

โรคมะเร็งในระหว่างการตั้งครรภ์: ประสบการณ์ 10 ปีในโรงพยาบาลศรีนครินทร์

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Cancer in Pregnancy: 10- year Experience in Srinagarind Hospital

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หลักการและวัตถุประสงค์: ถึงแม้ว่ามะเร็งในระหว่าง การตั้งครรภ์พบไม่บ่อย แต่มีอุบัติการณ์ความพิการและ เสียชีวิตต่อผู้ป่วยและทารกสูง ประกอบกับข้อมูลแนวทางการ รักษาในภาวะดังกล่าวค่อนข้างจำกัด ไม่ว่าจะเป็นการผ่าตัด รังสีรักษาและเคมีบำบัด นอกจากนี้การรักษายังก่อให้เกิดภาวะแทรกซ้อนต่อมารดาและทารกได้ การศึกษานี้จึงมี วัตถุประสงค์เพื่อศึกษาระบาดวิทยาและผลการรักษาผู้ป่วย มะเร็งในระหว่างการตั้งครรภ์

วิธีการศึกษา: ทบทวนจากแฟ้มประวัติการเจ็บป่วยและการรักษา รวมทั้งภาวะแทรกซ้อนที่เกิดขึ้นในผู้ป่วยมะเร็ง ในระหว่างการตั้งครรภ์ที่ถูกวินิจฉัยตั้งแต่ 1 มกราคม 2544 - 31 ธันวาคม 2553

ผลการศึกษา: ผู้ป่วยมีทั้งหมด 19 รายเข้าร่วมการศึกษา (0.64:1,000 ของการคลอด) จากจำนวนการคลอดทั้งหมด 26,446 ครั้ง ผู้ป่วยมีอายุเฉลี่ย 34.4 ปี อายุครรภ์เฉลี่ย ขณะวินิจฉัยโรค 24.6 สัปดาห์และอายุครรภ์เฉลี่ยที่คลอด 32.4 สัปดาห์ ผู้ป่วยส่วนใหญ่คลอดโดยผ่าตัดคลอด น้ำหนัก ทารกแรกคลอดเฉลี่ย 1,895.7 กรัม ผู้ป่วยส่วนมากได้รับการวินิจฉัยเป็นมะเร็งปากมดลูกและมะเร็งเม็ดเลือดขาว ชนิดเฉียบพลัน การรักษามะเร็งในระหว่างการตั้งครรภ์ โดยการผ่าตัดร้อยละ 22.2 และเคมีบำบัดร้อยละ 22.2 การคลอดก่อนกำหนดและภาวะขาดออกซิเจนของทารก แรกเกิดเป็นภาวะแทรกซ้อนที่พบได้บ่อย (ร้อยละ 76.4 และ 23.5 ตามลำดับ) ทารกส่วนใหญ่มีน้ำหนักต่ำกว่าเกณฑ์ มาตรฐาน (ร้อยละ 70.5) พบทารก 1 รายที่ถูกวินิจฉัยว่าเป็น Down syndrome ในมารดาที่เป็นมะเร็งเต้านมอายุ 43 ปี

สรุป: ถึงแม้ว่าภาวะมะเร็งในระหว่างการตั้งครรภ์พบได้ไม่บ่อย แต่มีความสำคัญอย่างยิ่งในการดูแลเพราะส่งผลกระทบต่อ

Background and objective: Although prevalence of cancer during pregnancy is rare, it leads to high morbidity and mortality in both mother and fetus. Treatment is a challenge because options are limited; cytotoxic agents, radiation, and surgery possibly lead to several maternal and fetal complications. There is no epidemiological data of cancer during pregnancy in Thailand. This study aim to describe characteristics and treatment outcomes of cancer diagnosed during pregnancy.

Method: Retrospective case series was reviewed, which included pregnancy women diagnosed with cancer in Srinagarind Hospital from 1st January 2001 to 31st December 2010.

Results: Nineteen pregnant women were diagnosed cancer during the observed period (0.64:1,000 deliveries); with mean age of 34.4 years, mean gestational age at diagnosed of 24.6 weeks and mean gestational age at delivery of 32.4 weeks. Cesarean section was the most common mode of delivery. Mean birth weight of baby was 1,895.7 grams. Cervical cancer and acute myeloblastic leukemia were the two most common types of cancer during pregnancy. Surgical treatment was performed in 22.2% of patients and 22.2% were treated by chemotherapy. Preterm delivery and neonatal asphyxia were the two most frequent obstetric complications. 70.5% of babies had low birth weight. One child with Down syndrome was born from maternal breast cancer.

Conclusion: Although cancer during pregnancy is uncommon, it is considered as an important problem due to unfavorable maternal and fetal outcomes, and lack of standard management guideline.

ผู้ป่วยและทารกอย่างมากรวมทั้งยังขาดแนวทางการรักษาที่ชัดเจน

คำสำคัญ: มะเร็ง, ภาวะตั้งครรภ์, ผลทางสูติศาสตร์ และ ผลทารกแรกคลอด

Keywords: Cancer, Pregnancy, Obstetric outcomes, Neonatal outcomes

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Introduction

The incidence of cancer during pregnancy is about 1:1000 pregnancies and it is probably lower in developing countries than in developed countries due to the younger age of pregnant women¹. The incidence of cancer during pregnancy is rising over the last thirty years because of an increasing number of women being pregnant at older age². Cancer is the second leading cause of death of reproductive-aged women³. The most frequent diagnosed malignant diseases are malignant melanoma, breast and cervical cancer; whereas the less common are lymphoma, leukemia, ovarian, gastrointestinal tract and genitourinary tract cancer^{1,2}.

Investigation and treatment of cancer during pregnancy is a challenge. Diagnostic work up should limit exposure to ionizing radiation in order to protect the fetus. Moreover, radiation which is a standard treatment for various cancers is too dangerous for fetus. Most cytotoxic agents are toxic to fetus and neonate, especially in the first trimester when organogenesis takes place. Most chemotherapeutic agents are classified as category D for FDA drug risk factor during pregnancy. Though, the benefits from these agents during pregnancy may outweigh the risks.

Since breast cancer is commonly diagnosed during pregnancy, there are several guidelines and numerous data about the management and safety of chemotherapeutic drugs⁴. However, the data is still limited for other types of cancer.

Incidence of cancer diagnosed during pregnancy is estimated to increase. Studying the outcomes of treatment of cancer during pregnancy would provide useful information for the future development of treatment protocol. Therefore, we reported a case series of cancer during pregnancy in our institution. The focus is

on epidemiology, management and the effects on the obstetric and neonatal outcomes.

Patients and Methods

All pregnant patients diagnosed with cancer in our institution were included in the study. Medical records were obtained from the obstetric and pediatric files.

Obstetric data included gestational age at diagnosis and delivery, mode of delivery (spontaneous labor, induction, cesarean section) and obstetric complications. Birth weight and congenital malformations are recorded as pediatric information. Cancer type, staging, treatment modalities as well as chemotherapy regimen were included in oncologic records.

All data were processed in SPSS software version 11.5. The study was approved by Ethic Committee of Medicine Faculty, Khon Kaen University under the respect of Helsinki Declaration (HE551052).

Results

Between 2001 and 2010, 26,446 deliveries and 19 pregnant women diagnosed with cancer were recorded (0.64:1,000 deliveries). At the diagnosis, mean maternal age was 34.4 years and gestational age was 24.6 weeks. The mean gestational age at delivery was 32.4 weeks and most of the patients underwent cesarean section. The indications were previous cesarean section and tumor obstruction. The patient characteristics were shown in Table 1.

Types of cancer were demonstrated in Table 2. Cervical cancer (21.0%) and acute myeloblastic leukemia (15.7%) were the two most common encountered tumors followed by cholangiocarcinoma, head and neck cancer and osteosarcoma.

Stages of cancer were revealed in Table 3. Advanced stage which defined as stage 3 and 4 was the most frequent (60%). Early stage which defined as stage 1 and 2 was found in 6 of 15 patients (40%). 50% of these groups were cervical cancer.

Managements of cancer during pregnancy by trimester at diagnosis were shown in table 4. The pregnancy was terminated at a gestational age of 12 weeks in one of 19 pregnant patients. In eight of 18 patients (44.4%), a single modality was initiated during pregnancy after cancer diagnosis at a gestational age of 23.3 weeks (range 13-28). The types of cancer in the treatment group were two for acute myeloblastic leukemia and one each for brain tumor, cervical cancer, non-small cell lung cancer, colon cancer, osteosarcoma, and liposarcoma. Therapies used during pregnancy were surgery (50%) and chemotherapy (50%). In nine of 19 patients (42.3%), treatment was delayed until postpartum. Types of cancer in these patients were cervical carcinoma (33.9%), osteosarcoma (11.1%), maxillary carcinoma (11.1%) and acute myeloblastic leukemia (11.1%), hepatocellular carcinoma (11.1%), and cholangiocarcinoma (11.1%).

Four patients were treated with chemotherapeutic agents. These drugs were combination of paclitaxel and carboplatin for non-small cell lung cancer, all-trans retinoic acid for acute promyelocytic leukemia, hydroxyurea for acute myeloblastic leukemia, and combination of cisplatin and doxorubicin for osteosarcoma.

Obstetric complications according to treatment modality were shown in table 5. One patient had terminated the pregnancy during the first trimester; data of one patient in treatment group was incomplete. Obstetric outcomes were analyzed in seventeen pregnant women. Preterm delivery (76.4%) and neonatal asphyxia (23.5%) were the two most common obstetric complications. There were three pregnant women with preterm premature rupture of membranes (PPROM) in no treatment group. The obstetric complications of surgery were preterm delivery and still birth. Neonatal hypoxia and preterm delivery were obstetric complications found in three patients and still birth found in one patient in chemotherapy group. Down

syndrome was found in the no treatment group.

Neonatal outcomes were shown in table 6. Data on the gestational age at delivery were available for 17 of 18 births. 47% of deliveries occurred before 32 weeks of gestation, another 38.2% of babies were born at gestational age between 32 and 37 weeks, and 17.6% of babies were delivered at full term (≥ 37 weeks). The average birth weight was 1895.7 gram. The birth weight below the 10th percentile for gestational age was found in 4 of 17 children (23.5%) whose maternal cancer were brain tumor, osteosarcoma, and cervical cancer. Two of these children's mother received chemotherapy, one received surgical treatment, and another received no treatment. Twelve of 17 babies (70.5%) had low birth weight which defined birth weight below 2,500 grams; nine of these babies had very low birth weight which defined birth weight below 1,500 grams. One baby with Down syndrome was from maternal breast cancer. In this case, the maternal age was 43 years. Two intrauterine deaths were observed in a woman with brain tumor who received tumor removal and acute myeloblastic leukemia who received hydroxyurea.

Discussion

In this retrospective study, we reported a data of cancer diagnosed during pregnancy in a single institution. The mean maternal age was 34 years old which was rather old due to a trend toward older age of pregnant women. Cervical cancer was the most frequent cancer during pregnancy, consistent with other studies^{1,5}. Other tumors were acute myeloblastic leukemia, osteosarcoma, head and neck cancer, and cholangiocarcinoma. The distribution of cancer was similar to the general population in the same age group of our area. Differences in incidence and screening program may be the explanation of the dissimilarity in types of cancer reported in our study compared with the others⁶. Our report found the advanced stage of cancer during pregnancy. This may be caused by high estrogen levels from pregnancy which can aggravate a preexisting malignant lesion by suppression of the immune system during pregnancy⁷.

Table 1 Clinical characteristics of cancer during pregnancy

Characteristics	Total (n=19)
Age in years, mean (range)	34.4 (22-43)
Gestational age at diagnosed in weeks, mean (range)	24.6 (12-31)
Gestational age at delivery in weeks, mean (range)	32.4 (27-39)
Mode of delivery, N (%)	Total (n=17)
Cesarean section	11 (64.7)
vaginal delivery	6 (35.3)
Indication of cesarean section, N (%)	Total (n=11)
Tumor obstruction	4 (36.3)
Previous cesarean	3 (27.2)
Abnormal position	1 (9)
Fail induction	1 (9)
Fetal distress	1 (9)
Post mortem	1 (9)
Mean birth weight in gram, mean (range)	1895.7 (985-3520)

Table 2 Distribution of tumor types

Tumor Types	No. (total 19)	%
Cervical cancer	4	21.0
Acute myogenous leukemia	3	15.7
Cholangiocarcinoma	2	13.3
Osteosarcoma	2	13.3
Head and neck cancer	2	13.3
Breast cancer	1	5.2
Colorectal cancer	1	5.2
Brain tumor	1	5.2
Lung cancer	1	5.2
Hepatocellular carcinoma	1	5.2
Liposarcoma	1	5.2

Table 3 Oncologic data of cancer during pregnancy

Stage of cancer, N (%)	Total (N=15)
4	6 (40)
3	3 (20)
2	5 (33.3)
1	1(6.7)
Sites of metastases, N (%)	Total (N=5)
Liver	3 (60)
Brain	1 (20)
Lung	1 (20)
Chemotherapy regimen, N (%)	Total (N=4)
Paclitaxel and Carboplatin	1 (25)
Cisplatin and Doxorubicin	1 (25)
All-trans retinoic acid	1 (25)
Hydroxyurea	1 (25)

Table 4 Management of cancer during pregnancy by trimester at diagnosis

Management	1 st trimester (N=1)	2 nd trimester (N=15)	3 rd trimester (N=3)
Termination of pregnancy	1	0	0
Treatment of cancer	0	8	0
No treatment of cancer	0	7	3

Table 5 Obstetric complications according to treatment modality (N=17)

Treatment group	No.	%	Complication (n)
No treatment	10	55.5	Preterm (8) Neonatal asphyxia (3) Premature rupture of membrane (3) Antepartum hemorrhage (1) Breech presentation(1) GDM (1)Down syndrome (1)
Surgery	3	22.2	Preterm (2) Neonatal death (1)
Chemotherapy	4	22.2	Preterm (3) Neonatal asphyxia (1)Hypoxia (2) Neonatal death (1)

Table 6 Distribution of birth weight expressed in percentile for gestational age

Percentile of birth weight for gestational age	Treatment (N=8)	No treatment(n=10)
< 10	3	1
10-49	2	4
50-90	2	2
> 90	1	0

Diagnosis of cancer during pregnancy is difficult. Physical examination which is limited due to physiological change in pregnancy contributes to delay the diagnosis⁸. Limited exposure to ionizing radiation and restricted procedures aim to prevent risk of fetal health. Most of treatments of malignancy in our report were in the second trimester. Organogenesis is complete since the first trimester, toxic effects to overt teratogenesis during the second and third trimesters are rare⁹.

The most common obstetric complication in our study was preterm delivery due to physical or psychological stress from cancer itself and complication of treatments, such as chemotherapy. Treatment can induce preterm labor through activation of the maternal hypothalamic-pituitary-adrenal axis^{10, 11, 12}.

Neonatal asphyxia, the second obstetric complication in our finding, may be an effect of supine hypotension. After a gestational age of 16 weeks, uterus becomes an extra pelvic organ, the enlarging uterus had an increasing potential to obstruct returning of venous flow in the inferior vena cava when the gravid is supine¹³. Low birth weight and intrauterine growth retardation (IUGR) were also common neonatal outcomes in our report, consistent with previous research¹⁴. Mechanism of IUGR due to chemotherapy is unclear, however, it is possibly caused by placental underdevelopment from oxidative stress¹⁵. Mechanisms of tumor related IUGR are poor trophoblast invasion and/or placental insufficiency by tumor¹⁶. Additionally, we reported a case of Down syndrome from 43 years-old

mother with breast cancer. The older age of the mother is the most likely cause of this syndrome¹⁷.

Our study had some limitations. This study was based on retrospective data which may not provide complete data. We suggest the further prospective follow up outcomes about child growth and development in this group.

Conclusion

Although cancer during pregnancy is uncommon, it is considered as a significant problem due to unfavorable maternal and fetal outcomes. More studies and longer term for follow up may be useful in development of standard guideline for management.

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