# Clinical effect of mifepristone on patients with ovarian cancer in pregnancy

**Lili Shang[1], Yanjing Wang[2] and Yongli Lyu[3]***

[1]Dalian Maternal and Child Health Care Hospital, Dalian, China
[2]Yaoqiang Community Health Service Center, Ji'nan hi tech Zone, Jinan, China
[3]Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

**Abstract**: At present, the main methods of clinical treatment of ovarian cancer are cytoreductive surgery and multidrug combination chemotherapy, in which multidrug combination chemotherapy is based on platinum drugs. Mifepristone can be used as an adjuvant drug for the treatment of drug-resistant and refractory ovarian cancer because of its convenient oral administration, long half-life, low cytotoxicity to normal cells, anti-tumor activity and chemosensitizing effect. This article analyzed the clinical effect of mifepristone combined with bevacizumab in the treatment of patients with ovarian cancer. Sixty patients were randomly divided into experimental group and control group. Mifepristone combined with bevacizumab was used in experimental group and conventional anticancer drugs were used in control group. The results showed that the amount of bleeding during labor (6.38±1.85 mL), the rate of birth injury (0%) and the amount of bleeding 2 hours after delivery (63.12±19.86 mL) in the experimental group were significantly better than those in the control group ($P<0.05$), and the incidence of side effects and complications were significantly lower than those in the control group ($P<0.05$). In conclusion, mifepristone combined with bevacizumab in the treatment of high-risk pregnancy complicated with ovarian cancer can significantly reduce the patient's labor process and the amount of bleeding at different stages after surgery, the incidence of side effects and complications after surgery is significantly reduced, which is conducive to the recovery of the patient's body.

**Keywords**: Mifepristone, high risk pregnancy, ovarian cancer, bevacizumab, postpartum hemorrhage.

## INTRODUCTION

High-risk pregnancies often need abortion treatment, because the pregnant women themselves are in critical condition, resulting in extremely difficult surgery (Block *et al.*, 2017). Preoperative application of mifepristone can reduce cervical hyperexpansion, reduce the incidence of induced abortion syndrome, alleviate patients' pain, and improve patients' treatment compliance and satisfaction (Chao *et al.*, 2016). Pregnancy with ovarian cancer is a common gynecological malignancy. The incidence of pregnancy with ovarian cancer is increasing year by year. The incidence of pregnancy with ovarian cancer is the third highest among female malignant tumors, and the mortality is the first highest (Chen *et al.*, 2015). At present, the main methods of clinical treatment of pregnancy complicated with ovarian cancer are cytoreductive surgery and multidrug combination chemotherapy (Emir *et al.*, 2014). Multidrug combined chemotherapy, which is based on platinum drugs, can control the development of disease to a certain extent, but more than 80% of patients will acquire drug resistance in the course of clinical chemotherapy, which seriously affects the effect of chemotherapy and reduces the 5-year survival rate of patients (Fein *et al.*, 2015). Studies have shown that mifepristone reverses drug resistance in lung cancer, thymic adenocarcinoma and breast cancer-related cell lines (Espinel *et al.*, 2015).

At the same time, mifepristone has a certain selective inhibitory effect on cisplatin and paclitaxel-resistant gastric cancer, pregnancy with ovarian cancer, and can reverse drug resistance, so mifepristone can play an auxiliary role in the treatment of pregnancy with ovarian cancer (Gatter *et al.*, 2015). Studies have shown that progesterone and chorionic gonadotropin can achieve fetal protection by up-regulating the level of human leukocyte antigen G (HLA-G) (Golier *et al.*, 2018). Therefore, it can be inferred that the mechanism of mifepristone and other clinical induced abortion drugs may be related to the reduction of HLA-G level, so it can be inferred that this induced abortion drug can provide a new choice for clinical immunity and biological treatment of malignant tumors (Grossman *et al.*, 2015). Studies have found that endogenous and exogenous estrogen and progesterone antagonists can reduce the risk of pregnancy with ovarian cancer (Heer *et al.*, 2015). Mifepristone can inhibit the proliferation and induce apoptosis of ovarian cancer cells in pregnancy and its related mechanism is related to the change of progesterone receptor. It suggests that mifepristone can reverse cisplatin resistance and can be used as a chemosensitizer in clinic (Hjelm *et al.*, 2016).

**Corresponding author:* e-mail: 371220983@qq.com

The high-risk pregnant women in this study are all accompanied by ovarian cancer, which is a common clinical malignant tumor. The early symptoms are not obvious (Block *et al.,* 2017). When the body function is greatly affected, the cancer has developed to the late stage and the mortality rate is high. In this study, mifepristone combined with bevacizumab, a targeted drug, was used to treat high-risk pregnant women with ovarian cancer and satisfactory results were obtained.

## MATERIALS AND METHODS

### *General information*

60 cases of high-risk pregnancy complicated with ovarian cancer treated in our hospital from January 2015 to November 2017 were selected as the study subjects. They were randomly divided into two groups, the experimental group (n=30) and the control group (n=30). The experimental group was 31-37 years old with an average age of 33.6 years. The control group was 30-38 years old with an average age of 34.8 years. They were divided into experimental group and control group by random number table, 30 cases in each group. The age of the experimental group ranged from 27 to 75 years, with an average age of (53± 14.75) years. Pathological types included mucinous adenocarcinoma in 7 cases, serous adenocarcinoma in 13 cases, endometrioid adenocarcinoma in 4 cases, clear cell carcinoma in 3 cases, and other types in 3 cases. The clinical stages were 9 cases of stage II, 16 cases of stage III and 5 cases of stage IV. The patients in the control group were aged 25-75 years, with an average age of (51±13.62) years. Pathological types were mucinous adenocarcinoma in 8 cases, serous adenocarcinoma in 14 cases, endometrioid adenocarcinoma in 2 cases, clear cell carcinoma in 4 cases, and other types in 2 cases. The clinical stages were stage II in 8 cases, stage III in 17 cases and stage IV in 5 cases. There was no significant difference in age, pathological type and clinical stage between the two groups (P>0.05). All patients were approved by ethics committee of Dalian Maternal and Child Health Care Hospital, ethical approval number as 2014DMCHC-4 and all patients signed on the informed consent.

### *Inclusion criteria*

Preoperative blood biochemical and pathological examinations confirmed high-risk pregnancy with ovarian cancer, without surgical contraindications; no history of allergy to therapeutic drugs; patient survival is expected to be > 3 months. The condition is controllable, the body condition accords with the requirement of chemotherapy, and no other medicine is received within 4 weeks.

### *Exclusion criteria*

Pathological diagnosis has no definite results, and can not determine the treatment method; Preoperative routine chemotherapy has not been accepted, drug allergy to treatment. There was no significant difference in general information between the two groups (P>0.05). All patients were informed and agreed to cooperate with the treatment.

### *Method*

The control group was treated by intraamniotic injection of ethacridine combined with conventional anticancer drugs and terminated pregnancy. Paclitaxel, docetaxel, gemcitabine and doxorubicin were the most frequently used conventional chemotherapeutic drugs. The dosage regimen and dosage of ethacridine intraamniotic injection strictly follow the drug instructions and physician's prescriptions. At the beginning of the operation, 5 mg ethylstilbestrol was injected intramuscularly, and appropriate dosage of misoprostol was added according to the frequency of uterine contraction. The maximum dosage of misoprostol should not exceed 1.5 mg per day. Then 90 mg ethacridine was injected into the amniotic cavity of the patient, and 5 mg paclitaxel was given for adjuvant treatment. The duration of labor and the amount of bleeding and side effects and complications were recorded. The experimental group was treated with mifepristone combined with bevacizumab and terminated pregnancy. Mifepristone 120 mg was orally administered at 9 am and 8 pm one day before the operation. No food was allowed within 2 hours before and after taking the medicine. On the basis of the control group, bevacizumab (specifications: 100mg) 7.5mg·kg$^{-1}$ was added to 300 mL 0.9% sodium chloride injection intravenously. Some patients could undergo induced abortion after intravenous injection of 10 mg dexamethasone. During the operation, the patient's physical signs were closely observed, and the amount of bleeding, side effects and complications were recorded at different stages of labor and postoperation.

### *Observation index*

The amount of vaginal bleeding in 2h after delivery of fetal >80mL is severe postpartum hemorrhage. The vagina of pregnant women will be injured in different degrees during childbirth. The rate of birth injury is the probability of vagina and cervical orifice injury after induced labor. The best index of operation effect is the success rate of one-time induced labor, that is, the one-time successful operation of induced labor. Patients were followed up after operation or discharge to investigate the relationship between bleeding volume and menstrual volume, and the occurrence of complications or side effects after operation. The adverse reactions after operation were evaluated with reference to NCI version 3.0.

The levels of CAl25, CAl53, CAl99 and HE4 were compared between the two groups before and after treatment and the objective efficacy, quality of life and adverse reactions were observed. (1) Tumor markers: The patients were treated with fasting 3 ml venous blood in

the morning before and after treatment. The supernatant was centrifuged for 10 minutes (3 000 r/min, centrifugal radius: 3 cm) after 2 hours at room temperature. The serum levels of CAl25, cAl53, CAl99 and HE4 were detected by AccEE2 chemiluminescent immunoassay system. Normal range: CAl25<35 Ku/L, CAl53<28 Ku/L, CAl99<27 Ku/L, HE4<82.9 pmoL/L. (2) Objective curative effect: According to the short-term objective curative effect criteria of solid tumors formulated by WHO, it can be divided into complete remission, partial remission, stability and progress; total remission rate (%)= (total remission + partial remission) / total remission (%). (3) Quality of life: KPs score was used to assess the quality of life of patients before and after treatment.

## STATISTICAL ANALYSIS

SPSS18.0 software was used for data analysis. Measurement data were expressed by mean±deviation (x±s). P<0.05 had significant difference. Independent t-test was used for inter-group and intra-group comparisons, and X2 test was used for inter-group comparisons of counting data.

## RESULTS

***Comparison of injury in labor stage***

The amount of bleeding during labor, the rate of birth injury, the success rate of one-time induced labor and the amount of bleeding 2 hours after delivery in the experimental group were significantly better than those in the control group (P<0.05) (as shown in table 1).

***The amount of bleeding and menstrual volume in different periods after operation***

The amount of bleeding in the experimental group at 2, 4 and 6 weeks after operation was significantly less than that in the control group (P<0.05), as shown in table 2.

***Postoperative adverse reactions***

The incidence of side effects (nausea, vomiting, abdominal pain, diarrhea, etc.) and complications (arrhythmia, proteinuria) in the experimental group was significantly lower than that in the control group (P<0.05) as shown in table 3.

***Quality of life before and after treatment***

After treatment, the KPS scores of the two groups were significantly higher than those before treatment, and the experimental group was significantly higher than that of the control group, the difference was statistically significant (P<0.05) as shown in table 4.

## DISCUSSION

Mifepristone has the effect of promoting cervical ripening, which has been proved to be effective in terminating pregnancy and has been widely used in clinic (Isorni *et al.,* 2015). Mifepristone has a high affinity with progesterone, more than four times that of progesterone. It also has a competitive antagonistic effect on progesterone, which can reduce its activity and has a significant effect in the process of labor induction (Kawamoto *et al.,* 2016). In this study, the control group used ethylstilbestrol combined with ethacridine to induce labor, but also to promote uterine maturation and shorten the labor process. However, ethacridine has bactericidal effect (Landis *et al.,* 2015). When induced uterine contraction, pregnant women do not have autonomy and need the assistance of clinicians. Cervical contraction and other induced labor reactions can not be coordinated and orderly (Mannen *et al.,* 2010). It is easy to form compulsory uterine contraction, which causes greater damage to pregnant women's obstetric tract. The persistent high-intensity uterine contraction is not consistent with the maturity of the uterus (Norman *et al.,* 2018). It is easy to damage the uterus, resulting in increased bleeding during induced labor, prolonged operation time and increased body load of pregnant women (Perl *et al.,* 2015). The results of this study showed that the amount of bleeding during labor and related indicators such as the rate of birth injury and the success rate of induced labor in the experimental group were significantly better than those in the control group (P<0.05). The results showed that mifepristone had a more significant effect and success rate than the traditional ethacridine injection therapy, shortened the operation time, alleviated the obstetric tract injury of patients, especially in the course of labor and the amount of postpartum hemorrhage significantly reduced, and the operation was more simple and feasible, with higher safety and patient compliance (Presbitero *et al.,* 2003).

For high-risk pregnancy patients with ovarian cancer, ovarian cancer has undoubtedly become an important factor threatening their life safety (Schreiber *et al.,* 2018). The progression of ovarian cancer is closely related to angiogenesis (Sanomura *et al.,* 2014). The continuous growth and spread of ovarian cancer requires the continuous generation of new blood vessels to obtain adequate nutrition. Since the diameter of solid tumors exceeded 2 mm, blood vessels began to grow continuously (Trzeciak *et al.,* 2016). At the same time, neovascularization had loose basement membrane and promoted the metastasis of tumor cells because of its rapid synthesis and limited nutritional sources (Block *et al.,* 2017). When the diameter of solid tumors is larger than 2mm, the tumor tissue is hypoxic and vascular endothelial cells are stimulated by hypoxia to further form new blood vessels and accelerate the vicious cycle. Relevant data showed that the expression of vascular endothelial growth factor (VEGF) in ovarian cancer patients was higher than that in normal cells or benign tumors. The regulation of VEGF expression has become the focus of research on inhibiting the proliferation of ovarian cancer.

**Table 1**: Comparison of injury in labor between two groups of patients

| Groups | n | Bleeding volume in labor process (mL) | The rate of birth injury (%) | Bleeding volume of 2h after surgery (mL) | One-time success rate of induced labor (%) |
|---|---|---|---|---|---|
| Control group | 30 | 22.5±8.63 | 12.1 | 93.14±24.18 | 79.4 |
| Experimental group | 30 | 6.38±1.85 | 0 | 63.12±19.86 | 100 |
| t | | 19.294 | 17.391 | 24.115 | 21.435 |
| p | | <0.05 | <0.05 | <0.05 | <0.05 |

**Table 2**: Bleeding volume and menstrual volume in different periods

| Groups | n | More than menstrual volume | Less than menstrual volume | Similar to the menstrual volume | Normal bleeding rate |
|---|---|---|---|---|---|
| Control group | 30 | 15 (50.0) | 6 (20.0) | 9 (30.0) | 50.0% |
| Experimental group | 30 | 6 (20.0) | 15 (50.0) | 9 (30.0) | 80.0% |
| $\chi 2$ | | 5.384 | 5.284 | 2.985 | 7.834 |
| P | | <0.05 | >0.05 | <0.05 | <0.05 |

**Table 3**: Postoperative adverse reactions

| Groups | n | Nausea and vomiting | Abdominal pain and diarrhea | Arrhythmia | Proteinuria | Leukocyte reduction | Thrombocytopenia |
|---|---|---|---|---|---|---|---|
| Control group | 30 | 8 (26.6) | 5 (16.7) | 2 (6.7) | 5 (16.7) | 5(16.7) | 4 (13.3) |
| Experimental group | 30 | 4 (13.3) | 2 (6.7) | 0 (0) | 0 (0) | 4 (13.3) | 2 (6.6) |
| $\chi 2$ | | 6.364 | 5.331 | 4.173 | 7.915 | 5.134 | 6.124 |
| P | | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 |

**Table 4**: Comparison of tumor marker level and quality of life KPS score before and after treatment

| Group | Treatment stage | Cancer antigen 125 (kU/L) | Cancer antigen 153 (kU/L) | Cancer antigen 199 (kU/L) | Human epididymis protein 4 (pmol/L) | KPS score |
|---|---|---|---|---|---|---|
| Control group | Before treatment | 48±10 | 46±8 | 68±14 | 236±19 | 70±5 |
| | After treatment | 26±6 | 31±5 | 35±8 | 73±10 | 80±7 |
| Experience group | Before treatment | 48±9 | 46±7 | 67±13 | 237±18 | 70±6 |
| | After treatment | 20±5 | 24±5 | 24±6 | 36±7 | 87±8 |

Bevacizumab can directly reach the target and specifically bind to vascular endothelial growth factor, inhibit angiogenesis, and then prevent the continuous growth and proliferation of cancer cells (Vagnarelli *et al.,* 2015). Because of its good targeting and specificity, it has gradually developed into an effective method to kill cancer cells, and has played a significant advantage in the treatment of breast cancer, rectal cancer and other malignant tumors (Perl *et al.,* 2015). It has been allowed to be used in the treatment and control of these tumors in the United States, and has been widely used. This study found that the antineoplastic efficacy of bevacizumab was significantly higher than that of traditional antineoplastic drugs. The amount of bleeding in the experimental group was significantly less than that in the control group ($P<0.05$), and the incidence of adverse drug reactions and complications was significantly lower than that in the control group ($P<0.05$). Severe complications such as severe hemorrhage, arrhythmia and proteinuria in the experimental group were mild and fewer. The side effects disappeared when most patients stopped treatment and the safety was higher.

Mifepristone, as a glucocorticoid and progesterone receptor antagonist, is mainly used for induced labor, termination of early pregnancy and emergency contraception (Trzeciak *et al.,* 2016). Mifepristone can inhibit estrogen phosphorylation of Rb protein and increase the levels of cyclin-dependent kinase inhibitors p2cipl and p27kipl, thus inhibiting the activity of cyclin-dependent kinase. Relevant researches found that mifepristone inhibited the proliferation of ovarian cancer epithelial cells in a dose-dependent manner (Norman *et al.,* 2018). When the concentration of mifepristone exceeded 10 mg/L, the inhibition increased rapidly and basically inhibited the proliferation of all cancer cells. Mifepristone can regulate the level of fibroblast growth factor by inhibiting vascular endothelial growth factor to induce transformation, reduce the expression of macrophage colony-stimulating factor receptor and achieve anti-tumor effect. Therefore, mifepristone has a good anti-tumor activity (Landis *et al.,* 2015). Combined with paclitaxel and cisplatin, mifepristone can reverse the drug resistance and prevent the recurrence of ovarian cancer on the basis of its anti-cancer effect. In this study, TP chemotherapy combined with mifepristone was used to treat patients with recurrent ovarian cancer (Isorni *et al.,* 2015). The results showed that after treatment, the expression of tumor markers in the serum of the experimental group was lower than that of the control

group, and the quality of life score and objective efficacy were higher than those of the control group (P<0.05). The anti-cancer effect of high relapsing ovarian cancer patients can reduce the expression of tumor markers. There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05), indicating that mifepristone is safe. However, there are some shortcomings in this study, such as a small sample size, short observation time, no observation of the long-term efficacy and safety of patients and further research will be carried out in the future.

## CONCLUSION

Reasonable chemotherapeutic regimens can maximize the role of various drugs, but they still fail due to the emergence of drug resistance. Therefore, to study the mechanism of drug resistance in tumors, and to prevent drug resistance, resist drug resistance and try to reverse drug resistance has become a hot and difficult point in the treatment of pregnancy complicated with ovarian cancer. It has become one of the important goals to improve the therapeutic effect of pregnancy complicated with ovarian cancer and the survival of pregnancy complicated with ovarian cancer. Mifepristone can inhibit the growth of ovarian cancer cells in pregnancy and reverse the resistance of ovarian cancer cell lines in pregnancy. It is expected that mifepristone can play a dual role in the treatment of ovarian cancer in pregnancy. In conclusion, mifepristone combined with bevacizumab in the treatment of high-risk pregnancy complicated with ovarian cancer can significantly reduce the patient's labor process and the amount of bleeding at different stages after surgery, the incidence of side effects and complications after surgery are significantly reduced, which is conducive to the recovery of the patient's body.

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