

## Cervical cancer in pregnancy in Songklanagarind Hospital

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### Abstract:

Cervical cancer in pregnancy in Songklanagarind Hospital

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*Cervical cancer in pregnancy is increasingly reported worldwide nowadays. We studied eleven Thai pregnant women presenting with the clinical symptoms and signs of cervical cancer at Songklanagarind Hospital in Hat-Yai, Thailand between 1982-2001. Their mean age was 35.5 (range 30 to 41) years. The most common presenting symptom was vaginal bleeding, occurring in six patients (54.5%). Four patients (36.4%) were asymptomatic.*

*The diagnosis of cervical cancer was made by biopsy of a gross lesion in seven of the women (63.6%). Four patients were referred for an abnormal Papanicolaou smear, and invasive disease was confirmed by colposcopic directed biopsy. A cone biopsy was performed without complications to the pregnancy in one patient diagnosed with microinvasion. Five patients*

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(45.5%) were diagnosed before 20 weeks gestation. Most patients had stage I lesions. The predominant histologic cell type was squamous cell carcinoma in 8 cases (72.7%), followed by adenocarcinoma in 3 cases (27.3%). Eight patients postponed therapy to optimize fetal outcome, with a mean diagnosis-to-treatment interval of 134 days (range 27-327). Seven patients are free of disease after follow-up for 28 to 82 months.

Patients in this study mostly had a good outcome.

**Key words:** cervical cancer, pregnancy

### บทคัดย่อ:

คณะผู้รายงานได้ทำการศึกษาลักษณะทางคลินิกของผู้ป่วยมะเร็งปากมดลูกในสตรีตั้งครรภ์ที่เข้ามารับการตรวจรักษาที่โรงพยาบาลสงขลานครินทร์จำนวน 11 ราย อายุเฉลี่ย 35.5 ปี (ช่วงอายุ 30-41 ปี) ผู้ป่วยส่วนใหญ่มีอาการเลือดออกผิดปกติทางช่องคลอด ซึ่งพบได้ 6 ราย (ร้อยละ 54.5) และอีก 4 ราย (ร้อยละ 36.4) ไม่พบอาการผิดปกติ การวินิจฉัยมะเร็งปากมดลูกทำได้โดยการตัดชิ้นเนื้อที่ผิดปกติที่เห็นได้ด้วยตาเปล่าจากบริเวณปากมดลูก ซึ่งพบในผู้ป่วย 7 ราย (ร้อยละ 63.6) ส่วนอีก 4 ราย ไม่เห็นความผิดปกติด้วยตาเปล่าที่บริเวณนั้น แต่จากการส่องกล้องขยายพบมีส่วนที่สงสัยว่าจะผิดปกติจึงตัดชิ้นเนื้อยืนยัน การวินิจฉัยผู้ป่วย 5 ราย (ร้อยละ 45.5) ได้รับการวินิจฉัยตั้งแต่อายุครรภ์น้อยกว่า 20 สัปดาห์ ส่วนใหญ่ของผู้ป่วยทั้งหมดเป็นมะเร็งปากมดลูกระยะที่ 1 และลักษณะทางพยาธิวิทยาเป็นชนิด squamous cell ร้อยละ 72.7 และ adenocarcinoma ร้อยละ 27.3 มีผู้ป่วย 8 ราย ที่ตัดสินใจไม่รับการรักษามะเร็งปากมดลูกทันทีที่ได้รับการวินิจฉัย แต่รอดำเนินการทั้งหมดในครรภ์มีการเจริญเติบโตและการทำงานของปอดสมบูรณ์ ระยะเวลาที่รอดตั้งแต่วินิจฉัยจนรับการรักษาเฉลี่ย 134 วัน (ช่วงเวลา 27-327 วัน) ผู้ป่วย 7 ราย ไม่มีอาการแสดงของโรคเป็นกลับซ้ำ หลังจากตรวจติดตามการรักษานาน 28-82 เดือน และผู้ป่วยส่วนใหญ่มีการพยากรณ์โรคที่ดี

**คำสำคัญ:** มะเร็งปากมดลูก, สตรีตั้งครรภ์

### Introduction

Cervical cancer is the most common malignancy that occurs during pregnancy.<sup>1, 2</sup> The reported incidence varies from 1.6-10.6 cases of cervical cancer per 10,000 pregnancies depending upon the inclusion of cases of carcinoma in situ or postpartum patients.<sup>3</sup> Today the frequency of diagnosis of cervical carcinoma during pregnancy is increasing because of routine cytologic screening when women present to their physicians for prenatal obstetric care. However, when it is discovered, treatment of the cervical malignancy must incorporate concerns for both the fetus and the mother. Opinions have differed as to the best mode of therapy, the timing of therapy in regard to infant survival, the effect of the pregnancy on the 5-year survival rate, and the mode of delivery. The purpose of this report was to review the authors' experience

with cervical carcinoma during pregnancy, also as cervical cancer associated with intrauterine pregnancy is an uncommon problem, to offer an updated report.

This report describes all cases of cervical cancer associated with pregnancy treated in Songklanagarind Hospital between January, 1982 and December, 2001. The date of last follow-up was on August 1<sup>st</sup>, 2002.

### Materials and methods

The case records of all patients who were pregnant at the time of diagnosis and treatment of cervical cancer were reviewed. Information regarding the patients' age, parity, clinical presentation, histology, stage, time and mode of diagnosis, treatment, and pregnancy outcome were noted.

The diagnosis of malignancy was confirmed by histopathological examination of the tumors. Invasive cancer was diagnosed using standard punch biopsy of an abnormal gross lesion or abnormal lesion from colposcopy, and a cone biopsy was performed if microinvasive cervical cancer was suspected. Following diagnosis and physical examination, routine pre-treatment evaluation including a complete blood count, urinalysis, blood chemistry, and chest x-ray were done. All patients were staged according to the current International Federation of Gynecology and Obstetrics (FIGO) System<sup>4</sup> by at least two experienced gynecologic oncologists before initiation of therapy.

#### FIGO staging of carcinoma of the cervix uteri

##### *Preinvasive Carcinoma*

**Stage 0** Carcinoma in situ, intraepithelial carcinoma (cases of stage 0 should not be included in any therapeutic statistics).

##### *Invasive Carcinoma*

**Stage I** Carcinoma strictly confined to the cervix (extension to the corpus should be disregarded).

**Stage I<sub>A</sub>** Preclinical carcinomas of the cervix, that is, those diagnosed only by microscopy.

**Stage I<sub>A1</sub>** Lesion with  $\leq 3$  mm invasion.

**Stage I<sub>A2</sub>** Lesion detected microscopically that can be measured. The upper limit of the measurement should show a depth of invasion of  $> 3-5$  mm taken from the base of the epithelium, either surface or glandular, from which it originates, and a second dimension, the horizontal spread, must not exceed 7 mm. Larger lesions should be staged as I<sub>B</sub>.

**Stage I<sub>B</sub>** Lesions invasive  $> 5$  mm.

**Stage I<sub>B1</sub>** Lesion less than or equal to 4 cm.

**Stage I<sub>B2</sub>** Lesion larger than 4 cm.

**Stage II** The carcinoma extends beyond the cervix but has not extended onto pelvic the wall. The carcinoma involves the vagina, but not the lower one third.

**Stage II<sub>A</sub>** No obvious parametrial involvement.

**Stage II<sub>B</sub>** Obvious parametrial involvement.

**Stage III** The carcinoma has extended onto the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves

the lower one-third of the vagina. All cases with hydronephrosis or nonfunctioning kidney.

**Stage III<sub>A</sub>** No extension to the pelvic wall.

**Stage III<sub>B</sub>** Extension onto the pelvic wall and/or hydronephrosis or nonfunctioning kidney.

**Stage IV** The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV.

**Stage IV<sub>A</sub>** Spread of the growth to adjacent organs.

**Stage IV<sub>B</sub>** Spread to distant organs.

After staging, all patients and their families were counselled extensively regarding treatment options, the unique characteristics of the cervical lesion, with particular emphasis on prognosis and possible outcomes in relation to the gestational age of the fetus. The choice of treatment was based on the stage of cancer and gestational age of pregnancy at diagnosis. The patients, their families and the physicians then decided together about treatment plans.

Recommendations for therapy were individualized based on presenting stage, lesion size, and the patient's desire for the pregnancy.<sup>4-6</sup> Immediate therapy was recommended if frankly invasive cancer was diagnosed before 20 weeks' gestation. After 20 weeks' gestation, the timing of therapy depended upon stage, lesion size, and anticipated number of weeks necessary to achieve fetal maturity. In general, patients with stage I<sub>A</sub> or small I<sub>B</sub> ( $< 4$  cm) cervical cancers were counselled that treatment delay to achieve fetal maturity would be a reasonable option. Patients with bulky I<sub>B</sub> lesions or with advanced disease were advised that increased maternal risk due to treatment delay was possible, but not certain. Timing of treatment depended upon their willingness to accept the risk of a delay of treatment and their desire to continue the pregnancy to viability or maturity. However, during follow-up immediate therapy was recommended to all patients who demonstrated progression of disease.

All patients who decided to delay treatment were followed up closely from the time of diagnosis and were examined at 2- to 4- week intervals by the gynecologic oncology staff to assess the cervical lesion.

To calculate the incidence of cervical cancer complicating pregnancy, we examined the ratio of cases to the number of pregnancies during the study period. For the years 1982–2001, there were 38,421 deliveries and approximately 4,554 abortions and ectopic pregnancies recorded in the hospital delivery and statistical unit .

## Results

During 1982–2001, eleven patients were diagnosed with cancer in the antepartum period. In the first ten years, there was no patient diagnosed with cervical cancer in pregnancy but in following years there was an increase in the number of patients. The incidence of cervical cancer in pregnancy in this study was 3.8 cases in 10,000 pregnancies between 1992 and 1996 and 4.1 cases in 10,000 pregnancies between 1997 and 2001.

The mean age of all patients was 35.5 years (range 30 to 41 years). The mean parity was two births (range 0 to 4). One patient was primigravida. The most common presenting symptom was vaginal bleeding, occurring in six patients. Four patients were asymptomatic and the remaining had leukorrhea.

Six patients were categorized as having early stage disease (including stages I<sub>A1</sub> and I<sub>B</sub>) and five patients as advanced (comprising stages IIB and III<sub>B</sub>) (Table 1). The patient with stage I<sub>A1</sub> was asymptomatic and the diagnosis was made by finding an abnormal Papanicolaou smear and colposcopic directed biopsy showed microinvasion, when a cone biopsy was performed without complication. In the stage I<sub>B</sub> group, two patients had no symptoms, and the diagnosis was made by finding an abnormal Papanicolaou smear and invasive disease confirmed by colposcopic directed biopsy. In the advanced stage, four patients had vaginal bleeding as the presenting symptom and the diagnosis was made by biopsy of an abnormal gross lesion at the cervix. Eight patients had squamous cell carcinomas and the others had adenocarcinomas.

The diagnosis was made in the first trimester in three patients. Four patients presented in the second trimester and the remaining were diagnosed in the third trimester.

Eight of eleven patients decided to delay therapy to improve fetal outcome. The mean diagnosis-to-treatment interval was 134 days (range 27–327). Table 2 presents the gestational age, stage, lesion size, diagnosis-to treatment-interval, and outcome for the eight patients who delayed therapy.

**Table 1 Features of the eleven pregnant patients with cervical carcinoma**

Patient No.	Age (years)	Parity	Gestational age at diagnosis (weeks)	Presenting symptoms	Tumor size (cm)	Tumor pathology	FIGO staging
1	30	1	9	abnormal Pap smear	–	sq.ca	I <sub>A1</sub>
2	38	3	12	vaginal bleeding	3	sq.ca	I <sub>B1</sub>
3	41	3	15	vaginal bleeding	4	adeno.ca	I <sub>B1</sub>
4	38	0	18	abnormal Pap smear	–	adeno.ca	I <sub>B1</sub>
5	30	1	22	abnormal Pap smear	–	sq.ca	I <sub>B1</sub>
6	41	3	29	leukorrhea	5	sq.ca	I <sub>B2</sub>
7	34	1	5	abnormal Pap smear	0.5	sq.ca	II <sub>B</sub>
8	36	3	22	vaginal bleeding	6	sq.ca	II <sub>B</sub>
9	33	2	28	vaginal bleeding	5	sq.ca	II <sub>B</sub>
10	33	1	29	vaginal bleeding	4	sq.ca	II <sub>B</sub>
11	36	4	33	vaginal bleeding	5	adeno.ca	III <sub>B</sub>

sq.ca = squamous cell carcinoma

adeno.ca = adenocarcinoma

Table 2 Delayed-therapy group

Patient No.	GA (wks)	Stage	Lesion size (cm)	Dx-Tx interval (days)	F/U (DFS mo)
1	9	I <sub>A1</sub>	-	327	72
2	18	I <sub>B1</sub>	-	*	*
3	22	I <sub>B1</sub>	-	234	28
4	29	I <sub>B2</sub>	5	31	38
5	22	II <sub>B</sub>	6	138	3 mo then lost F/U
6	28	II <sub>B</sub>	5	155	lost F/U during Tx
7	29	II <sub>B</sub>	4	27	lost F/U during Tx
8	33	III <sub>B</sub>	5	32	82

GA = gestational age, Dx = diagnosis, Tx = treatment, Wk = weeks, F/U = follow-up, DFS = disease-free survival

\*as of 1/8/2002 she had not delivered

In the group of patients who decided to delay therapy, patient no.1 who had microinvasion (stage I<sub>A1</sub>) was seen in her second pregnancy at 9 weeks of gestation. After counselling by doctors, she and her family wanted to continue the pregnancy and she underwent cesarean section followed by extra-fascial type I hysterectomy with conservation of the ovaries at 38 weeks of gestation. Patient no.2 was in her first pregnancy and was diagnosed at 18 weeks of gestation with invasive cancer. She and her family decided to continue the pregnancy after discussion with her doctors. As of the last date of obtaining information in August, 2002 she had no progression of cervical cancer confirmed by physical examination, pelvic examination, and colposcopy. She was planning to have a classical cesarean delivery followed by radical hysterectomy with bilateral pelvic lymphadenectomy at 36 weeks of gestation.

Patients no. 3 and 5 presented in the second trimester of pregnancy, and even though the long time until fetal viability might give them a higher risk of cancer progression they still wanted to continue their pregnancies. Patient no.3 could continue her pregnancy until 34 weeks of gestation; she then underwent cesarean delivery followed by postpartum interval radical hysterectomy and bilateral pelvic lymphadenectomy. Patient no. 4 had planned to deliver at 34-36 weeks; however, she entered labor which could not be inhibited at 30

weeks of gestation, so a cesarean delivery, followed by radiation after postpartum 4 weeks, was performed.

All patients in stage II<sub>B</sub> were planned to deliver at 34-36 weeks of gestation, but two of them, patients no.5 and 7, had classical cesarean deliveries at 22 and 33 weeks of gestation respectively because they experienced massive vaginal bleeding from their tumors. All three patients received postpartum radiotherapy.

The diagnosis was made in the third trimester in four patients. In patient no.7 surgery was delayed only by 4 weeks because of massive vaginal bleeding. Patient no. 8 was in her fifth pregnancy with stage III<sub>B</sub> and had a large tumor but she and her family wanted to continue the pregnancy. After delaying for 2 weeks, she was underwent a hysterotomy because of massive vaginal bleeding at her local hospital and she returned to Songklanagarind Hospital 11 days after surgery for radiotherapy. She had clinical remission after treatment for 82 months, then she suffered obstructive uropathy from a tumor recurrence.

Three of the eleven patients chose immediate treatment for their cancer. All were treated by radiotherapy alone and they aborted spontaneously after 800, 4000, and 4600 cGy. No one underwent curettage after the abortion. All three patients had clinical remission at the last follow-up in August, 2002.

Table 3 Immediate-therapy group

Patient No.	GA (wk)	Stage	Lesion size (cm)	Dx-Tx interval (days)	F/U (DFS mo)
1	5	II <sub>B</sub>	0.5	13	75
2	12	I <sub>B1</sub>	3	41	34
3	15	I <sub>B1</sub>	4	5	58

## Discussion

Invasive cervical cancer is relatively uncommon during pregnancy. Depending on the patient population studied, the inclusion of cases of carcinoma in situ and postpartum patient, the estimated incidence ranges from 1.6 in 1,000 to 10.6 in 10,000 pregnancies.<sup>3</sup> However, cervical cancer remains the most common malignancy diagnosed during pregnancy.<sup>1,2</sup> It is difficult for health care team and the patient to manage such disease because treatment of cervical cancer makes it impossible to preserve fetal life. A decision must be made either to start therapy immediately or to wait for fetal lung maturity.

In this study, the incidence of invasive cervical cancer in pregnancy was comparatively high because Songklanagarind Hospital is a referral center and there is a high rate of cervical cancer in Thailand.<sup>7</sup> The incidence may be even higher than indicated here because patients diagnosed postpartum were not included in the study. This suggests that current educational and screening programs must be expanded and improved to prevent cervical cancer.

The mean age of the patients in this study was 35.5 years (range 30 to 41 years), thus these women not only faced the potential loss of the current pregnancy but also the loss of fertility and possible effects on future sexual function as a result of treatment. It is imperative that the health care provider be cognizant of these concerns and others.

The presenting symptoms of cervical cancer can vary depending on the number of patients with advanced cancer. Some investigators report that 70% or more of their patients are asymptomatic at presentation and cervical cancer is usually first suspected when abnormal cytology is detected during routine screening at the first prenatal visit.<sup>8</sup> With widespread

and increased screening by cytology, one would expect a decrease in invasive malignancy and advanced disease.

The diagnostic evaluation of patients with abnormal cytology but no gross abnormal lesion at the cervix is initially evaluated by colposcopy, but for patients with clinically obvious cervical lesions should be biopsied, regardless of the duration of the pregnancy. Considering that the risk associated with cervical biopsy in pregnancy is minimal and that the potential adverse effects of missed diagnosis and delay in the diagnosis of early cervical cancer which may result in progression of a potentially curable lesion over the course of the pregnancy to the point where a successful outcome is no longer possible, a biopsy should be performed as indicated. Because decidual reaction from pregnancy combined with increased vascularity can produce polypoid projections which may appear suspicious for malignancy, the physiologic cervical changes associated with pregnancy must be carefully excluded by the colposcopist without missing any abnormal lesions. The pregnant cervix lends itself to colposcopic visualization because the glandular epithelium is usually everted on to the ectocervix.<sup>9</sup> This eversion generally allows for complete visualization of the transformation zone in most patients. However, cervical changes in pregnancy related to elevated estrogen levels can confuse the colposcopist. There is an increase in cervical volume through hypertrophy of the fibromuscular stroma, increased vascularity, and enlargement of endocervical structures and the physiologic metaplasia can give the appearance of acetowhite changes, punctation, and mosaicism. So it is very difficult to see which is a normal physiologic change and which is an abnormal lesion. Thus, the detection of abnormalities on colposcopy during pregnancy requires an experienced colposcopist. In this study, there were four patients who

were asymptomatic and had an abnormal Pap smear, of which three were categorized as having early stage disease including stages I<sub>A1</sub> and I<sub>B</sub>. Of the remaining seven patients who had abnormal symptoms, only three had early stage disease. The most common presenting symptom of the patients from this report was abnormal vaginal bleeding (6 of 11), and one had leukorrhea. Because most of the patients (4 of 6) who had vaginal bleeding were in an advanced stage, and most of the patients (6 of 11) were diagnosed in the latter half of pregnancy, the prenatal examination and Papanicolaou smears should be performed as a routine screening at the first prenatal visit in all pregnant women for the early detection of cervical cancer. Also, all doctors should be aware of vaginal bleeding in pregnancy because diagnosis of cervical cancer is often delayed when bleeding is wrongly attributed to pregnancy-related complications.

The distribution of tumor histology seems to be similar between pregnant and nonpregnant patients. Eighty-one to eighty-seven percent of cervical tumors are squamous lesions, 7% to 15% are adenocarcinoma, and other types comprise 4% to 5%.<sup>10-12</sup> From this study there were 73% of squamous lesions.

Regarding the effect of pregnancy on cervical cancer, current data indicate that maternal survival and tumor characteristics are not adversely affected by pregnancy.<sup>13-15</sup> The decision to treat or delay treatment of cervical cancer during pregnancy is not difficult if the pregnancy is unwanted prior to 20 weeks, or if the cancer is diagnosed when fetal maturity has been attained. The difficult decision arises when the pregnancy is wanted and the fetus is not mature. Parents need to participate in the decision-making process and need adequate information on which to base their decision. Several studies suggest that a delay in treatment should be offered to pregnant women with early-stage disease who desire to maintain the pregnancy.<sup>16-20</sup> In this study there were eight patients who delayed therapy to improve fetal maturity and none demonstrated any progression of disease. Four patients were disease-free after 28-82 months of follow-up and three patients were lost to follow-up. One of four patients had a central tumor recurrent after 82 months of radiation and the remaining pa-

tients underwent clinical remission. One patient (no.2) had not yet delivered on the last date of follow-up. Although there are no randomized studies to confirm the benefits of cesarean section versus vaginal delivery, there have been reports of tumor recurrence at the episiotomy site after vaginal delivery,<sup>21-22</sup> and the possibility of hemorrhage, so all of the patients (except no.2 who had not delivered) were delivered by cesarean section. All the patients who received immediate radiotherapy had spontaneous abortions after 800-4600 cGy, and no tumor recurrence after 34-75 months of follow-up.

Until there are definite conclusions on the benefits or dangers of delayed treatment of cervical cancer in pregnancy, doctors who have such cases must discuss all risks with the patient and her family that may arise from delay of treatment.

## Conclusion

**Because the clinical stage is the most important prognostic factor of cervical cancer in pregnancy, overall survival is better for patients with early stage, thus pregnancy presents an ideal time for cervical cancer screening, and all pregnant women presenting for prenatal care should be carefully examined.**

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