Gestational Trophoblastic Disease And Its Complications: Review Of Patient Profiles And Management At A Tertiary Care Centre

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ABSTRACT

Gestational trophoblastic Disease refers to a spectrum of pregnancy related placental tumors, which is Classified into Hydatidiform Mole and Gestational Trophoblastic Neoplasia. This disease is characterized by abnormalities of chorionic villi in the form of excessive trophoblastic proliferation, oedema of villous stroma, invasion and metastasis. The incidence of Hydatiform mole is 1-2 per 1000 pregnancies. The risk factors are Adolescent and elderly women, Prior molar pregnancy, OC pill use, Smoking, various vitamin deficiency and increase paternal age. Clinical presentation is usually of varing duration of amenorrhea followed by irregular bleeding. Ultrasound appearance is characteristic snow storm pattern i.e a complex echogenic mass with numerous cystic Spaces with no fetus or amniotic sac in complete mole. The two basic tenets for management is Suction Evacuation and regular follow up to detect trophoblastic disease. Most clinicians obtain pre operative x-ray chest hemogram , baseline beta HCG, blood grouping, liver enzymes routinely before suction Evacuation. Prophylactic chemotherapy is routinely not recommended. If no further pregnancy is required, hysterectomy preferred over suction curettage ion women aged more than 40 years. It is also an important adjunct to treatment of chemo resistant tumors.

Post evacuation Surveillance is done for a minimum of 6 months using hormonal contraception with beta HCG follow up 48 hours after evacuation and every 1-2 weeks, while still elevated and every month for another 6 months after it falls to normal levels. Gestationla trophoblastic neoplasia almost always develops with or follow some form of recognized pregnancy. Most follow a hydatidiform mole. Invasive mole are localy invasive but generally lack the pronounced tendency to wide spread metastasis. Choriocarcinoma is extremely malignant tumor. Metastasis often develop early in choriocarcinoma and are generally blood borne and most common sites are lungs and vagina. Placental site trophoblastic tumors are rare variant characterized by prolactin producing intermediate trophoblast with relatively low beta HCG, a high proportion of free beta HCG, chemo resistant and hysterectomy being the best treatment. Epitheliod tumors are rare characterized by non conformation of preceding pregnancy, nodular growth and microscopically resembles placental site tumors but the cells are smaller and display less pleomorphism. Risk assessment is done by using modified WHO prognostic scoring system. Score 0-6 generally include low risk neoplasia. In general methotrexate is given for non meta static or low risk metastatitic neoplasia. High risk GTN{score more then 7}usually requires EMA-CO regimen, surgery, radiotherapy. Survillence is one year for GTN and upto 2 years if there is metastasis. The purpose of this study was to study the incidence, epidemiological correlates of GTN, the clinical behavior, the complications and management of this disease in our hospital, and to review the literature on this uncommon disease.

Key words: Gestational Trophoblastic Disease And Its Complications

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INTRODUCTION

Gestational trophoblastic Disease refers to a spectrum of pregnancy related placental tumors. It is Classifiedas[1] :-
Hydatidiform Mole
A] Complete
B]Incomplete
2) Gestational Trophoblastic Neoplasia
A] Invasive Mole
B]Choriocarcinoma
C] Placental site tumour
D] EpitheliodTumour

Hydatidiform Mole or molar pregnancy is characterized by abnormalities of chorionic villi in the form of
1] Trophoblastic proliferation
2] Eodema of villous Stroma
The degree of tissue changes and absence or presence of a fetus is used to describe them as complete or partial. (Table A)
(Table B)

TABLE 11-2. Features of Partial and Complete Hydatidiform Moles

The incidence of Hydatiform mole has been constant in USA and Europe at 1-2 per 1000 pregnancies [2]. It is found to be more frequent in some asian countries, however Data is insufficient.

The risk factors are Adolescent and elderly women, Prior molar pregnancy, OC pill use, Smoking, various vitamin deficiency and increase paternal age.
Clinical presentation is usually of varying duration of amenorrhea followed by irregular bleeding. This almost always prompts Pregnancy testing and Ultra-sonography. If left untreated spontaneous expulsions occurs at around 16 weeks.

Ultrasound appearance is characteristic snow storm pattern i.e a complex echogenic mass with numerous cystic Spaces with no fetus or amniotic sac in complete mole.

Diffrential diagnosis is usually a fibroid uterus and Mu tiple pregnancies [3]

Current mortality rate from molar pregnancy has been reduced to zero by prompt diagnosis and therapy. The two basic tenets for management is Suction Evacuation and regular follow up to detect trophoblastic disease. Most clinicians obtain pre operative x-ray chest hemogram , baseline beta HCG, blood grouping, liver enzymes routinely before suction Evacuation. Prophylactic chemotherapy is routinely not recommended. If no further pregnancy is required, hysterectomy preferred over suction curettage ion women aged more than 40 years. It is also an important adjunct to treatment of chemo resistant tumors [4].
Post evacuation Surveillance is done for a minimum of 6 months using hormonal contraception with beta HCG follow up 48 hours after evacuation and every 1-2 weeks

While still elevated and every month for another 6 months after it falls to normal levels. Such intensive monitoring has high non-compliance rate. A number of investigatorsstates that no women with partial or complete mole whose serum beta HCG level undetectable subsequently developed persistent disease[5,6,7]. Post evacuation sonography, uterine Examination may reveal myometrial nodules or hyper vascularity which may be predictors of subsequent GTN. Gestationla trophoblastic neoplasia almost always develops with or follow some form of recognized pregnancy. Most follow a hydatidiform mole but neoplasia may follow pregnancy abortion or even an ectopic pregnancy [8 ,9].

Invasive mole are localy invasive but generally lack the pronounced tendency to wide spread metastasis. Choriocarcinoma is extremely malignant tumor with incidence of 1 in 30,000 [regnancies and only $1/3^{rd}$ of it develops after a normal delivery and $1/3^{rd}$ after molar pregnancy. Metastasis often develop early in choriocarcinoma and are generally blood borne and most common sites are lungs and vagina.Ovarian theca leutein cysts are identified in $1/3^{rd}$ of such cases. Placental site trophoblastic tumors are rare variantcharacterized by prolactin producing intermediate trophoblast with relatively low beta HCG, a high proportion of free beta HCG, chemoresistant and hysterectomy being the best treatment. Epitheliodtumors are rare characterized by non conformation of preceding pregnancy, nodular growth and microscopically resembles placental site tumors but the cells are smaller and display less pleomorphism.

Clinical staging is similar to that of ovarian cancer except that stage 3 allows pulmonary involvement. Risk assessment is done by using modified WHO prognostic scoring system. Score of 0-4 is given to each category that includes 1] age 2] type of antecedent pregnancy and interval from it 3] serum beta HCG 4] size of tumor, site and number of metastasis 5] previous chemotherapy Score 0-6 generally include low risk neoplasia. In general methotrexate is given for non meta static or low risk metastatiticneoplasia.Actinomycin D is another option but more toxic .response to chemotherapy is assessed by beta HCG estimation, however phantom HCG caused by heterotrophic antibodies may interfere with HCG assay. High risk GTN {score more then 7}usually requires EMA-CO regimen, surgery, radiotherapy. Survillence is one year for GTN andupto 2 years if there is metastasis.
The purpose of this study was to study the incidence, epidemiological correlates of GTN, the clinical behavior, the complications and management of this disease in our hospital, and to review the literature on this uncommon disease.

Fig 1 - A complete or classical hydatidiform mole. (Courtesy of Dr. Michael G. O'Connor.) Williams obstetrics 23rd edition.

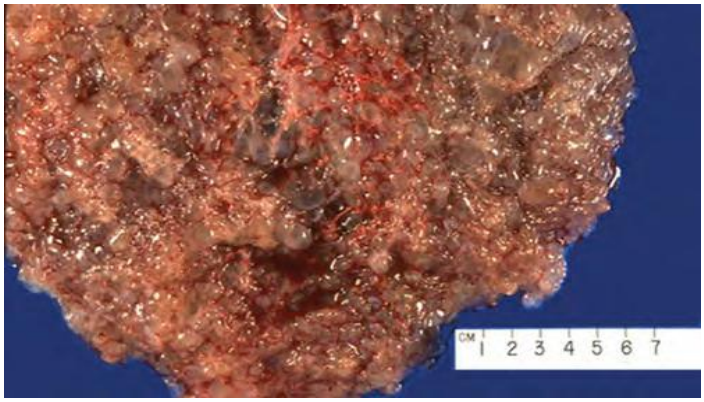


Fig 2 - Sagittal sonogram image of a 20-week-sized uterus with a complete hydatidiform mole (black arrows) and associated ovarian theca-lutein cysts (white arrows).

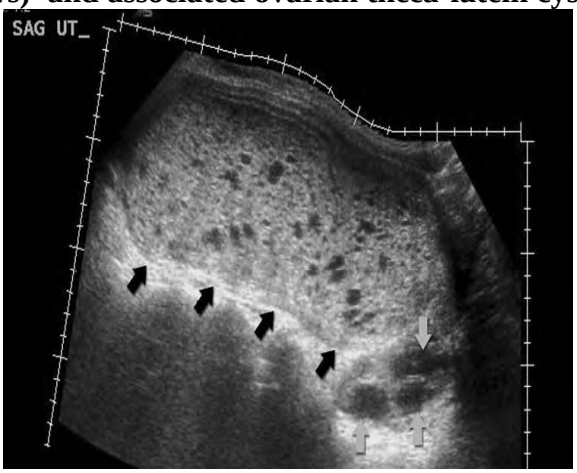
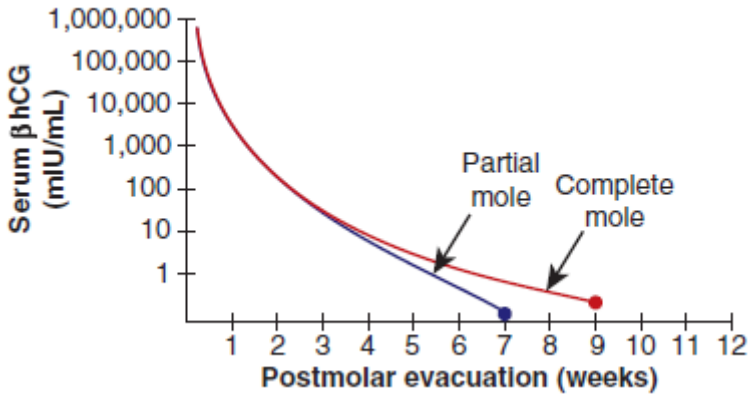


Figure 3 - Schematic illustration of composite medians of -subunit chorionic gonadotropin regression curves in women with a partial or complete hydatidiform mole. (Composite con- structed using median data reported by Golfier (2007), Schlaerth (1981), Wolfberg (2004, 2005,



MATERIAL AND METHODS

We conducted a retrospective observational study of all the cases of hydatidiform mole/GTN admitted to our hospital from 2010 to 2014. The details of maternal characteristics, clinical presentation, management and complications of the condition were noted from the case records. All the observations documented on excel sheet and results tabulated. There were total 21 cases of GTN. The diagnosis of HM was based on a pelvic ultrasound scan, quantitative estimation of serum beta human chorionic gonadotrophin (BhCG) and histopathological examination of the specimen. During this period 17,500 patients delivered in our hospital.

RESULTS

Our observations are as follows :-

1. Incidence-

There were 17,500 deliveries during the period giving an incidence of GTN as one in 761deliveries.

2. Age –

Table 1 - Age distribution of patients with GTN.

Age	Number(N=23)	%
<=19	1	4.3
20-25	10	43
26-30	7	30.4
31-35	1	4.3
36-40	2	8.6
>=41	2	8.6

Table 1 shows that the patients ages ranged from 19 to 44 years with a mean Age is of 28 years..

3. Parity

Table 2 A -Parity distribution of the patients.

Parity	Number(N=23)	%
0	4	17.3
1	11	47.8
2	2	8.6
3	3	13
4	2	8.6
5	0	0
>6	1	4.3

The parity of the patients ranged from 0 to 7 with a mean of 2, with 47.8% of cases with parity 1(gravid =2).

Table 2b - Previous abortion distribution of the patient.

Previous History of Abortion	Number(N = 23)	%
0	13	56.5
1	7	30.4
2	2	8.6
3	1	4.3

The previous Abortion of the patients ranged from 0 to 3 with a mean of 1.56.5%of the patients did not have any previous Abortion

4. Fetal Maturity In weeks of the present pregnancy

A] Period of amenorrhea

Table 3.1- Period of amenorrhea in weeks of the present pregnancy

Period of amenorrhea in weeks	Number(N=23)	%
1-5	1	4.3
6-10	9	39.1
11-15	6	26
16-20	4	17.3
21-25	3	13

Table 3.1 shows that the Fetal maturity by dates of the patients ranged from 4weeks to 23 weeks with a mean of 13 wks. 65.1% of cases had maturity between 6 weeks to 15 weeks

b] Fetal maturity on Abdominal palpation

Table 3.2 - Fetal maturity on Abdominal palpation

Fetal Maturity in weeks	Number(N=23)	%
1-5	0	0
6-10	11	47.8
11-15	4	17.3
16-20	8	35,7
21-25	0	0

Table 3.2 shows that the Fetal maturity by Abdominal Palpation of the patients ranged from 6weeks to 20 weeks with a mean of 14. 65.1% of cases had maturity between 6 weeks to 15 weeks

C] Complete or partial mole on ULTRASOUND

Table 3.3 - Complete or partial mole on ULTRASOUND

Table 3.3 shows that 87% of study cases were of complete mole on ultrasound.

Type of mole	Number(n=23)	%
Complete	20	87
Partial	1	4.3
Normal pregnancy	2	8.6

5. Investigations-

1] Beta human chorionic gonadotrophinharmone[Beta HCG]- Baseline

As two cases were retrospectively diagnosed as molar pregnancy after MTP, N=21

Table 4.1 - Baseline Beta HCG values.

Beta HCG	Number(N=21)	%
<10,000	9	39.1
10,000-99,999	5	21.7
1,00,000-1,49,999	2	8.6
1,50,000-1,99,999	1	4.3
2,00,000-2,49,999	0	0
2,50,000-2,99,999	1	4.3
>=3,00,000	3	13

Table 4.1 shows that 39% of all patients had their Baseline beta HCG less than 10,000, and 13% cases had baseline beta HCG more than 3,00,000.

2] Hemoglobin[Hb]%

Table 4.2 - Baseline hemoglobin values.

Hb %	Number(N=23)	%
8 - 8.9	1	4.3
9 - 9.9	9	39.1
10 – 10.9	6	26
11 – 11.9	6	26
12 – 12.9	1	4.3

Table 4.2 shows that 43.4% of patients had their hemoglobin levels less than 10

3] Blood Group

Table 4.3 Blood group of study population

Blood group	Number(N=23)	%
A+	9	39.1
B+	5	21.7
AB+	3	13
O+	6	26

Table 4.3 shows 39.1% of total patient had blood group A positive

6. Associated obstetric and Medical Risk factor

Table 5.1 - Associated obstetric and Medical Risk factor in the study population

Risk Factor	Number(N=23)	%
Previous LSCS	4	17.3
PIH	0	0
Hyperthyroidism	1	4.3
Hemorrhage	6	26
HIV	1	4.3
Hyperemesis gravidanum	1	4.3
None	10	43.3

Table 5.1 shows that a 17.3% patients exhibit hemorrhage and 26% Patientsexhibited risk factors as previous LSCS. Hyperthyroidism, hyperemesis gravidanum and HIV was present in 4.3% of cases each. 43.3% had no obstetric or medical risk factor associated with it.

7. Management of GTN

Table 6.1 - Management of GTN

Procedure	Number(N=23)	%
Mtp	2	8.6
Suction Evacuation	18	78.2
Hysterectomy	1	4.3
Evacuation With Check Curettage	2	8.6
Spontaneous Expulsion	0	0

Table 6.1 shows that 78.2% of all patients were treated with suction evacuation while other methods comprised 21.8%. 8.6% of total study population were retrospectively diagnosed as molar pregnancy after undergoing the routine MTP procedure.

8. Complications of GTN

Table 7.1 - Complications of GTN in study population.

Complications	Number(N=23)	%
Shock	1	4.3
Embolism	0	0
Thyroid Storm	0	0
None	22	95.6

Table7.1 shows that 95.6 percent of all patients exhibit no complications, pre-operative, intra-operative and post-operative period.

9. **Follow up investigation**

1] **BHCG-**

Table 8.1 - Decline in beta HCG concentration during follow up (in-door as well As out-door basis) considering zero as baseline.

Baseline Bhcg	Duration Of Follow Up (Days)	Follow-Up B. Hcg	% Decrease
50000	7	6852	86.3
8318	30	637	92.3
530000	6	31417	94
45372	5	5719	87.39
112054	3	47000	58
1746	14	37	97.88
54308	42	3.42	99.99
154446	6	14524	90.59
405	4	194	52
4249	3	921	78.32
10650	7	2790	73.80
710175	23	1972	99.7
5080	30	0.5	99.7
627007	14	3696	99.41
6034	36	11	99.8
78456	8	8012	89.8
4367	4	382	91.25
109865	21	14078	87.18
7491	8	621	91.7
4691	14	26.43	99.4
2,71,514	4	3034	98.8

Table 8.1 shows that with average duration follow-up of 13.76 days, average fall in beta HCG values is 89%.

2] Endometrial thickness on Follow up USG-

Two cases who underwent MTP has not followed up. So N = 21

Table 8.2 -Endometrial thickness on Follow up USG

Endometrial thickness (mm)	Number (N=21)	%
<=6	11	47.8
7-12	8	35.7
13-18	0	0
19-24	2	8.6
>=25	0	0

Table 8.2 shows that 83.5 % had less than 12 mm thickness, ranging from 1.4 to 24 mm on follows up USG.

10. Histopathology of GTN

Table 9.1 - Histopathology of GTN in study population

Histopathology	Number(N=23)	%
Complete Vesicular mole	21	91.4
Partial Vesicular mole	2	8.6
Choriocarcinoma	0	0
Placental site tumor	0	0
Epitheliod tumor	0	0

Table 9.1 91.4 % of patients were having Complete Vesicular mole on Histopathology and 8.6% had Partial Vesicular mole. None reported as choriocarcinoma and other Tumors which are rare.

11. Chemotherapy

Table 10.1 - Chemotherapy received in study population

Chemotherapy	Number(N=23)	%
Single dose methotrexate	3	`13
Multiple dose methotrexate	10	43.4
EMA-CO Regimen	1	4.3
No chemotherapy	9	39.1

Table 10.1 shows that 60.9% of patients were given chemotherapy of some modality.43.4 % cases received multiple dose methotrexate and 13% received single dose. 4.3% pateints received combined regimen for persistent trophoblastic disease

12. Beta HCG follow upupto 1 year with barrior contraception:

7 cases were yet to complete the 1 year follow up criteria so not included in this table so (N = 16)

Table 11.1- Follow up upto 1 year

Nature of follow upto 1 year	Number(N=16)	%
No Follow up	3	18.75
Follow up with others	2	12.5
Regular follow up with contraceptive	6	37.5
Irregular Follow up	5	31.25

Table 11.1 shows that only37.5% of all patients were in regular follow up and 31.2 %with irregular follow up with us over a period of year and none reported with pregnancy with barrier methods used as contraception.

DISCUSSION

There were 17,500 deliveries during the period giving an incidence of GTN as one in 761 deliveries. The incidence of hydatidiform mole (HM) in this series corroborates the reports from some oriental countries.10, 11 The true incidence in the population may be even lower than this hospital-based study. In a Korean study, Kim and colleagues (2004) reported a population-based incidence of 2 per 1000 deliveries.

The patients ages ranged from 19 to 44 years with a mean of 28 years..The parity of the patients ranged from 0 to 7 with a mean of 2, with 47.8% of cases with parity 1. As the data on maternal age and parity for all the mothers delivered during the same period of time was not available, it was not possible to calculate the incidence of hydatidiform mole in the different age and parity groups. However, some studies indicate an increase in the incidence of HM with decreasing maternal age below 20 years,12,13 while others report an increased risk in patients over 35 years.14-15Early marriage and teenage pregnancy are the norm in many Asian countries and child bearing often continues into the later years of reproductive life. It is relevant to note that the number of HM analyzed in this report was rather small and this may have affected the results.

Previous abortions excluding the present gravid status done by the study patients ranged from 0 to 3 with a mean of 1. 43.5% of the patients had 1 or other previous Abortion. This association of previous miscarriage is not much discussed in literature. However, there is definitely high incidence of hydatidiform mole in patients with previous history of miscarriages. Recurrent hydatidiformmole were not found in our study. This could be because of small sample size. There is a substantial increased risk for recurrent trophoblastic disease. In a review of 12 series totaling almost 5000 molar pregnancies, the frequency of recurrent moles was 1.3 percent 16. The risk is 1.5 percent for a complete mole and 2.7 percent for a partial mole 17. With two prior molar pregnancies, Berkowitz and associates (1998) reported that 23 percent of women had a third mole! 18. Repetitive hydatidiform moles in women with different partners suggest that an oocyte defect leads to molar development.

The Fetal maturity by dates of the patients ranged from 4 weeks to 23 weeks with a mean of 13 weeks. 65.1% of cases had maturity between 6 to 15 weeks. This may be because of high spontaneous expulsion rate in GTN beyond 16 weeks. The Fetal maturity by Abdominal

Palpation of the patients ranged from 6 weeks to 20 weeks with a mean of 14weeks. In our study ultrasound suggesting partial mole was 8.6 %. As more than 90% of total study group comprised of complete mole, height of uterus on palpation was 1 week greater than period of amenorrhoea. As Most women present for pregnancy care early and undergo sonography early, clinical criteria of fundal height more than period of gestation should not be missed and molar pregnancy should be suspected.

39% of all patients had their Baseline beta HCG less than 10,000 and13% cases had baseline beta HCG more than 3,00,000. 43.4% of patients were anaemic on admission. 39.1% of total patient exhibit blood group as A positive, while 17.3% patients exhibit hemorrhage. Hyperthyroidism, hyperemesis gravidanum and HIV was present in 4.3% of cases each. PIH was not present in our study population. 26% patients exhibited risk factors as previous LSCS.43.3% patients had no obstetric or medical risk factor associated with it. 78.2% of all patients were treated with suction evacuation while 8.6% patients were retrospective accidental finding. Another 8.6% patient's required check curettage and hysterectomy rate was 4.3%. Hysterectomy was done in view of multiparity with persistent trophoblastic disease. 95.6 percent of all patients exhibit no complication during intra-operative and post-operative period. Soto-Wright et al (1995) postulated that the clinical presentation of hydatidiform mole has changed in recent years and fewer current patients in their study as compared to historic control presented with traditional symptoms of molar pregnancy (large uterine size, hyperemesis gravidarum, anemia, pre-eclampsia, and hyperthyroidism).19 Our study confirms this trend.

91.4 % of patients were having Complete Vesicular mole on Histopathology and 8.6% had Partial Vesicular mole. None reported as choriocarcinoma and other Tumors which are rare.

In the follow up USG, 83.5 % had less than 12 mm thickness ranging from 1.4 to 24 mm. With average duration follow-up of 13.76 days, average fall in beta HCG values is 89%.so around 11% to 12.5% cases exhibit persistent trophoblastic disease in our study group. MRI suggesting of invasive mole were present in only 4.3 % cases.

60.9% of study patients received chemotherapy post surveillance. 43.4 % cases received multiple dose Methotrexate and 13% received single dose methotrexate.Prophylactic chemotherapy is not given in our study as the long-term prognosis for women with a hydatidiform moleis not improved with prophylactic chemotherapy 20.Single-agentchemotherapy is given for nonmetastatic or low-risk metastaticneoplasia 21. Abrao and colleagues (2008) reviewed 108 low-risk cases and foundmethotrexate or actinomycin D alone equally effective comparedwith a combination of the two. Methotrexate is less toxicthan actinomycin D, but both are usually curative 22. Virtually all women with nonmetastatic tumorsor low-risk gestational trophoblastic neoplasia are cured withmethotrexate if treated early 23. In 150 women with low-risk GTN, Growdenand co-workers (2009) found that metastatic disease, singledaymethotrexate infusion, and complete mole histology wererisk factors for additional chemotherapy beyond the first course 24.4.3% pateints received combined regimen for persistent trophoblastic disease in consultation with oncologist in our study population.

37.5% of all patients were in regular follow up with us over a period of 1year.Barrier methods are prescribed as contraceptivesof choice in our study and none reported with pregnancy. Oral contraception is an alternative option.

CONCLUSION

The incidence of hydatidiform mole in this study is comparable to theworldwide incidence. There is high incidence of hydatidiform mole in patients with previous history of miscarriages.Most patients presesnt in early second trimester and clinical criteria of fundal height more than period of gestation should not be missed and molar pregnancy should be suspected. Our study postulates the trend that the clinical presentation of hydatidiform mole has changed in recent years and presents less with traditional symptoms of molar pregnancy as hyperemesis gravidarum, pre-eclampsia, and hyperthyroidism maybe because of early diagnosis by ultrasound. Persistent trophoblastic disease needs to be defined precisely and also the judicious use of methotrexate and follow up with contraception in management of persistent trophoblastic disease is the key to 100% survival in GTN.

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