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Subsequence Pregnancy Outcomes after Treatment of Gestational Trophoblastic Disease in King Chulalongkorn Memorial Hospital

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ABSTRACT

Objectives: To review subsequent pregnancy outcome in gestational trophoblastic disease (GTD) patients at King Chulalongkorn Memorial hospital.

Materials and Methods: Retrospective cohort study was done between 2001 and 2015. Women whom diagnosed with gestational trophoblastic disease at King Chulalongkorn Memorial Hospital, Bangkok, Thailand were recruited. Data were reviewed by medical record and telephone interview regarding subsequent pregnancy outcome and clinical data.

Results: There were 147 GTD patients enrolled during study period, 82 pregnant women were observed. Final diagnosis was complete hydatidiform mole 40 cases (48.78%), partial hydatidiform mole 11 cases (13.41%), postmolar gestational trophoblastic neoplasia 28 cases (34.15%) and non-molar gestational trophoblastic neoplasia 3 cases (3.66%). Mean age at diagnosis was 25.04 years (range 14-36 years). Median interval from remission to subsequent pregnancy was 36 months (range 3-132 months). There were 80 from 82 cases spontaneous pregnancy. Three patients (3.66 %) was pregnant before 1 year. For first subsequent pregnancy outcomes, 71 cases (86.66%) were term live birth, 3 cases (3.66%) were preterm birth and 8 cases (9.76%) were spontaneous abortion. There was no significant difference in pregnancy outcomes between patients who received chemotherapy and who did not receive chemotherapy treatment. Similarly, patients who received single agent chemotherapy and multi-agent chemotherapy had no significant difference in pregnancy outcomes.

Conclusion: Around 86% of subsequent pregnancy after GTD remission were term live birth. Subsequent pregnancy outcomes after GTD were not significantly different between patients with hydatidiform mole and gestational trophoblastic neoplasia.

Keywords: gestational trophoblastic disease, molar pregnancy, subsequent pregnancy, gestational trophoblastic neoplasia

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ผลของการตั้งครรภ์ในผู้ป่วยที่เคยตั้งครรภ์ไข่ปลาอุกหรือมะเร็งเนื้อรกที่รักษาในโรงพยาบาลจุฬาลงกรณ์

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บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลของการตั้งครรภ์ในผู้ป่วยภายหลังการรักษาครรภ์ไข่ปลาอุก หรือมะเร็งเนื้อรกในโรงพยาบาลจุฬาลงกรณ์*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลัง ตั้งแต่ปีพ.ศ. 2544-2558 โดยเก็บข้อมูลในผู้ป่วยที่ได้รับการวินิจฉัยเป็นครรภ์ไข่ปลาอุกหรือมะเร็งเนื้อรก ซึ่งเป็นกลุ่มโรค Gestational Trophoblastic Disease ในโรงพยาบาลจุฬาลงกรณ์ ข้อมูลรวบรวมมาจากบันทึกในเวชระเบียนและการโทรศัพท์สัมภาษณ์ผู้ป่วย โดยรวบรวมข้อมูลทางคลินิกและผลของการตั้งครรภ์หลังการรักษาโรค*

ผลการวิจัย: *ในช่วงเวลาที่ทำการศึกษา มีผู้ป่วยในโรคนี้ 147 ราย และมีการตั้งครรภ์ 82 ราย ผู้ป่วย 40 ราย (ร้อยละ 48.78) ได้รับการวินิจฉัยเป็น complete hydatidiform mole 11 ราย (ร้อยละ 13.41) ได้รับการวินิจฉัยเป็น partial hydatidiform mole 28 ราย (ร้อยละ 34.15) ได้รับการวินิจฉัยเป็นมะเร็งเนื้อรกที่เกิดตามหลังครรภ์ไข่ปลาอุก และ 3 ราย (ร้อยละ 3.66) ได้รับการวินิจฉัยเป็นมะเร็งเนื้อรกที่ไม่ได้เกิดตามหลังครรภ์ไข่ปลาอุก อายุเฉลี่ยของผู้ป่วยคือ 25.04 ปี ระยะเวลาตั้งแต่หายจากโรคจนตั้งครรภ์มีค่ามัธยฐานที่ 36 เดือน ผู้ป่วย 80 ราย สามารถตั้งครรภ์ได้เอง แต่พบผู้ป่วย 3 รายที่ตั้งครรภ์ก่อน 1 ปีนับจากระยะเวลาหายจากโรค ผลของการตั้งครรภ์พบว่า 71 ราย (ร้อยละ 86.66) คลอดครบกำหนด มี 3 ราย (ร้อยละ 3.66) คลอดก่อนกำหนด และ 8 ราย (ร้อยละ 9.76) แท้งบุตรไม่พบความแตกต่างในผลของการตั้งครรภ์อย่างมีนัยสำคัญระหว่างกลุ่มที่เป็นครรภ์ไข่ปลาอุก และกลุ่มที่เป็นมะเร็งที่ได้เคมีบำบัด เมื่อเทียบผลการตั้งครรภ์ในกลุ่มที่ได้เคมีบำบัดตัวเดียวกับกลุ่มที่ได้หลายตัวก็ไม่พบความแตกต่างเช่นกัน*

สรุป: *ผู้ป่วย Gestational Trophoblastic Disease ที่ตั้งครรภ์หลังการรักษา พบว่าร้อยละ 86 เป็นการคลอดครบกำหนด ไม่พบความแตกต่างในผลของการตั้งครรภ์อย่างมีนัยสำคัญระหว่างกลุ่มที่เป็นครรภ์ไข่ปลาอุกและกลุ่มที่เป็นมะเร็งที่ได้เคมีบำบัด*

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Introduction

Gestational trophoblastic disease (GTD) is the spectrum of disease caused from abnormal trophoblast cells or placenta which included benign disorder or hydatidiform moles to malignant conditions (Gestational trophoblastic neoplasia, GTN) such as choriocarcinoma, placental-site trophoblastic tumor and epithelioid trophoblastic tumor[1]. Incidence of GTD varies among countries, in Thailand prevalence was 1-2 per 1,000 pregnancies[2-4]. The incidence trends to be lower in western country[1]. Treatment of hydatidiform mole is primary evacuation of molar tissue and monitoring serum human chorionic gonadotropin (hCG) level. About 10-30% of hydatidiform mole patients develop postmolar GTN[1, 3]. Primary treatment of GTN is chemotherapy. So far, outcomes of GTN patients are excellent because most of them achieve remission[4].

Due to the pathogenesis of this condition results from abnormal fertilization, most of patients are in reproductive age[5]. Reproductive outcomes after treatment are critical issues for patients. There were several studies reported about pregnancy outcomes after hydatidiform mole and GTN[6-9]. However, there still lack of data from Thailand. Since the pathogenesis of GTD may relate to race and ethnicity. Therefore, the objectives of this study aimed to explore subsequent pregnancy outcomes after treatment in GTD patients and to compare outcomes of pregnancy between hydatidiform mole and GTN patients.

Materials and Methods

This retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. All patients whom diagnosed GTD between 2001 and 2015 were recruited. Hydatidiform mole was diagnosed by histologic specimens and GTN was diagnosed by the International Federation of Gynecology and Obstetrics (FIGO) criteria[10]. Patients who lost to follow-up or patients with medical conditions which contraindicated for pregnancy, or had no ability to pregnant (e.g. hysterectomy, tubal resection) were excluded. Data collection was retrieved from medical record and telephone interview. Clinical characteristics and data related to pregnancy outcomes in term of total pregnancy, total delivery, term live birth, preterm live birth, stillbirth, congenital anomaly, spontaneous abortion, therapeutic abortion, ectopic pregnancy, and repeat mole were collected. The pregnancy outcomes were collected only the first subsequent pregnancy after treatment of GTD. For single agent chemotherapy, we used either methotrexate or actinomycin D. For multi-agent chemotherapy, we used either EMACO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) or VAC regimen (vincristine, actinomycin D, cyclophosphamide). This study was approved by the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University. The methods were performed in accordance with approved guidelines.

Sample size calculation was based upon the prevalence of normal pregnancy outcome after GTD from previous study[6]. SPSS version 22 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Mean, median, standard deviation (SD), percentage for nonparametric variables, student t-test for continuous variables, chi square for proportional data and analysis of variance (ANOVA) for many continuous variables. Statistically significant was considered if $p < 0.05$.

Results

From 1 January 2001 to 31 December 2015, there were 229 GTD patients registered at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. One hundred and twenty three patients were diagnosed as hydatidiform mole with remission, 70 patients were diagnosed as postmolar GTN and 36 patients diagnosed as non-molar GTN. Forty patients were excluded due to contraindicate or no ability to pregnant and 42 patients lost to follow-up. A total of 147 patients were recruited. The number of first pregnancy after remission of GTD were 82 patients. Among these patients, final diagnosis was complete hydatidiform mole 40 cases (48.78%), partial hydatidiform mole 11 cases (13.41%), postmolar GTN 28 cases (34.15%) and non-molar GTN 3 cases (3.66%).

Mean age at diagnosis was 25.04 years (range 14-36 years, SD 5.71). Median interval from remission to first subsequent pregnancy was 36 months (range 3-132 months). There were 80 from 82 cases acquired spontaneous pregnancy. Three patients (3.66 %) were pregnant before 1 year, 2 of 3 cases were postmolar GTN with previous exposed to methotrexate. One of them had preterm birth, the other delivered term newborn. The third case was previously diagnosed of hydatidiform mole and achieved uneventful term delivery.

For pregnancy outcomes, 71 (86.66%) cases were term live birth, 3 (3.66%) and 8 (9.76%) cases were preterm birth and spontaneous abortion, respectively. There were no stillbirth, congenital anomalies, therapeutic abortion, ectopic pregnancy and repeat mole in this report. There were 48 (64.86%) cases delivered by normal labor and 26 (35.13%) cases by cesarean section. Average birth weight of newborn was 3,089.24 gram (SD 400.86).

Table 1. Clinical characteristics and pregnancy outcomes compare between hydatidiform mole and GTN patients.

	Diagnosis		
	Hydatidiform mole (n=51)	**GTN (n=31)**	**p value**
Mean age at diagnosis (years, mean ± SD)	25.35 (5.87)	24.52 (5.48)	0.46
Median interval to pregnancy (months, range)	36 (10-132)	36 (3-132)	
Total number of pregnancy after remission			
1	35 (68.62%)	25 (80.64%)	0.55
2	14 (27.45%)	6 (19.36%)	
3	1 (1.96%)	0 (0%)	
4	1 (1.96%)	0 (0%)	
Method to pregnancy			
Natural	49 (96.08%)	31 (100%)	0.54
IUI	1 (1.96%)	0 (0%)	
IVF	1 (1.96%)	0 (0%)	
Delivered hospital			
KCMH	18 (35.29%)	9 (29.03%)	0.56
Other	33 (64.71%)	22 (70.96%)	
Route of delivery			
normal labor	30 (65.22%)	18 (64.28%)	0.94
LT C/S	16 (34.78%)	10 (35.72%)	
First subsequent pregnancy outcome			
term live	44 (86.27%)	27 (87.10%)	0.99
preterm live	2 (3.92%)	1 (3.22%)	
spontaneous abortion	5 (9.80%)	3 (9.68%)	
Sex of fetus			
male	27 (58.70%)	20 (71.43%)	0.27
female	19 (41.30%)	8 (28.57%)	
Average weight of fetus (gram, mean ± SD)	3,105.98 ± 327.30	3,061.75 ± 504.63	0.65

P value corresponds to independent t test and chi-square.

GTN: Gestational trophoblastic neoplasia, SD: standard deviation, IUI: intrauterine inseminization, IVF: in vitro fertilization, KCMH: King Chulalongkorn Memorial Hospital, LT C/S: low transverse cesarean section

When compare between hydatidiform mole and GTN patients. There was no significant difference in term of age, interval from remission to pregnancy, route of delivery and fetal outcomes (Table 1).

Similarly, patients who received single agent chemotherapy compared to multiple agent chemotherapy had no significant difference in age, duration to pregnancy and fetal outcomes (Table 2).

Table 2. Clinical characteristics and pregnancy outcomes compare between GTN patients who received single agent and multiple agent chemotherapy.

	Previous treatment		
	Single agent CMT (n=24)	**Multi agent CMT (n=7)**	**p value**
Mean age at diagnosis (years, mean ± SD)	24.12 (5.07)	26.17 (7.25)	0.12
Median interval to pregnancy (months, range)	36 (3-132)	30 (12-60)	
Total number of pregnancy after remission			
1	20 (83.33%)	5 (71.43%)	0.48
2	4 (16.67%)	2 (28.57%)	
Delivered hospital			
KCMH	9 (37.50%)	0 (0%)	0.05
Other	15 (62.50%)	7 (100%)	
Route of delivery			
normal labor	14 (63.64%)	4 (66.67%)	0.89
LT C/S	8 (36.36%)	2 (33.33%)	
First subsequent pregnancy outcome			
term live	21 (87.50%)	6 (85.71%)	0.78
preterm live	1 (4.17%)	0 (0%)	
spontaneous abortion	2 (8.33%)	1 (14.29%)	
Sex of fetus			
male	16 (72.73%)	4 (66.67%)	0.77
female	6 (27.37%)	2 (33.33%)	
Average weight of fetus (gram, mean ± SD)	3,124.73 ± 541.95	2,830.83 ± 245.16	0.21

P value corresponds to analysis of variance test and chi-square.
GTN: Gestational trophoblastic neoplasia, SD: standard deviation, CMT: chemotherapy,
KCMH: King Chulalongkorn Memorial Hospital,
LT C/S: low transverse cesarean section

Discussion

In general, GTD occurred in childbearing age. Hydatidiform mole can be treated by evacuation of molar tissue and GTN is mainly treated by chemotherapy. Therefore, treatment of GTD was primarily fertility preserved. As a result, most of GTD patients can pregnant after remission. For this reason, subsequent pregnancy outcomes in these patients are important. Joneborg U, et al,[11] conducted a population-based cohort study in Sweden showed that women with a history of hydatidiform mole had an increase risk in large for gestational age, preterm birth and stillbirth. In

our data, the incidence of spontaneous abortion was approximately 10% in both hydatidiform mole and GTN patients which were comparable with spontaneous abortion in normal population[12, 13].

Vargas R, et al reported data about pregnancy outcome in 2,342 patients from New England Trophoblastic Disease Center after treatment of GTD and showed slightly increase stillbirth rate in GTD patients compared to normal population[6]. There was no stillbirth case in our finding, possibly due to small number of pregnant cases.

From our study, patients with previously diagnosed molar pregnancy or GTN had no significant difference in subsequent pregnancy outcomes with regard to term live birth, preterm birth and spontaneous abortion. Furthermore, interval to pregnancy, route of delivery, sex and weight of fetus were not different in both groups. This finding comparable to other studies in the world[7, 8, 14, 15].

Median interval from remission to first subsequent pregnancy was 36 months in this study. Compare to study from Kim JH, et al, more than half of patients became pregnant within 1 year after pregnancy was permitted[7]. This may explain from our follow-up protocol that strongly recommended for effective contraception at least 1 year after remission or complete chemotherapy. Furthermore, possible cause of long interval to subsequent pregnancy may be from patients' concern about following pregnancy after GTD. Leenharattanarak P, et al[16] reported quality of life after treatment in GTN patients were in mild impairment range. However, patients who desire fertility suffer lower quality of life in the emotional well-being domain. This data showed that fertility function was a major concern in this cancer survival patients. We found no statistical difference of interval to pregnancy between hydatidiform mole and GTN patients. Moreover, no difference in interval to pregnancy between patients who received single and multi-agent chemotherapy.

The results from this study can be applied to recommend patients who previously diagnosed GTD either hydatidiform mole or GTN that principally they can achieved reproductive outcome as normal population. However, limitations of this study were single institute and retrospective design that may result in small number of patients and some missing data.

Conclusion

In conclusion, around 86% of subsequent pregnancy after GTD remission were term live birth. Subsequent pregnancy outcomes after GTD were not significantly different between hydatidiform mole and GTN patients.

Potential conflicts of interest

The authors declare no conflict of interest.

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