The reproductive outcome after fertility preserving treatment for premalignant and malignant gynecologic diseases: An experience of a tertiary care center

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Abstract

Background: Treatment of gynecologic cancers in young women is a real challenge as obtaining the future women's fertility is almost always keened by the patient and her family. However, there are reported adverse outcome of pregnancy after treatment.

Objective: To evaluate the obstetric outcome of patients who had undergone fertility preserving treatment for gynecologic premalignant and malignant diseases.

Patients and methods: The study reviewed the pregnancy course and delivery data of 60 patients,who conceived after fertility sparing treatment for gynecologic premalignant and malignant diseases at department of Obstetrics and Gynecology and department of Clinical Oncology & Nuclear Medicine at Mansoura University Hospital from January 2012 to December2015. We reported pregnancy complications, abnormalities during labor, neonatal outcome and any recurrence after delivery.

Results: The mean age (± SD) of the studied patients was 24.9 (± 6.03) years. The median follow upwas 13 months (range:1-40).The preceding lesions included gestational trophoblastic neoplasia (GTN), 43 cases(71.7%) while early ovarian carcinoma (14 cases, 23.3 %) and least CIN III (2 cases, 3.3%) and micro-invasive cervical carcinoma (one case, 1.7%). All cases of GTN were treated with single or multiple agents' chemotherapy. The 3 cases of cervical micro-invasive carcinoma and CIN III were treated with loop electrosurgical excision procedures (LEEP). Cases with stage 1a ovarian cancer were treated with unilateral salpingo-oophorectomy with peritoneal cytology and biopsy of the other ovary. Missed abortion was diagnosed in 4 cases (6.7%). The rate of caesarean delivery (CD) was high (70.9%). Intra-abdominal adhesions during CDwere seen in (20.5%) of cases. The neonatal outcome was normal in 53 cases, and 2 cases (3.6%) of had congenital fetal malformations. The poor neonatal outcome was significantly correlated to number of chemotherapy cycles (P=0.04).

Conclusion: The reproductive outcome after fertility preserving treatment of GTN, micro-invasive carcinoma of cervix, CINIII, and stage 1 ovarian cancer is comparable to those of general population. However, there were increased rate of CD, Intra-abdominal adhesions, missed abortion and congenital fetal malformations

Keywords: Gynecologic cancers; reproductive outcome.

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Introduction

Treatment of gynecologic cancers in young women represents actually a clinical challenge. Gynecological cancers occur variably at different ages, it may occur at younger age in 12 % of ovarian cancer, 5 % of endometrial cancer, and 2 % of cervix cancer (1).The preservation of the future fertility is usually requested by the patient and desired by her

family. Gestational trophoblastic neoplasms (GTN) are well known tumors of reproductive age and mostly chemo-sensitive. However, the rate of recurrent mole, a benign one of this group was reported in 2.5-9% of cases (2). Gato and colleagues (3) studied the outcome of 50 patients who underwent fertility-preserving treatment for choriocarcinoma, 23 conceived for a total of 43 pregnancies, meanwhile, congenital cardiac defects were observed in 2 of their neonates, namely, ventricular septal defect (VSD) and tetralogy of Fallot.

On the other hand; some cases of cervical cancer occur before the age of 40 years where conservative surgery is to be applied. For these young patients with early stage of the disease, the loop electrosurgical excision procedures (LEEP) and conization provide a hope to preserve their fertilities (4). Despite radical trachelectomy is considered as a more invasive surgical maneuver; some authors (5) reported in a study involving 210 cases, 35 had live births after this surgery. However, the rate of second trimester miscarriage and preterm labor was recorded to be higher than normal.

Looking to ovarian cancer; conservative surgery remains the ideal for young patients with FIGO Stage I epithelial tumors and also for the borderline tumors (6, 7). A systematic review carried by Darai et al (8) and concluded that conservative management of BOT resulted in a spontaneous pregnancy rate of 54% for early stage and 34% for advanced stage without increase of the risk of lethal recurrence. Some other authors (9, 10) reported that it is possible to maintain good reproductive function after conservative surgery for ovarian dysgerminoma followed by chemotherapy. Moreover, Vicus et al (11) studied the treatment outcome and reproductive function in women with ovarian immature teratoma and demonstrated the 6 of 11 patients conceived, 3 of them had received chemotherapy.

To the best of our knowledge, there are few published studies in our locality about pregnancy and delivery criteria after fertility preserving treatment of premalignant and malignant gynecologic lesions. So, we conducted this retrospective study.

Patients and methods

We reviewed in a retrospective descriptive manner the subsequent pregnancy and delivery data of 60 patients who conceived after fertility sparing treatment of premalignant and early malignant gynecologic diseases at the department of Obstetrics and Gynecology as well as department of Clinical Oncology, Mansoura University from January 2012 to December 2015. The study was approved by the Institutional Research Board (IRB) at Faculty of Medicine, Mansoura University.

Patients included were those who had undergone fertility preserving treatment for premalignant and malignant gynecologic diseases, available for follow up during pregnancy and delivery after treatment and those who accept to participate in the study. We excluded patients with incomplete follow up data or inability to contact her or the treating physician.

The data were retrospectively collected by checking the patients' files at MUH and new data recorded by the managing physician outside. The initial criteria of the patient during admission as age, parity, medical condition, diagnosis and stage of the disease, surgical intervention if any, postoperative chemotherapy (type and number of courses) and follow-up data were preliminary registered. The data about subsequent pregnancy and delivery were collected by contacting the patient and her managing colleague at our center or at the private clinics where we reported pregnancy complications, type and abnormalities during labor, neonatal outcome and also any recurrence after delivery. All gathered data are then subjected to statistical analysis.

Statistical analysis

All data collected were statistically analyzed by using SPSS for windows version 17.0 (SPSS, Chicago, IL). Continuous data were expressed as mean ± standard deviation (SD) and proportions for the socio-demographic characteristics. Multivariate analyses were performed where outcome of pregnancy was the dependent variable and number of cycles as well asinterval between chemotherapy and pregnancy were independent variables.Mann-Whitney test and Kruskal-Wallis test were adopted to analyze the differences under different items. . P-value equal or <0.05 was set statistically significant.

Results

Sixty patients got pregnant after fertility preserving treatment of premalignant and malignant gynecologic lesions. The median follow upperiod was 13 months (range:1-40).The mean age ± SD of our patients was set 24,9 ± 6,03 years meanwhile the median parity was 1.0 (range:1-4). The mean time interval from surgery or last cycle of chemotherapy till pregnancy ± SD was 14.47 (8.21) months and ranged from (1- 40) months. The predominant recorded lesions were gestational trophoblastic neoplasia (43 cases, 71.7%) followed by early ovarian carcinoma (14 cases, 23.3 %), lastly CIN III (2 cases, 3.3%) and micro-invasive cervical

carcinoma (one case, 1.7%). The initial diagnosis and FIGO stage of the disease were presented and obviously all patients were in stage 1 except for 2 cases with cervical intraepithelial neoplasia (CIN III), table [1]. In addition; the same table represented the fertility preserving treatment of the studied cases. Low-risk GTN cases were treated with methotrexate (50 mg/kg body weight) alternating with folinic acid (0.1mg/kg) but 5 cases failed to respond, so they received multiple agent chemotherapy (EMACO) together with one case of high-risk GTN. Three cases of cervical microinvasive carcinoma and CIN III were treated with LEEP. Furthermore, cases with stage 1a ovarian cancer were treated with unilateral salpingo-oophorectomy with peritoneal cytology and biopsy of other ovary. Three cycles of adjuvant chemotherapy (Carboplatin-Paclitaxel) were added to patients with stage 1c epithelial tumors and 4 cycles of (Bleomycin-Etoposide-Cisplatinum) for stage 1c germ cell tumors.

The pregnancy outcome was presented in table [2]. There were 3 cases (5%) of preterm labor at 36 weeks, none of them needed incubator care, 2 of them had performed LEEP whilst one after treatment of GTN. There were 4 cases of missed abortion (6.7%), 3 of them were after chemotherapy, and a case of induced abortion (due to short interval between chemotherapy and pregnancy). The occurrence of missed abortion was significantly correlated to shorter interval between chemotherapy and pregnancy (P = 0.049). No reported maternal complications during pregnancy except for pregnancy-induced hypertension in one case.Regarding delivery; 55 cases were delivered, 39 (70.9%) delivered by caesarean delivery (CD) and 16 (29.1%) delivered vaginally. Two cases of ovarian tumors (stage 1c) performed total abdominal hysterectomy and salpingo-oophorectomy with surgical staging during CD under request of the patients. However, there was no evidence of disease recurrence after histopathological examination of their specimens. During caesarean delivery, 8 of 39 cases (20.5%) had adhesions between the uterus and intestine. Seven of them had undergone conservative surgery for ovarian cancer and one case received combination chemotherapy for GTN. Two of 39 cases (5.1%) had congested uterine wall with edema and tearing of the stitches. One case received single whereas the other received combination chemotherapy. Furthermore, one case (2.6%) previously treated choriocarcinoma with combination chemotherapy; the fundus of the uterus was found to be thin which probably the site of the initial tumor. Biopsies from the other ovary, adhesions, omentum, and peritoneum were taken during CD and proved free [Table 2]. The neonatal outcome was normal in 53 cases, and 2 cases (3.6%) had congenital fetal malformation (both received chemotherapy).One case of them had congenital intestinal obstruction (received 10 courses of methotrexate) and the other case of ventricular septal defect (received 6 courses of EMACO). The poor neonatal outcome was significantly correlated to number of chemotherapy cycles (P=0.04).However, neonatal outcome was not correlated to interval between pregnancy and chemotherapy (P=0.2) [table 3]. No reported cases of recurrence after treatment of cervical and ovarian lesions in our study. Only one case of GTN recurrence was reported after one month of delivery (1.7%). She was presented by secondary postpartum hemorrhage and received EMACO protocol [table 2].

Discussion

During the decision making forgynecologic cancer, the tumor board usually faces a challenge between the both oncological and reproductive outcomes. This particularly occurs when the gynecologic cancer patient is at young age and needs a future pregnancy. This raised our attention for retrospective analysis of 60 patients who conceived after fertility preserving treatment for GTN, microinvasive cervical carcinoma, CIN III, and early ovarian cancer.

It is well known that, the prognosis of GTN after fertility sparing treatment is excellent as the tumor is chemosensitive. Single agent Methotrexate is used as first line for low risk cases and EMACO is the commonly used second-line combination chemotherapy protocol (12,13). We reported that pregnancy following chemotherapy resulted in 4 missed abortions (6.7%) and one case of induced abortion. The adverse pregnancy outcome for patients was not correlated to number of chemotherapy cycles (P=0.17) but was significantly correlated to the shorter interval betweenthe last chemotherapy and pregnancy (P=0.049). The miscarriage after chemotherapy was also reported by Gadducci et al (14).The long term effect of chemotherapy on obstetric outcome is unclear and needs to be evaluated in a large prospective study. Moreover, one case developed recurrence one month after delivery which necessitated continuing postpartum surveillance of the cured patients.

In our study 3 cases had undergone LEEP procedure for treatment of CIN III and microinvasive carcinoma, however 2 of them developed preterm labor. The association between LEEP and preterm births was also proved by Bjorge et al (15).The oncological and reproductive outcome of the managed 14 cases of early ovarian cancer were relatively excellent as the authors

did not report any case of recurrence during the follow up period and with a satisfactory neonatal outcome even after receiving adjuvant chemotherapy, this comes similar to results found by many other authors (6-10).

The mode of delivery of the studied cases was CS in 39 (70.9%) which is considered a very high figure compared to the reported national figures (22%) (16). The high rate of CS may be attributed to the concept of the treating physician to perform "second-look" during CS or request of the patient due to fear of limited fertility after surgery and chemotherapy. However, this explanation was not supported by other authors.

Regarding the neonatal outcome in our study, we reported 2 cases (3.6%) of congenital fetal malformation (both received chemotherapy). This rate is higher than general population which reported to be 2.4% (17). The poor neonatal outcome was significantly correlated to the number of chemotherapy cycles (P=0.04) [table 3].This finding is supported by some other study done by Gato et el (3) who reported that total dose of methotrexate was higher in patients who delivered a child with cardiac anomaly. However, our finding did not agree with Gadducci et al (18) who reported that there was no increase of risk of CFMF after chemotherapy for GTN. This disagreement may be due to small sample size of our study.

One limitation of this study is lack of data about the total number of cases who had underwent fertility preserving treatment during the study period, so we could not estimate the ratio of pregnancy among the patients who had received the same treatment. Smallnumber of cases with cervical lesions as well as adverse pregnancy and neonatal outcome might result in statistical confusion. Lastly; the authors also recommend a multicenter not a single center study, like ours, for the results to be more clarified and satisfactory.

Conclusion

Fertility-sparing treatment is a viable tool to enable gynecological cancer patients of young age to fulfill their family building without impairment of oncological outcome and the reproductive outcome of GTN, micro-invasive carcinoma of cervix, CINIII and stage 1 ovarian cancer is comparable to those of general population but with increased rate of CD, Intra-abdominal adhesions, missed abortion and congenital fetal malformations.

Conflict of interest:

The authors declare no conflict of interests with content of this manuscript.

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Table 1: Patients' demographic data.

Variable	Total number (60)			
Age in years (mean &SD)	24.92 (6.03)			
Parity (median & range)	1.0 (1 - 4)			
Mean interval from treatment to pregnancy in months (SD)	14.47 (8.21)Range: (1-40) months			
Type of tumor:	**Number (%)**	**FIGO stage**	**Treatment offered**	
			Surgery	**Chemotherapy**
1. GTN	43 (71.7)	1 (43 cases)	No	Methotrexate (37), EMA/CO (6)
2. Ovarain:				
Borderline tumors	1 (1.7)	1a (1 case)	USO	No
Serous cystadenocarcinoma	5 (8.3)	1a (3 cases)	USO	No
		1c (2 cases)	USO	Carboplatin-Paclitaxel
Mucinous cystadenocarcinoma	2 (3.3)	1a (1case)	USO	No
		1c (1 case)	USO	Carboplatin-Paclitaxel
Immature teratoma	2 (3.3)	1a (1 case)	USO	No
		1c (1 case)	USO	BEP
Mixed GCT	1 (1.7)	1c	USO	BEP
Dysgerminoma	1 (1.7)	1a (1 case)	USO	No
Granulose CT	2 (3.3)	1a (2 cases)	USO	No
3. Cervical carcinoma	1 (1.7)	1a1 (1 case)	LEEP	No
4. CIN III	2 (3.3)	0 (2 cases)	LEEP	No
Mean cycles of chemotherapy(SD)	4.15 (2.08)			

Abbreviations: USO; unilateral salpingoopherectomy, LEEP; loop electrosurgical procedure, EMACO; Etoposide, Methotrexate, Adriamycine, Cyclophosphamide, and Vincristine, BEP; Bleomycin, Etoposide and Cisplatinum.

Table 2: Pregnancy and labor courses among the studied cases.

Variable	Number (%)
Pregnancy course: (n=60)	
FTNP	51 (85%)
PIH	1 (1.7%)
Preterm pregnancy	3 (5%)
Missed abortion	4 (6.6%)
Induced abortion	1 (1.7%)
Labor course: (n=55)	
VD	16 (29.1)
CD	39 (70.9)
Findings during CD: (n=39)	
-Intraoperative adhesions	8 (20.5%)
-Congested uterus	2 (5.1%)
-Thin uterine wall	1 (2.6%)
-Caesarean hysterectomy	2 (5.1%)
Neonatal outcome: (n=55)	
Normal	53 (96.4%)
CFMF	2 (3.6%)
Recurrence after delivery:	1 (1.7%)

Abbreviations: FTNP; full term normal pregnancy, PIH; pregnancy induced hypertension, VD; vaginal delivery, CD; cesarean delivery, CFMF; congenital fetal malformation.

Table 3: Correlation of missed abortion and neonatal outcome to chemotherapy.

	Pregnancy		**P value**	**Neonate**		**P value**
	Normal	Missed abortion		Normal	CFMF	
1.Number of cycles Median (range)	4(1-10)	5(2-6)	0.17	4(1-9)	8(6-10)	0.04
2.Interval* Median (range)	13(1-40)	9(3-13)	0.049	13(1-36)	13(8-18)	0.23

-Interval*: From surgery or last cycle of chemotherapy till pregnancy.
-Small number of cases in adverse pregnancy and neonatal outcome might result in statistical inaccuracy.