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Management of Hydatidiform Mole with or Without Methotrexate: A Hospital Based Cohort Study

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Abstract

Background: To study the rate of gestational trophoblastic neoplasia in the complete hydatidiform mole with and without methotrexate and to observe any side effects of methotrexate as prophylactic chemotherapy. **Methods:** It is a prospective study of 72 patients registered as cases of complete hydatidiform mole admitted in SCB medical college, Cuttack from July 2018 to July 2020 out of which after suction and evacuation of all patients, 16 patients categorised as high risk groups were given Methotrexate and folinic acid and rest were only followed up. **Results:** Total 72 cases of complete molar pregnancy were registered with 22010 deliveries in this period with an incidence of 3.2 per 1000 pregnancies. The mean age of presentation was 27.73 ± 6.9 years. Maximum patients were primigravida(40%) and most patients (88.89%) patients presented with vaginal bleeding. Maximum patients presented in the first trimester with average gestational age of presentation 12.2 weeks ± 4.2 weeks. Out of 16 patients who received Methotrexate and folinic acid none had developed gestational trophoblastic neoplasia but 21.42% cases (n=12) who did not received methotrexate developed GTN (p value = 0.043). Only 3 patients developed minor side effects like stomatitis and pruritus. **Conclusions:** Prophylactic chemotherapy with methotrexate and folinic acid in high risk molar pregnancy patients may be beneficial in preventing gestational trophoblastic neoplasia where there is a high chance of patients being lost to follow up without imparting major toxic effects.

Keywords:- Molar Pregnancy, Gestational Trophoblastic Neoplasia, Methotrexate, Prophylactic Chemotherapy.

INTRODUCTION

Molar pregnancy occurs due to abnormal proliferation of trophoblastic cells of placenta where there occurs multiple cyst formation instead of a healthy foetus.[1] Hydatidiform mole is the benign counterpart of gestational trophoblastic neoplasia which includes choriocarcinoma, invasive mole, placental site trophoblastic tumour and epitheloid trophoblastic tumour. The incidence varies worldwide from 0.5-1 per 1000 pregnancies in North America and Europe to 1 per 125 pregnancies in Taiwan.[2,3] The burden and morbidity has decreased over time due to early diagnosis by ultrasonography and follow up with an effective biomarker like serum β-hCG. But there is 20% chance of progression to gestational trophoblastic neoplasia more specifically when associated with some high risk factors.[4] Prophylactic chemotherapy with

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methotrexate and folinic acid to this high risk patients may decrease the progression to malignancy. This study was undertaken to study the effectiveness of Methotrexate as prophylactic chemotherapy to prevent the progression to Gestational Trophoblastic Neoplasia.

Aims and objectives

- To study the rate of gestational trophoblastic neoplasia in complete hydatidiform mole with and without methotrexate.
- To report any side effect of methotrexate as prophylactic chemotherapy.

MATERIAL AND METHODS

This study was carried out in a tertiary care hospital in the department of Obstetrics and Gynaecology, SCB medical college, Cuttack, Odisha. All the patients diagnosed with complete molar pregnancy were included. Patients who failed to give consent, patients with gestational trophoblastic neoplasia, with abnormal renal and hepatic functions or any contraindications to methotrexate were excluded from the study. Approval from institutional ethics committee was taken.

After explaining the study and follow up period of 6 months, written consent was taken. Detailed history regarding age, menstrual cycles, parity, abortion, presenting complaints like vaginal bleeding, expulsion of grape like structures were taken. Thorough physical examination was done including body built, pallor, pulse, blood pressure, respiratory rate, thyromegaly, any respiratory difficulties etc. Uterine size, consistency, mobility, tenderness was noted.

Routine laboratory investigations like CBC, serum electrolytes, RFT, LFT, thyroid profile, coagulation profile were done. Quantitative serum β-HCG levels was determined. Ultrasonography of abdomen and pelvis was done to conform the diagnosis and to rule out other pathologies and to see the size of ovarian cysts if present. Chest x-ray PA was done to rule out pulmonary metastasis.

In all patients suction and evacuation was done with wide bore cannula after correction of anaemia with blood products and the specimens were sent for histopathological evaluation. After completion of evacuation oxytocin drip was started.

All the cases were classified as either high risk or low risk molar pregnancy. The high risk factors included :-

- Serum β-HCG more than or equal to 1,00,000 U/ml
- Uterine size more than twenty weeks
- Age more than 40 years

Any patient fulfilling any criteria from above were considered as high risk and were given one cycle of prophylactic chemotherapy with methotrexate and folinic acid on alternate days.

Methotrexate IM - 1mg/kg/day on days 1,3,5,7

Folinic acid IM – 0.1mg/kg/day on days 2,4,6,8.

Serum β-HCG levels were monitored at weekly interval till the values become normal for 3 consecutive weeks and thereafter monitored every monthly for 6 consecutive months.

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All the patients were advised to avoid pregnancy during the follow up period and use oral contraceptives or barrier method for contraception.

On each follow up following signs and symptoms were looked upon.

Amenorrhoea, bleeding per vaginum, difficulty in breathing, haemoptysis, uterine enlargement, shadows on chest x-ray, headache, focal neurological deficit. Post molar gestational trophoblastic neoplasia was diagnosed if:

- When the plateau of hCG lasts for four measurements over a period of 3 weeks or longer; that is, days 1, 7, 14, 21.
- When there is a rise in hCG for three consecutive weekly measurements over at least a period of 2 weeks or more; days 1, 7, 14.
- If there is a histologic diagnosis of choriocarcinoma.

Statistical analysis was done using student T test and Chi square test. All the statistical analysis were done by using SPSS version 21.0.

RESULTS

Total of 72 patients were registered as a case of complete molar pregnancy and total 22010 deliveries occurred in this period with an incidence of 3.2 per thousand deliveries. Maximum patients (59.7%) presented in the age group of 21- 30 years with mean age of 27.73±6.9 years. Most patients (40%) were primigravida. Most common presentation was vaginal bleeding (88.89%). 9.72% patients had hyperemesis, 6.94% patients had hyperthyroidism, and only 4.16% patients had pain abdomen and expulsion of grape like vescicles. Maximum patients (57%) presented in the first trimester with an average gestational age of presentation 12.2 weeks± 4.2 weeks. 47. 23% patients were having blood group of A positive. Most patients (70%) had uterine size larger than the gestational age. Among all the patients (n=16) who received prophylactic chemotherapy with methotrexate and folinic acid , none had developed gestational trophoblastic neoplasia, but those who did not received prophylactic chemotherapy, 21.42% cases developed GTN(p value=0.043). Mean β-hcg normalisation time was 5.13 weeks in methotrexate group and 4.05 weeks in non-methotrexate group but the rate of regression of β-hcg values in methotrexate group was significant with p value of 0.001. Only 3 patients developed only milder side effects like stomatitis and pruritus. None had any lethal side effect or mortality.

Table 1: Sign and symptoms pf patients

Clinical features	No. Of cases	Percentage (%)
Amenorrhoea	72	100
Bleeding per vaginum	64	88.89
Pain abdomen	3	4.16
Hyperthyroidism	5	6.94
Hyperemesis	7	9.72
Expulsion of mole	3	4.16
Enlarged uterine size	51	70.8

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Table 2: β – HCG Values

S.βhcg Range	No.of participant	Percentage
1 (<1000)	11	15.27
2 (1000-10,000)	32	44.45
3 (10,000-1,00,000)	14	19.45
4 (>1,00,000)	15	20.83
Total	72	100

Table 3: Incidence of GTN in Patients

GTN	Patient Taking Methotrexate (%) n=16	Patient Not Taking Methotrexate (%) n=56	P value	ODDS ratio
Present	0(0.00)	12(21.42)	0.043*	1.273 (1.110-1.459)
Absent	16(100)	44(78.58)		

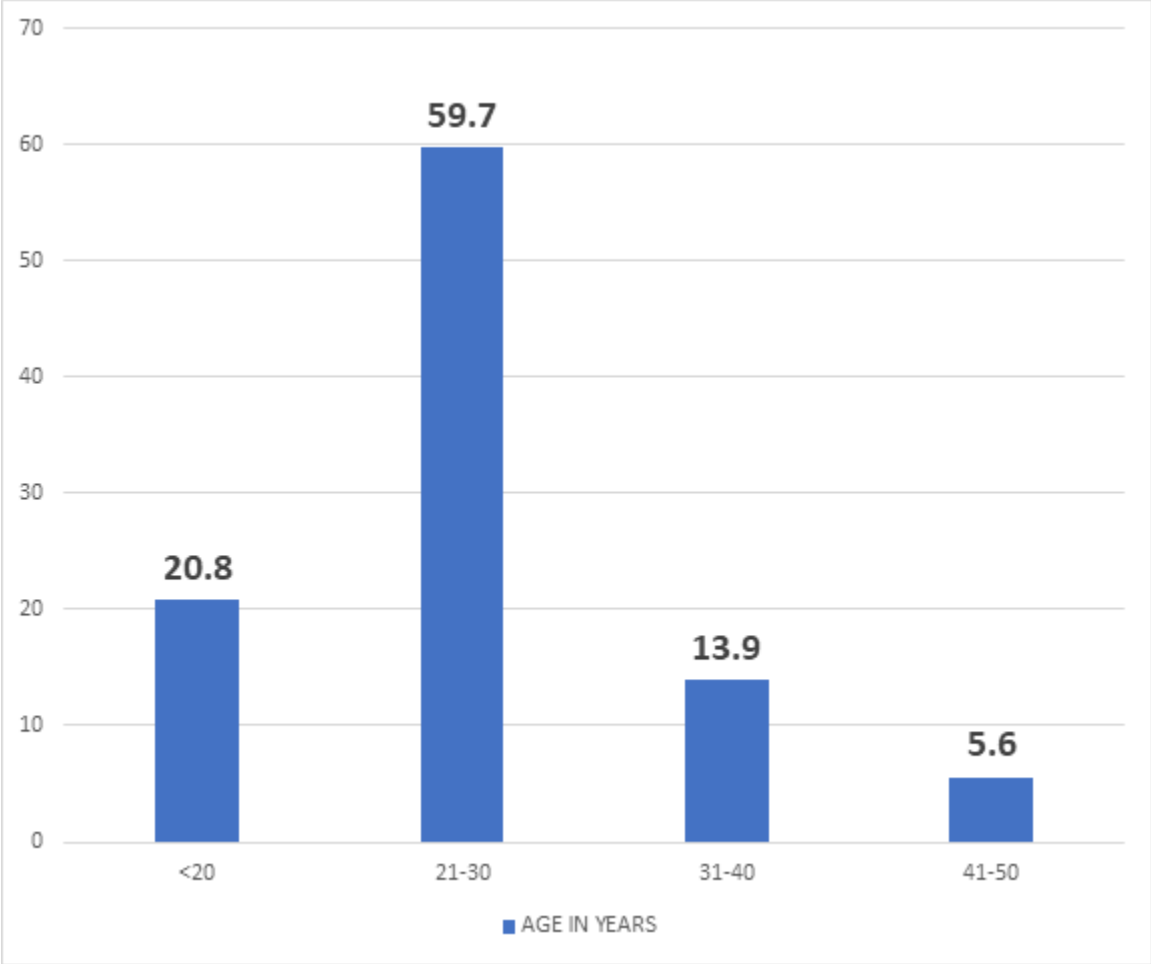

Figure 1: Age Distribution Among Participants

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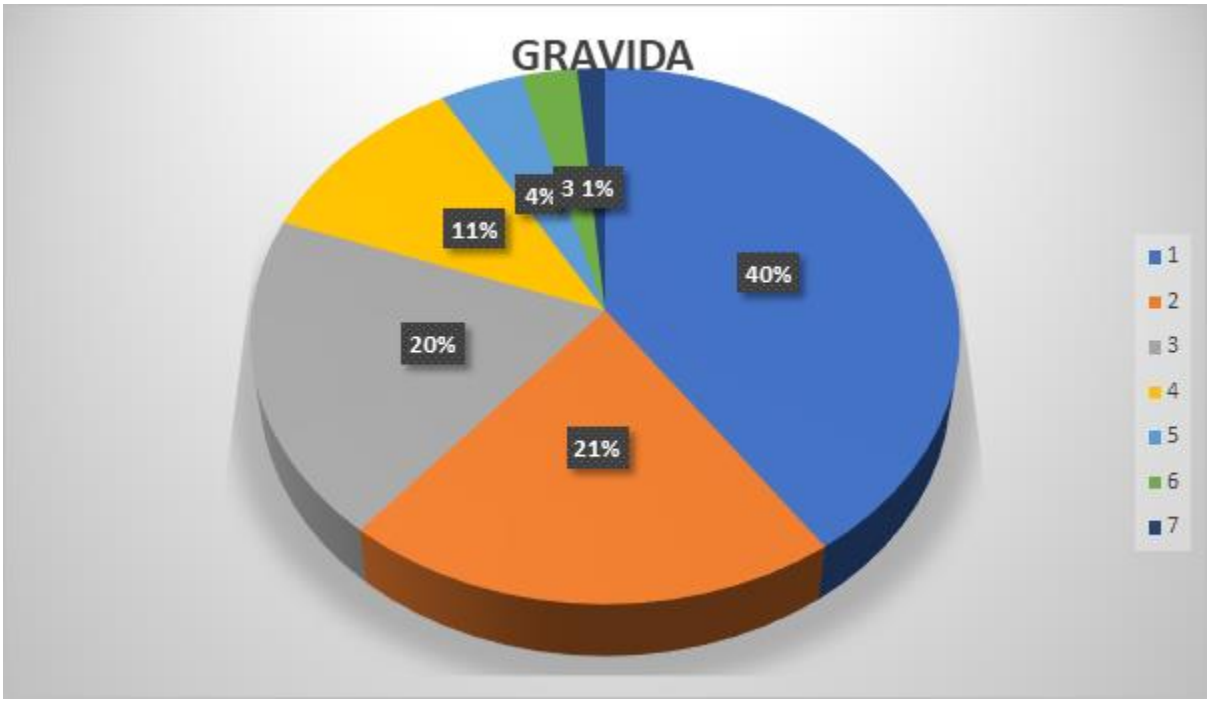

Figure 2: Gravidity of patients

DISCUSSION

This study entitled "Management of Hydatidiform mole with or without methotrexate : A Hospital based Cohort Study" was conducted from July 2018 to July 2020 in the department of Obstetrics & Gynaecology, SCB Medical College & Hospital, Cuttack.

In this study total 72 patients of complete molar pregnancy were registered and total 22010 deliveries were done in this period giving an incidence of 3.2 per 1000 deliveries. This was similar to Igwegbe et al(2013) who reported an incidence of 0.4% in a 10 year retrospective study in South-East Nigeria.[5] In contrast, Al Talib et al (2016) conducted a 10 year study in Saudi Arabia reported an incidence of 0.9 cases per 1000 pregnancy.[6] Fatima et al (2011) reported an incidence of 5.1 per 1000 patients admitted to the hospital in Pakistan from 1994 to 1996.[7] As this is a tertiary care hospital, so due to higher number of referrals from peripheral hospitals, the incidence of molar pregnancy was high in our study. Geographic differences in incidence may be due to environmental, cultural, socioeconomic or racial (genetic) factors.

Maternal age is considered as one of the major risk factors for molar pregnancy. In this study maximum patients (59.7%) presented in the age group of 21-30 years with a mean age of 27.73±6.9 years. Similar findings were also reported by Igwegbe et al who showed maximum patients (29%) were in the age group of 21-25 years.[5] Sharma et al (2010) also reported that the mean age of presentation was 27.1 ± 6.6 years.[8] This was in contrast to the study by Seckl MJ et al (2010) who reported that increased risk of molar pregnancy is seen in <16 years and >45 years.[9] Lurain et al also

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reported increased risk of molar pregnancy 7.5 times higher in age >40 years.[1] This may be because in India maximum girls marry between 21-30 years and conceive early after marriage.

In this study out of 72 patients maximum patients (40%) were primigravida. Similar results were reported by Igwegbe et al, Al Talib et al, Pundir S et al (2019).[5,6,10] In contrast Fatima et al reported that maximum patients were multigravida.[7] Though some studies claim that there is no clear relation between parity and molar pregnancy.

Due to advancement in the health care system nowadays most cases of molar pregnancies are diagnosed in early gestational period with ultrasonography. The characteristic snowstorm appearance is seen in ultrasound due to diffuse hydropic swelling of the trophoblastic tissue. But some presents undiagnosed with adverse complaints, most common being vaginal bleeding. In this study 100% patients developed amenorrhoea and 88.89% patients presented with vaginal bleeding. Fatima et al and Jethwani et al also reported that amenorrhoea and vaginal bleeding was the most common presenting symptom.[7,11] Pundir S et al (2019) in their study reported 100% patients had amenorrhoea and 90.62% had vaginal bleeding.[10] Seckl et al (2010) also reported vaginal bleeding as the most common presenting symptom.[9]

In the present study maximum patients (57%) presented in the first trimester with an average gestational age of presentation 12.2 weeks ± 4.2 weeks. 41% presented in the second trimester and only 1 patient (1.38%) presented in third trimester. Al talib et al showed the mean age of presentation was 11.4 ± 0.3 weeks.[6] Igwegbe et al also reported that 71% patients were diagnosed in the first trimester.[5] In a study by Pundir S et al the mean age of presentation was 14.8 ± 8.weeks.[10]

In this study 47.23% patients were having blood group of A positive. This was comparable to studies by Koirala et al and Lakra et al.[12,13] But Jethwani et al showed majority patients had blood group of O positive.[11] Previously blood group was a criteria in the FIGO scoring of GTN but in the recent revised scoring blood group criteria has been removed.

Due to rapid proliferation of trophoblastic cells the uterine size is usually more than the period of amennorrhoea. This study showed that 70% of patients had uterine size larger than the gestational age. Other studies also showed similar results. Sharma et al,[8] in their study showed that 44% had large for date uterus. In a study by Fatima et al,[7] 70% patients had large for date uterus. Al Talib et al also showed similar results in 27.3% patients.

Out of the 72 patients, 11 patients (15.27%) had serum β- hcg levels less than 1000mIU/ml, 32 patients (44.45%) within 1000- 10000mIU/ml, 14 patients (19.45%) within 10000-100000mIU/ml and 15 patients (20.83%) had more than 1,00,000mIU/ml.

In this study among all the patients (n=16) who received prophylactic chemotherapy none had developed GTN but those who did not received prophylactic chemotherapy, 21.42% cases developed GTN among which 66.67% were invasive moles and 33.33% were choriocarcinoma. Aminimoghaddam S et al (2020),[14] also reported that there was a significant difference between the number of

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patients with GTN in methotrexate (13.7%) with non-recipient group (31.4%) with a p value of 0.03. Wang et al (2017),[15] also reported similar results with p value of 0.001. Fatima et al (2011),[7] in their study reported none of the patients in the prophylactic chemotherapy group had GTN. Armstrong et al (2010),[8] reported the development of GTN as 0% vs 33.3% in prophylactic vs non-prophylactic group. Fasoli et al, Goldstein et al, Kim et al, Kashimura et al also reported similar results.[16,17,18,19] In contrast Vo T (2015),[20] did not showed any significant decrease in incidence of GTN in prophylactic chemotherapy group with a p value >0.05 as incidence of GTN in chemotherapy vs non-chemotherapy group were 14.3% vs 25%. Ratnam et al & Ayhan et al also did not showed any significant decrease in incidence of GTN.[21,22] Some studies also report that prophylactic hysterectomy is the best treatment for preventing post molar gestational trophoblastic neoplasia. But this shows advantage when the family is complete and age is more than 40 years. But our study showed and increased incidence in the twenties for whom hysterectomy cannot be a choice rather chemotherapy is a better alternative.

In this study the mean the mean β- hcg normalisation time was 5.13 weeks in methotrexate group and 4.05 weeks in non-methotrexate group which was in contrast to other studies. This may be because all the patients in methotrexate group had >1 lakh values and non-methotrexate group had significantly low β-hcg values.

The rate of regression of β-hcg values in methotrexate group was significant with p value of 0.001. Similar results were also seen by Fatima et al.[7]

Of all patients who received prophylactic chemotherapy only 2 patients developed stomatitis and one patient developed pruritus without any derangement in the liver function test. None had any lethal side effects or mortality. Similar results were also seen in other studies.

CONCLUSIONS

The incidence of molar pregnancy is high in our study. In a less developed country like India, more of the people belong to low socioeconomic background and have less educational status. So there is a high chance of lost to follow up as these people are reluctant to seek medical attention routinely. This study showed that prophylactic chemotherapy with a single cycle of methotrexate and folinic acid is cost effective and highly effective in preventing GTN in high risk molar pregnancy group which is more prone to develop into GTN, with less and mild toxicity. So prophylactic chemotherapy can be recommended to high risk molar pregnancy group in patients with a high chance of lost to follow up.

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