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The Association of Gestational Trophoblastic Neoplasia and Misoprostol Administered Before Suction Curettage of Molar Pregnancy

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ABSTRACT

Background & Objective: Gestational trophoblastic neoplasia contains a group of abnormal trophoblastic tumors including hydatidiform moles (partial and complete) and non-molar trophoblastic neoplasms (invasive mole, choriocarcinoma, placental site trophoblastic tumor). The incidence is 1-2 per 1000 deliveries both in the United States and Europe. The aim of this study was to prove the noninferiuority and safety of misoprostol use in cervical ripening in patient with molar pregnancy.

Materials & Methods: This retrospective cohort study was performed on 150 women with molar pregnancy referred to Firuzgar and Mirza-koochack-khan hospitals in Tehran, between 2006 and 2013. We defined group 1 as 100 patients without Misoprostol pretreatment and group 2 as 50 patients with Misoprostol pretreatment. There was no significant difference in the number of complete or partial mole between the two groups. They were followed by serum ß-hCG level and if it became plateaued in 4 measurements or rose more than 10% in 3 measurements in a period of three weeks, would be defined as persistent.

Results: We found no significant difference of maternal age, fundal height, gestational age, gravity, parity, number of previous abortions and prevalence of complete and partial moles between the two groups. A total of 27 (27%) patients in non-Misoprostol group and 5 (10%) patients in Misoprostol group developed Persistent GTN (P<0.05). We observed no case of trophoblastic embolism in the misoprostol group.

Conclusion: Misoprostol cervical ripening resulted in lower Persistent GTN incidence. Also, trophoblastic embolism following misoprostol administration is so rare that we observed no case.

Keywords: Cervical ripening, Molar pregnancy, Misoprostol, Persistent GTN

Introduction

Gestational trophoblastic disease (GTD) contains a group of tumors characterized with abnormal trophoblastic proliferation. It is histologically divided into Complete and Partial Hydatidiform moles (characterized by villi presence) and Non-molar trophoblastic neoplasms (which lack villi) **(1)**. There are some causes that have been reported about etiology of trophoblastic disease for instance, previous consumption of oral contraceptive pill, mal nutrition, genetics and abnormal uterine bleeding.

Hydatidiform moles are excessively edematous immature placentas, including complete and partial moles **(2)**. The other terms for malignant forms of GTD are Gestational Trophoblastic Neoplasia (GTN) or Persistent Gestational Trophoblastic Disease. These include invasive mole, choriocarcinoma, placental site trophoblastic tumor **(1)**. The incidence of molar pregnancy in the United States and Europe has been relatively constant at 1 to 2 per 1000 deliveries **(6-8)**. It is more prevalent among Asians, Hispanics and American Indians **(6,9,10)**. The risk is twofold in adolescents and 36-40 years of age; however, it becomes tenfold in those older than 40 years **(11,12)**. In Iran molar pregnancy incidence is reported 5.4 per 1000 pregnancies in Ahwaz **(18)**, 11 per 159 first trimester abortions in Tehran **(19)**, 2.02 per 1000 pregnancies in Sanandaj **(20)** and 3.34 per 1000 pregnancies in Hamadan **(21)**.

Diagnosis and treatment of GTD is based on measurement of serum β-hCG combined with clinical findings **(1)**. Trophoblasts produce human chorionic gonadotropin (hCG), thus measurement of this peptide hormone in serum is necessary for GTD diagnosis, management and surveillance **(1,16)**, especially because none of the cases with partial or complete mole whose serum β-hCG level became undetectable

developed neoplasia subsequently **(4,5)**. If a 10% rise in three measurements or plateau level of ß-hCG for 4 measurements during a period of 3 weeks or a detectable ß-hCG after 6 months or any pathologies of choriocarcinoma, are noticed during the course of follow-up, the case is defined as Persistent Trophoblastic Neoplasia (GTN) **(1)**. The incidence of GTN following molar pregnancy in Iran is reported 20% in Yazd. Almost the same is reported in the United States.

Suction curettage is frequently the treatment of choice in cases of molar pregnancy, regardless of their uterine size. Whenever the cervix is not adequately dilated to insert a 10-14 mm suction curette, a cervical dilator which is usually an osmotic one, is used preoperatively. Whereas Misoprostol (PGE_1) (Cytotec) is usually recommended as a uterotonic agent to prevent or cease postevacuational vaginal bleeding **(1,3)**.

For minimizing trauma from mechanical dilation, there are some other methods which soften and slowly dilate the cervix **(13)**. Based on a Chochran review, both hygroscopic dilators and cervical ripening medications (such as Misoprostol) had the same efficacy in shortening the length of first-trimester procedures **(14)**. The most frequently used medication for this purpose is Misoprostol, administered orally and/or vaginally. The advantages in comparison with osmotic dilators are ease of use, lower cost and a lower composite complication rate **(15)**.

Considering the issues mentioned above, some questions arise. The first, whether following misoprostol administration, any changes in the incidence of invasive mole occurs. The second following Misoprostol-induced uterine contractions, how much would the incidence of molar embolism be.

Materials and Methods

This retrospective cohort study was performed on 150 women with molar pregnancy referred to Firuzgar and Mirza-koochack-khan hospitals in Tehran, Iran between 2006 and 2013. We defined group 1 as 100 patients without Misoprostol pretreatment and group 2 as 50 patients with Misoprostol pretreatment. There was no significant difference in the number of complete or partial mole between the two groups. They were followed by serum ß-hCG level and if it became plateaued in 4 measurements or rose more than 10% in 3 measurements in a period of three weeks, it would be defined as persistent. The patients were divided into two groups; one group received misoprostol whereas another group was ripped by dilator before curettage of molar product. Gravity, age of pregnancy, level of Bhcg and volume of hemorrhage were considered. Data was collected and entered to SPSS 22 (SPSS Inc., Chicago, Illinois, USA). Statistical analysis was done and P-value below 0/05 was considered as meaningful. In our study we obtained signed consent form from each patient and our study has been approved by ethical committee in our research center.

Results

A total of 150 patients were evaluated in two groups to investigate the effect of Misoprostol on GTN incidence or trophoblastic embolism in this study. Group1 defined as patients without Misoprostol administration before their suction curettage and group2 as those with Misoprostol administration before their suction curettage. The study was based on the data recorded from their files during the course of treatment and follow-up. The sample was selected from the patients referred to the two most referral centers for this disease in Tehran, Iran from 2006 till 2013. Group1 consisted of 100 patients, 17 to 42 years of age (mean: 27.3±6.1) and group2 included 50 patients between 15 to 48 years (mean: 28.7±6.3). We detected no significant statistical difference between the mean age of the two groups (P>0.05) (Figure 1).

From the obstetrical-history point of view, both groups were matched.

Mean gestational age at diagnosis was 11±2.8 weeks in group1 and 11.6±2.9 weeks in group 2, with no significant difference between the two (P>0.05) (Figure 2).

Mean uterine size before suction curettage was 13.3±3.4 mm in group 1 and 13±2.3 mm in group 2, with no significant difference between the groups (P>0.05) (Figure 3).

Molar pathology report in group 1 contained 62 (62%) complete moles and 38 (38%) partial moles out of 100 patients. In group 2, 31 per 50 (62%) were reported as complete moles and 19 per 50 (38%) partial moles. There was no significant difference between the two groups (P>0.05) (Figure 4).

Mean ß-hCG titer before and after curettage in both groups and the mean time charted when it became serologically undetectable. The mean titer decrease was more in misoprostol group (group 2) with significant difference (P=0.002). However, there seemed to be no significant difference for the time consumed for undetectable ß-hCG.

We detected Persistent GTN in 27% (27 per 100 patients) in non-Misoprostol-administered group whereas in Misoprostol-administered group it was 10% (5 per 50 patients); which demonstrated a significant difference among the two groups (P=0.017).

Theca-lutein cysts were detected in 11% (11 out of 100 patients) in group 1 before the intervention, this was 10%

(5 out of 50 patients) in group 2, without any significant difference between the two groups (*P*>0.05).

Indicated cases for chemotherapy in group 1 were 1 course in 2 patients (2%), 2 courses in 6 patients (6%), 3 courses in 4 patients (4%), 4 courses in 2 patients (2%), 5 courses and more in 3 patients (3%). In group 2, there were 1 course in 2 patients (4%), 2 courses in 2 patients (4%) and more than 5 courses in 1 patient (2%); there seemed to be no statistical difference among the two groups in this point (*P*=0.152)

We encountered no cases of trophoblastic embolism in this research (with or without Misoprostol pretreatment).

There was a record of 12% (6 patients per 50) of gastrointestinal complications of Misoprostol, all of which were treated conservatively and were tolerable by the patient.

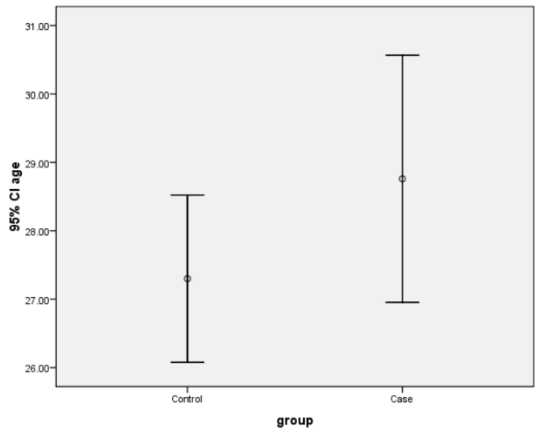

Figure 1. Transfusion between two groups

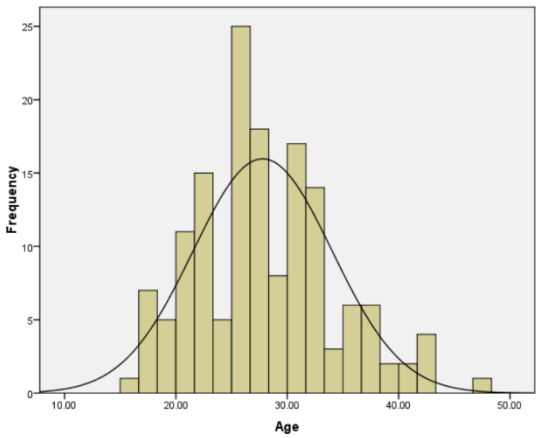

Figure 2. Major complications between two groups

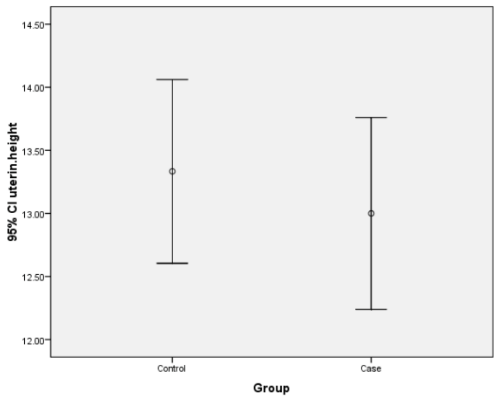

Figure 3. Theca-lutein cysts between two groups

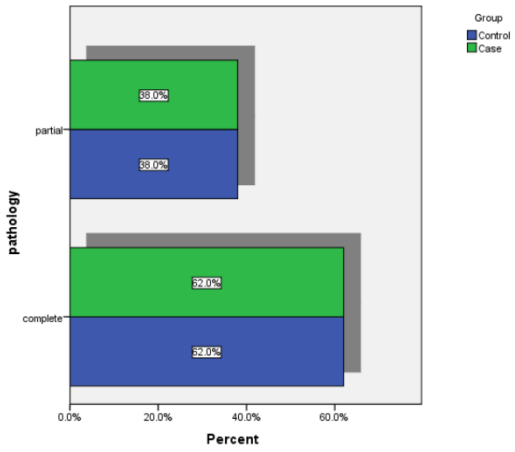

Figure 4. Gastrointestinal complications between two groups

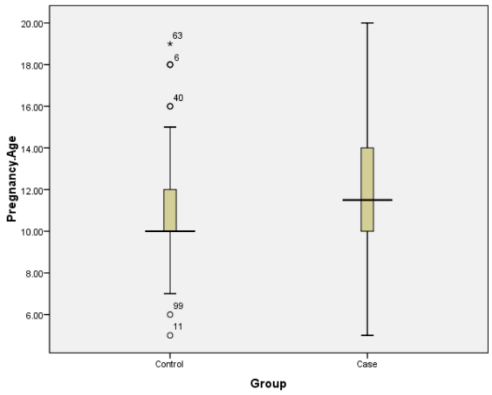

Figure 5. Need to chemotherapy between two groups

Discussion

Based on previous research in our country, the incidence of hydatiform are increasing. There are two steps in treatment of gestational trophoblastic diseas. In the first step, suction and curettage is mandatory and in the second step we weekly check Bhcg level. If during the weekly checkings, Bhcg is reduced gradually, it would be optimal and if there is a Plateau or increase in Bhcg, it is necessary to find out any evidences of persistent trophoblastic disease in universal physical examination and imaging study **(12)**. Brain MRI (magnetite resolution imaging), chest CT (computerized tomography), and pelvic ultrasonography are the main portions of metastatic evaluation in this step. If we find a specific site for metastasis, scoring based on patient's characteristic such as age, gravida, blood group, the distance between previous pregnancy and tumor characteristic such as site, number, and finally with or without previous chemotherapy will be performed **(13)**.

For suction and curettage due to the huge amount of pregnancy product in molar pregnancy, adequate cervical dilation is crucial. There are some methods for dilation for example hydropic devises, hegar devises and misoprostol **(14,15)**. There are concerns about trophoblastic emboli and uncontrolled vaginal bleeding during the use of misoprostol in ripening of cervix. In this study we investigated the differences between the two groups of patients with or without misoprostol to find the percentage of uncontrolled vaginal bleeding, trophoblastic emboli, as well as incidence of persistent trophoblastic disease. Demographic information and parity in our study was the same as another study and most patients were between 25 and 35 years old **(16)**. In our study it is proved that incidence of molar pregnancy increases before 20 and after 35 years of age. In our study there was no difference between the two groups in age, gestational age and parity. Fundal height and proportion of partial and complete mole were similar in two groups. Absence of significant differences between two groups in term of demographic and clinical characteristics, is one of the high-quality issue of our study and made the least bias in the trial. Persistent trophoblastic disease was the main end point of our research; the rate of persistent trophoblastic disease was less than the other group 5% versus 27%. In terms of complications of using misoprostol such as uncontrolled vaginal bleeding, trophoblastic emboli and incomplete evacuation of pregnancy product all of which have been reported in previous studies **(17,18)**. We observed only on patient with uncontrolled vaginal bleeding who survived after transfusion. Also, we did not face an incomplete evacuation.

Misoprostol is considered as a drug for ripening of the cervix when dilation is necessary for example in hysteroscopic methods, abortion and vaginal delivery **(19-21)**. But use of misoprostol in evacuation of pregnancy product in molar pregnancy is not clarified in gynecologic and obstetric guidelines. It seems that it is because of some concerning in this issue. Here we conducted a trial and examined and determined the complications and rate of persistent disease in patients with partial and complete molar pregnancy and founded out that there are significant differences between two groups in persistent trophoblastic disease and use of misoprostol was correlated with lower rate of persistent disease **(22,23)**. And another end point of our study was the complications of use of misoprostol we addressed to the potential complications and eventually found that there is no major and life-threatening complication of misopristol. Therefore, we strongly recommended misoprostol in ripening of cervix before suction and curettage of molar pregnancy. According to the lack of researches in this field, more studies should be done.

Conclusion

To sum up, this study proved that there is no major complication in use of misoprostol for cervical ripening in patients with molar pregnancy and therefore we recommend misoprostol before evacuation of molar pregnancy without concerning about life-threatening complications. Moreover we did not find any differences in persistent trophoblasdtic diseases between two groups.

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Conflict of Interest

Authors declared no conflict of interests.

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