	media	the hazard ratio

[19]	IB1 (30) IB2 (33) II (28) III–IV (7)	(5–31) COP: 30.8 (6–41)	abortion + RH (20) abortion + CCRT (2) HT + RH (19) ND (3)	VD (1) CD + RH (3)		(11) RH + CCRT (8) RH (3) CCRT (4) NT/UT (9)	n follow-up was 61 ± 6 months (1–173)	for overall survival was 1.063 (95% CI: 0.24–4.71, p = 0.964)
Köhler, 2015 [22]	ND (21)	17 (13–23)	NACT (21)	CD (2) CD + RH (16) CD + SH (1) CD + TMMR (1) CD + pelvic LND (1)	33 (30–36)	ND	median follow-up was 33 months (7–88)	the overall survival rate was 95.3%
Ustaalioglu, 2010 [23]	IB2 (1)	1st trimester	therapeutic abortion	ND	ND	RT + CT	median follow-up was 19.7 months (2–122)	the prognosis was poor due to the early diagnosis
Zhang, 2015 [26]	in situ (1) IA1 (1)	2nd trimester (4) 1st	S (3) S + RT (3) S + CCRT	CD (4) VD (3)	ND	ND	median follow-up was	women with cervical cancer during pregnancy

	IB1 (5) IB2 (1) IIA (8) IIB (3) IIIB (1)	trimester (8) 3rd trimester (2) PP (6)	(5) NACT + S + CCRT (1) S + CCRT + CT (2) NACT + S + CT (1) NACT + CCRT (1) CCRT (2) RT (1) CCRT + CT (1)				68 months (14–142)	require personalized treatment
Bo, 2021 [29]	IA1 (4) IA2 (2) IB1 (1) IB3 (1) IIA1 (1) IIA2 (3) IIB (2)	18 (7-36) *	CKC + NSD (2) CT (2) TOP + RH (1) NSD (1)	VD (3) CD + RH (7) miscarriage (1) CD (2)	35 (9–39)	RT (6) RT + CT (1) CCRT (1) RH (1)	NA	early diagnosis and effective treatment improve the survival rate of pregnant women

* – hard to estimate; CCRT – concurrent chemoradiotherapy; CD – cesarean delivery; CKC – cold knife conization; COP – continuation of pregnancy; CT – chemotherapy; DC – dilation and curettage; DL – delay; DV – delivery; ExL – exploratory laparotomy; HT – hysterotomy; LND – lymphadenectomy; NA – not applicable; NACT – neoadjuvant chemotherapy; ND – no data; NSD – nominal standard dose; NT/UT – no treatment/unclear treatment; PP – postpartum; PTD – pre-term delivery; RAH – radical abdominal hysterectomy; RH – radical hysterectomy; RT – radiotherapy; S – surgery; SH – simple hysterectomy; TAH – total abdominal hysterectomy; TMMR – total mesometrial resection; TOP – termination of pregnancy; VD – vaginal delivery