

## Perinatal invasive malignant diseases: a review of twenty-five cases in South China

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### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Materials and Methods
  - 3.1. Approval
  - 3.2. Patients
  - 3.3. Patients' management
  - 3.4. Data analysis and statistical comparison
4. Results
  - 4.1. Characteristics of pregnancy patients with malignancy diseases
  - 4.2. Patient outcomes and prognostic factors
  - 4.3. Pregnancy and fetal outcomes
5. Discussion
6. Acknowledgment
7. References

### 1. ABSTRACT

Malignant neoplastic diseases (MND) are unusual complications during perinatal period and compose a dilemma for both patients and the health practitioners. Little is known about the information in Chinese suffering perinatal MND. Analyzing medical records and questionnaire, information on a series of 25 patients with a diagnosis of perinatal MND was collected from 3 medical centers between 1992 and 2004. Among all the 25 patients, 10 selected termination of the pregnancies and the other 15 continued their pregnancies until labor voluntarily, both groups obtain anti-malignancies therapies during the perinatal period. The two groups were not statistically different for the age of pregnancy, gravid and parity number, interval weeks between symptoms emergence and diagnosis of invasive malignant disease, as well as the occurrence rates of major side effects induced by malignant therapies. No statistical differences in overall survival and disease-free survival between the two groups, including the age of pregnancy, gravid and parity number, obstetric bleeding rates, neonatal distress rates, neonatal weight and puerperal morbidity rates. The patients' neonates all show no serious complications. In conclusion, pregnancy may not affect the course of MND, and termination of pregnancy may not benefit the maternal-fetal conditions, in a macroscopical point of view.

### 2. INTRODUCTION

Incidence of malignancies has been increasing dramatically during the last 30 years and neoplastic diseases are now one of the leading causes of death for women in childbearing ages both in China and most of the other parts around the world, which may partly owe to the wide spread of western life style and environmental pollution(1-4). Malignant diseases accompanied with pregnancy and/or delivery is an unusual but not rare event, with a reported occurrence of ranging from approximately 1 per 1000 to 6000 pregnancies (5-7). Insight into the diagnosis and management of perinatal neoplastic diseases has been accumulated gradually in the last decade. The former studies indicate that the most common cancerous conditions associated with pregnancy include carcinomas of the genital tract, breast, leukemia and malignant melanoma (7, 8).

Nevertheless, most previous published discussions regarding malignancies in pregnancy were limited in lacking multi-center epidemiological investigations and by a limited ability to analyze the actual maternal and neonatal outcome. Besides that, as we have known, no detailed studies about the perinatal malignancies in Chinese had been reported.

In this current study, we present 25 patients with perinatal malignancies from 3 teaching hospitals in South China over the last 13 years and analyze their characteristics and outcomes, attempting to explore possible interactive impacts between the diseases and pregnancy. We try to provide some fundamental data of pregnant women with cancer in South China and offer certain vital information for optimal health care for this subpopulation of pregnant women.

### 3. MATERIAL AND METHODS

#### 3.1. Approval

This study received approvals from the Ethics Committees of the Southern Medical University, Jinan University and Peking University, People's Republic of China, respectively.

#### 3.2. Patients

In this retrospective analysis, information was collected from 3 major tertiary medical centers in South China on patients with invasive malignancies during perinatal period diagnosed between January 1992 and December 2004. The perinatal period was defined as commencing at 20 completed gestational weeks and ending at 28 completed days after birth (9). Patients with pregnancies that occurred during and after treatment for malignancies were excluded, those whose carcinomas were diagnosed beyond that period or as in situ lesions and secondary malignancy were also excluded. Patients' medical records had been collected and questionnaires or phone call follow-up had been performed to obtain their elaborate information beyond hospitals.

Occurrence rate for invasive malignant disease (IMD) associated with perinatal period was defined as the number of cancer cases per 1000 births, in which twins or multiple births were counted as one obstetric delivery.

#### 3.3. Patients' management

All patients have been managed and followed up by oncologists from different subspecialties based on their idiosyncratic diseases, and obstetricians who majored in high-risk pregnancy complications followed them comprehensively throughout their pregnancies. These patients and their families were kept fully informed during the diagnosis and management period. Treatment strategies were planned and carried out adequately taking into consideration each family's decisions. Their gestational ages and the fetal development were ascertained through menstrual periods inquiring, physical examinations and ultrasonography by experienced obstetricians. Pathological tissue slices of all the assessed patients were obtained and reexamined and confirmed by two senior clinical pathologists. All the patients' offspring, including the fetus and infants, had been evaluated by obstetricians and pediatricians.

#### 3.4. Data analysis and statistical comparison

Categorical data were expressed as number and percentage, and numerical data as mean and standard deviation. For continuously distributed variables other than

event times, differences between groups also were tested using the Wilcoxon rank-sum test. Overall survival (OS) and disease-free survival (DFS) curves were estimated by the Kaplan-Meier method, and the symmetrical 95%CI was calculated according to the method of Greenwood. OS was defined as the time from the start of induction therapy to death or last follow-up, and DFS was defined as the time from remission after induction therapy to recurrence or death. Survival curves were compared using the log-rank test. Probability (*P*) values  $<0.05$  were considered statistically significant. The statistical analysis was performed using the Statistical Package for the Social Sciences, version 10.0 (SPSS Inc., Chicago, IL)

### 4. RESULTS

#### 4.1. Characteristics of pregnancy patients with malignancy diseases

A total of 25 cases of IMD that occurred in the perinatal period were identified among 37352 women who labored in the enrolled hospitals, for an overall occurrence rate of 0.67 cases per 1000 births. The median patient age was  $31.7 \pm 5.2$  years (range, 22–40 years). Mean follow-up was for  $8.3 \pm 4.4$  years (range, 0–11.5 years). Pretreatment and management characteristics of the 25 patients are shown in table 1. The interval between the beginning of pregnancy and the diagnosis of IMD ranged from 22 weeks to 39 weeks (median, 29 weeks). Fifteen patients had IMD diagnosed during the second trimester, and 10 patients had IMD diagnosed during the third trimester. The median interval between symptoms emergence and diagnosis of IMD was  $6.2 \pm 2.7$  weeks. The median interval between symptoms emergence and diagnosis of IMD was 8.1 weeks and 6.8 weeks for those who delivered without and with actively pregnancy-termination, respectively. All of the patients had singleton pregnancy.

#### 4.2. Patient outcomes and prognostic factors

Among the 25 cases, 10 pregnancies were terminated actively by following the patients and their families' demands, and there were no spontaneous abortions in our cases. The proportion of every malignancy has been shown in figure 1. Based on therapeutic termination of pregnancy or not, we can classified these patients into two groups: terminated pregnancy group (Patient Code 1~10 in table 1) and continuous pregnancy group (Patient Code 11~25 in table 1). As table 2 shows, the two groups were not statistically different for the age of pregnancy, gravid number, parity number, interval between symptoms emergence and diagnosis of IMD, as well as the occurrence rates of major side effects induced by malignant therapies.

No parameters, including the age of pregnancy, gravid number, parity number, interval between symptoms emergence and diagnosis of IMD, interval between therapy onset and delivery gestational age, was correlated with DFS and OS. For the continuous pregnancy group, the OS and DFS rates were 68% and 59% at 5 years, respectively (figure 2 and 3). For the terminated pregnancy group, the OS and DFS rates were 80% and 87%, respectively (figure 2 and 3). No statistical differences demonstrate in OS and

**Table 1.** Characteristics and outcomes in 25 pregnant patients with malignancies diagnosed during perinatal period

Age (yrs)	G/P	ISED (ws)	Malignant type	GAACD (ws)	ITOD (ws)	Therapy during perinatal period	Pregnancy outcome	Fetal outcome	Patient outcome
29	1/0	1.2	Ovarian mucinous cystadenocarcinoma	23	-	TAH-BSO	TA	-	Tumor-free Survival
30	3/2	1.0	Cervical squamous cell carcinoma	22	-	RH-PL	TA	-	Tumor-free Survival
28	2/1	3.9	ALL	28	-	CT	TPP	-	Survival with tumor
25	1/0	0.5	melanoma	30	-	CT	TPP	-	tumor-induced death
22	1/0	2.8	brain stem spongiocytoma	23	-	Lumpectomy	TPP	-	Tumor-free Survival
27	1/0	4.3	Rectal mucinous adenocarcinoma	24	-	Curative Resection	TPP	-	Tumor-free Survival
26	2/1	7.5	nasopharyngeal carcinoma	22	-	RT+CT	TPP	-	Tumor-free Survival
32	2/0	1.0	Cervical squamous cell carcinoma	25	-	RT	TPP	-	Tumor-free Survival
38	3/1	7.3	Breast duct carcinoma	30	-	RG-AL+ CT	TPP	-	tumor-induced death
32	2/1	6.1	nasopharyngeal carcinoma	24	-	RT	TPP	-	Tumor-free Survival
29	3/0	1.2	Ovarian immature teratoma	24	14	Oophorectomy+CT	CS	Term infant	Tumor-free Survival
26	2/1	0.5	Ovarian serous cystadenocarcinoma	37	0	Oophorectomy + CT	CS	Term infant	Tumor-free Survival
22	1/0	3.1	AML	32	1.3	CT	SVD	Term infant	Survival with tumor
35	2/1	2.2	ALL	30	2.3	CT	SVD	Premature birth	Tumor-free Survival
34	2/1	6.2	breast squamous cell carcinoma	24	14.2	Mastectomy+CT	CS	Term infant	tumor-induced death
27	2/0	3.1	Breast cystosarcoma phyllodes	24	11.1	RG-AL	CS	Premature birth	tumor-induced death
26	1/0	10.2	Gastric carcinoma	27	10.7	Curative Resection	CS	Term infant	tumor-induced death
23	1/0	9.3	spongiocytoma in vertebral canal	24	13.4	Lumpectomy	CS	Term infant	Tumor-free Survival
31	1/0	2.1	ALL	32	5.1	CT	SVD	Term infant	Tumor-free Survival
36	4/1	1.2	Ovarian granulose cell tumor	38	0	Oophorectomy+CT	CS(scar uterus)	Term infant	Tumor-free Survival
40	3/2	4.5	Cervical squamous cell carcinoma	38	0	RH-PL+CT	CS	Term infant	Tumor-free Survival
40	2/1	2.1	Non-Hodgkin lymphoma	39	0	CT	SVD	Term infant	tumor-induced death
29	1/0	6.0	nasopharyngeal carcinoma	26	12.4	RT	CS	Term infant	Tumor-free Survival
31	3/1	2.1	Sigmoid adenocarcinoma	23	14.1	CT+curative resection	CS	Term infant	Tumor-free Survival
36	2/1	2.6	nasopharyngeal carcinoma	25	11.7	RT	CS	Term infant	Tumor-free Survival

Ys: years; G/P: gravid/ parity; ws: weeks; ISED: interval between symptoms emergence and diagnosis of invasive malignant disease; GAACD: gestation age at cancerous diagnosis ;ITOD: interval between therapy onset and delivery gestational age; TAH-BSO: total abdominal hysterectomy-bilateral salpingo-oophorectomy; TA: therapeutic abortion; CS: cesarean section; CT: chemotherapy; RH-PL: radical hysterectomy and pelvic lymphadenectomy; AML: acute myeloid leukemia; SVD: spontaneous vaginal delivery; ALL: acute lymphoblastic leukemia; TPP: therapeutic termination of pregnancy; RG-AL: radical galactophorectomy and axillary lymphadenectomy, RT: radiotherapy

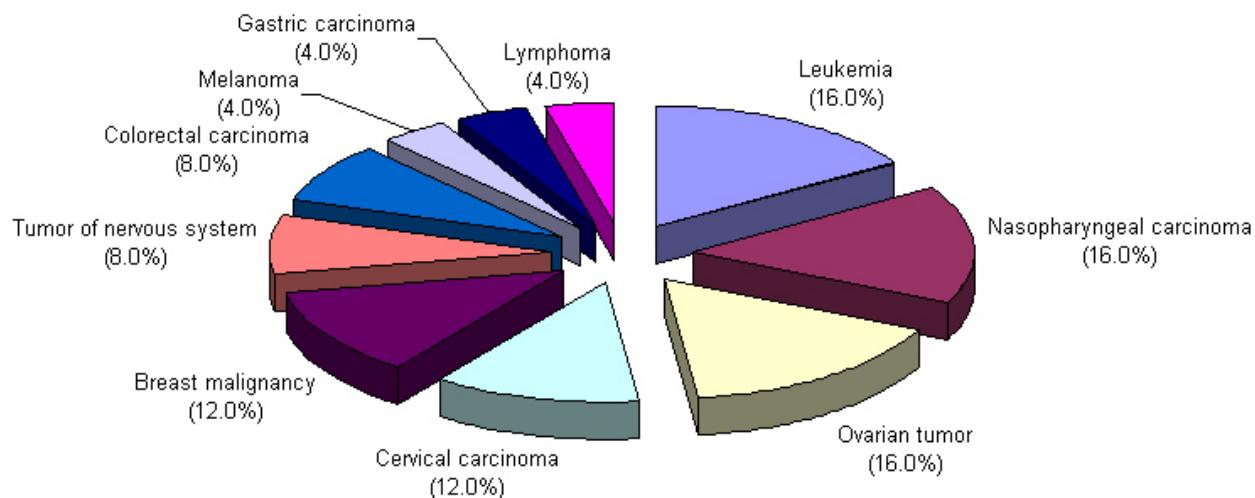
DFS between the two groups. At a median follow-up of 21.9 weeks, 6 of 25 pregnant women had died of IMD.

#### 4.3. Pregnancy and fetal outcomes

Among all the 37352 deliveries during the studied period, 18967 women had singleton pregnancy and had no obvious maternal complications. So we took them to serve as a control group to compare with the delivery group. As table 3 shows , no parameters, including the age

of pregnancy, gravid number ,parity number ,obstetric bleeding rates, neonatal distress rates, neonatal weight and puerperal morbidity rates, were statistically different between the control group and the delivery group.

Overall, 15 healthy babies survived, 13 of whom had been exposed to chemotherapeutic agents and 2 of them had been exposed to radiotherapy. Premature delivery occurred in 2 cases and none of the 15 neonates suffered



**Figure 1.** The proportion of malignancies complicated with pregnancy in 25 patients.

**Table 2.** Characteristics of terminated pregnancy group and continuous pregnancy group

	Terminated pregnancy group	Continuous pregnancy group	P value
n	10	15	
median age of pregnancy(ys)	28.5	31.2	0.374
gravid number	1.8±0.6	2.0±0.4	0.581
parity number	0.6±0.2	0.7±0.1	1.000
ISED(weeks)	3.6±1.1	3.8±1.6	0.865
rate of bone marrow inhibition (%)	40.2±8.3	33.3±9.1	0.530
rate of liver enzyme elevation(%)	30.6±10.2	33.3±9.8	0.607
rate of creatine elevation (%)	40.1±11.2	26.7±17.1	0.393

ISED: interval between symptoms emergence and diagnosis of invasive malignant disease

**Table 3.** Characteristics of continuous pregnancy group and control group

	Continuous pregnancy group	Control group	P value
n	15	18967	
median age of pregnancy(years)	31	27	0.237
gravid number	2.0±0.9	1.7±0.5	0.230
parity number	0.6±0.1	0.5±0.2	0.550
neonatal weight(g)	2868±141	3171±127	0.126
rate of neonatal distress (%)	6.7±2.1	5.2±3.9	0.603
rate of obstetric bleeding (%)	13.3±7.1	9.8±6.9	0.676
rate of puerperal morbidity (%)	6.7±2.2	6.5±3.1	0.513

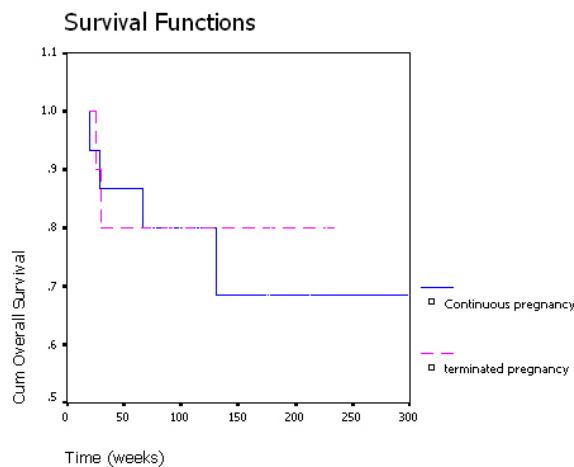
neonatal distress or other obvious complications. None of the fetuses or neonates of the 25 pregnancies, including the stillborns presented with morphologic abnormalities, and the evolution has been normal with regard to growth and development in those who have been followed.

## 5. DISCUSSION

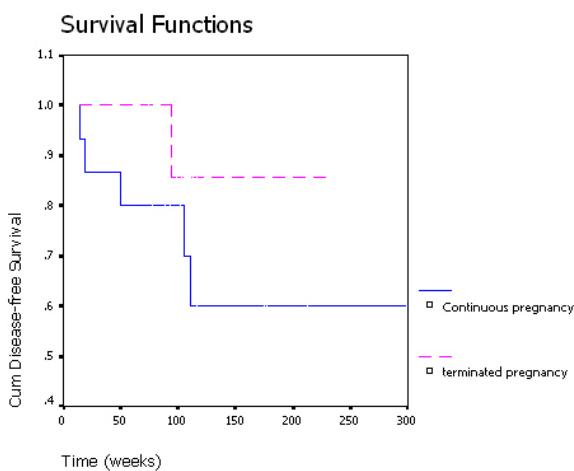
Similar to the health conditions in the western world (10, 11), in the past several decades, malignancies have gradually become a crucial public health issue in China. According to the latest report on Chinese death causes, malignant neoplasms are the third major death cause for adult Chinese women, and in the reproductive age women, the leading cause (4). With the rapid development in economics

and great changes in traditional life custom, Chinese women in reproductive age are inclined in marrying and procreating at a more mature age, especially in south China. Thus, it is reasonable to presume that malignancies may become one of the significant pregnancy complications in the foreseeable next decade. With the improvements in health information systems and medical staffs' alerts, more and more case reports on pregnancy complicated with malignancies have been published in the last twenty years (12). But until now, very few reports of well-designed, large-scale and multi-center epidemiological investigations in this field have emerged, and to our knowledge, none in China.

Some reports have suggested that most malignancies diagnoses generally are made during the



**Figure 2.** Kaplan-Meier estimate of overall survival (OS) in the 25 patients.



**Figure 3.** Kaplan-Meier estimate of disease-free survival (DFS) in the 23 valid patients.

second and third trimesters (2, 7, 11, 13), so perinatal malignancies may account for a majority of carcinomas complicated with pregnancy. Therefore more attention should be paid to detect this subpopulation of pregnant women.

In order to obtain a holistic impression in the alternating influence between neoplasms and pregnancy, we perform this study by analyzing the malignant conditions as a whole but not categorizing them.

Similar to other reports, our study indicate an occurrence rate for of 0.67 cases per 1000 births for invasive malignant diseases (5-7, 10), and the types of cancer observed in pregnancy mirror those seen in non-pregnant women of the same age (13-15). Genital malignancies account for most of our cases, nearly 30%, partly because the patients were inclined to consulting an obstetrician when they felt uneasy during the pregnancies. Our study also shows that nasopharyngeal carcinoma accounts for 16% of the cases, which is a quite impressive ratio. Nasopharyngeal carcinoma is one of the most

common carcinomas in local South China (16-18) and this result urge the local obstetricians to be alert to the early symptoms of this covert disease, such as unexplained nasal mucus bleeding, snuffle, tinnitus, headache and lymphadenopathy in the neck (19, 20). The obstetricians should consult the ENT physicians about the questionable symptoms if necessary.

The management for perinatal carcinomas is always a challenging dilemma for the physicians, the patients as well as their families, because the most appropriate and timely treatment for the mother may not be in the best interest of the fetus. The reason mainly attributes to their concerns for the fetuses. The following are some of the concerns: whether to start the anti-malignant therapies immediately once the diagnosis confirmed; whether delaying those therapies until the labor; whether the delay would impair the patient's prognosis and whether the therapies would injure the fetus and in a long run. There are still many vague issues in the interaction between the malignant diseases and the pregnant state. Whereas the other authors believe that pregnancy may accelerate the course of some kind of malignancies such as leukemia (21), most authors do not find any support for this hypothesis (12, 22, 23). A few reports say delays or modifications in therapy to ensure the birth of a healthy infant may affect the maternal prognosis adversely (24, 25). Our results do not reveal any positive impact on the whole malignant outcomes by terminating the pregnancy. Besides the possible biases originated from sample size, race, therapy and malignancies proportion, most carcinomas involved in this study are not sex hormone-dependent and their natural courses are far more beyond the normal pregnant period, so perinatal malignancies may not be affected by the gestation.

The only cancers that have been reported to affect the fetus are melanoma, hematopoietic malignancies and lung cancer, although those cases were extraordinary rare (25-30). In our study, no transplacental metastatic carcinomas had been found among the fetus and the followed-up infants.

It's generally believed surgery undergone after the first trimester has little influence to the fetus (12, 25), therefore perinatal surgery may be the most suitable procedure for those who need operations to heal carcinomas. During the last decade, great improvements have taken place in chemotherapy for carcinomas; more effective but less toxic schemes have appeared. Many papers have reported perinatal cases experiencing chemotherapy management obtained successful maternal-fetal outcome (31-33), including ovarian carcinoma (34-36), breast cancer (37-41), acute leukemia (12, 42) and lymphoma (42, 43). Compared with the mentioned two methods ahead, radiotherapy may be used much more limitedly during perinatal carcinomas. Most authors believe that radiotherapy during the pregnant period would seriously injure the fetal growth and development(12), but Kal and Struikmans recently point out that the injure lies on radiation dose, tissue sensitivity and gestational age, so it can be reduced by keeping the irradiation position away

from the fetus and rigorous radioprotection (44). The current study indicates that the anti-malignant therapies, including operations, chemotherapies and radiotherapies, seem do no obvious harm to the labor, the fetus or the neonates. This satisfying sequel may also be associated with the sample size, race, malignancies types and stages and gestation age when the therapies were put into practice. Our results suggest that careful therapy selection and close monitoring on the fetuses benefit both the malignant and pregnant outcomes. Moreover further active follow-up for the infants should be provided to understand their physical and mental development.

Obviously, Pregnant women complicated with carcinomas belong to the population of high risk pregnancies, but the sufferers should not be deprived of reproductive rights. Considering the humanity and ethics, it is almost impossible to carry out randomized, double-blinded and prospective studies among the perinatal malignant patients. So the best and evidence-based methods to manage these patients, as well as the long term impact brought by these methods on reproductive capability are still unknown. But by accumulating multi-center data and adequate experiments in animal models may benefit our decision to deal with these patients. As medical staffs, favorable and sufficient communications with the patients and their families as well as the excellent cooperation between oncologists and obstetricians are critical for satisfying patients' outcome.

## 6. ACKNOWLEDGMENT

This work was supported by project grant from Joint Brainstorming Foundation of Guangdong Provincial Significant Community Issue, Guangdong Provincial People's Government (2KB04701S).

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**Key Words:** Perinatology, Pregnancy Complications, Neoplasms, Retrospective Studies

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