DISSERTATION ON

A STUDY OF EPIDEMIOLOGICAL FACTORS AND CLINICAL PRESENTATIONS OF MOLAR PREGNANCIES IN IOG

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OBSTETRICS AND GYNAECOLOGY

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BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"A study of epidemiological factors and clinical presentations of molar pregnancies in IOG"**, is a bonafide work done by **Dr.S.Sujatha**, at the Institute of Obstetrics and Gynaecology and Government Hospital for Women and Children, Egmore attached to Madras Medical College, Chennai from 2006 – 2008 under our supervision and guidance in partial fulfillment of the regulations laid down by the Tamil Nadu Dr.M.G.R. Medical University – Chennai, for the award of the degree of M.D. in Obstetrics and Gynaecology.

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CONTENTS

INTRODUCTION

This is a Prospective study of Gestational Trophoblastic Diseases from one of the largest maternity centers of South Asia – Institute of Obstetrics and Gynecology of Madras Medical College, Chennai. This is a tertiary referral center in South India giving tertiary care to the people from the state of Tamilnadu and also the neighbouring states of Andra Pradash and Karnataka. This study was conducted over a period of one year covering Ninety Patients.

Gestational trophoblastic neoplasms (GTN) are proliferative as well as degenerative disorders of placental elements and includes complete (or) partial hydatidiform mole (90%), invasive mole 5.8% which could also be metastatic villous (or) avillous choriocarcinoma. (1-2%) and placental site tumor (1-2%), GTD is a discrete pool of epidemiological and clinicopathological entities. Therefore, every geographical region should be studied separately. The Indian subcontinent is under reported for this disease. Hence this analysis comes from one of the largest maternity center of India.

In this study we have analyzed the epidemiological factors and clinical presentation of molar pregnancy and compared the changing trends in the clinical presentation.

GESTATIONAL / TROPHOBLASTIC / DISEASE

Gestational Trophoblastic Disease
(Principles and Practice of Gyanecology, Oncology – 3rd Edition)
Ross.S, Berkowitz and Donald P. Goldstein

GTD are one of the rare Human Malignancies that are highly curable with chemotherapy even with widespread metastasis. It is a heterogenous neoplastic disorders arising from the placental trophoblastic tissue after a normal or abnormal fertilization, with varying potential for local invasion and metastasis.

There are four main types of gestational trophoblastic disease. These are:-

1. Hydatidiform Mole:-
    - Complete
    - Partial
2. Persistent / Invasive gestational trophoblastic disease
3. Choriocarcinoma
4. Placental site trophoblastic tumors.

These diseases are characterished by distinctive tumor marker – B subunit of Human Chorionic gonadotrophins except placental site trophoblastic tumor by Human placental lactogen.

Trophoblasts are specialized epithelial cells derived from the outer most layer of the blastocyst that originates in early embryonic

differentiation. On the basis of morphological, Immunophenotypical and functional studies trophoblasts are classified into 3 detective population.

1. Cyto trophoblast
2. Syncytio trophoblast
3. Intermediate trophoblast

In early gestation cytotrophoblast differentiate along villous and an extra villous pathway. On the villous surface cytotrophoblast differentiate into syncytotrophoblast – a poly nucleated structure with complete loss of proliferative activity. The second pathway of cytotrophoblast differentiates in the placental bed as the intermediate trophoblast which infiltrate the deciduas, the myometrium and the arteries of the implantation site and establish materno fetal circulation.

Hydatidiform Mole:-

Hydatidiform mole (The term hyd means water and refers to the fact that HM are shaped like water droplets) Characterized by a hydropic swelling of the chorionic villi and trophoblastic proliferation. It is classified as a complete hydatidiform mole and partial hydatidiform mole on the basis of histopathological features and karyotype (Table:1).

Complete Hydatidiform Mole:

Complete mole lack identifiable embryonic (or) fetal tissues and the chorionic villi exhibit generalized hydatidiform swelling and diffuse trophoblastic hyperplasia. Most complete hydatidiform moles are cytogenetically diploid usually have a 46xx karyotype and the molar chromosomes are entirely of paternal origin. Complete moles appear to arise from an ovum that has been fertilized by a haploid sperm, which then duplicates its own chromosomes and the ovum nucleus may be either absent (or) inactivated. Most complete moles have a 46xx chromosomal pattern / 10% have a 46xy Karyotype. Chromosomes in a 46xy; also appear to be entirely of paternal origin, but in this circumstance an apparently empty egg is fertilized by two sperm[38].

Partial Hydatidiform Mole (ACS – 2007)

Partial Hydatidiform mole develops when two sperm fertilize a normal egg, these contains some fetal tissue. But this tissue is often mixed in the trophoblastic tissue. It is important to know that no viable fetus is being formed. Partial hydatidiform mole occurs when an ovum with haploid set of chromosomes is fertilized by two spermatozoa that carry either of the sex chromosomes. It results in a zygote with a 69

chromosomes (triploid) with extra set (haploid) set of chromosomes derived from the father (69xxy, 69xxx, Occasionally 69xyy).

Histopathological and cytogenetic features of complete and partial mole and choriocarcinoma.

TABLE-1

Characteristic	**Complete Mole**	**Partial Mole**	**Choriocarcinoma**
Karyotype	Paternal Origin 46xx (90%) 46xy (10%)	Maternal / Paternal 69xxy (58%) 69xyy (2%) 69xxx (40%)	Aneuploidy
Fetal (or) Embryonic tissue	Absent	Present	-
Hydatidiform Swelling of Chorionic villi	Diffuse	Focal	Absent
Trophoblastic Hyperplasia	Diffuse	Focal	Diffuse Necrosis Hemorrhage
Scalloping of Chorionic villi	Absent	Present	-
Trophoblastic stromal inclusions	Absent	Present	-

Invasive Mole:

An invasive mole (formerly known as chorioadenoma destruens) is a hydatidiform mole that penetrates the muscular wall of the uterus (myometrium). These develop in about 20% of women who have had a complete mole removed by curettage. The risk of developing these in women with complete mole in increased if.

- ✓ There is a long time (more than 4 months) between the time periods had stopped and treatment.
- ✓ The uterus has become very large
- ✓ The women is older than 40 years
- ✓ The women has had GTD in the past

Invasive moles can be complete (or) partial, but complete moles invades much more often than partial mole. These moles sometimes disappear on their own, but most require treatment with chemotherapy. In 15% cases the tumor spreads through the blood stream (metastasis) to other sites usually lungs. Morphologically, an invasive mole is distinguishable from choriocarcinoma by the presence of villi which are generally absent in choriocarcinoma. Cyto genetically invasive moles are mostly diploid and some are aneuploid.

Choriocarcinoma:-

Choriocarcinoma is a malignant form of GTD, invasive neoplasm of the trophoblastic epithelium of the placenta. It is characterized by masses of cells invading adjacent tissues and penetrating vascular spaces (Microscopically, the neoplasm to composed of an avillous invasive proliferation of syncytoio trophoblasts and cytotrophoblasts surrounded by necrosis and haemorrhage. Although choriocarcinoma most often develop from a complete hydatidiform mole, it can occur after a normal pregnancy (or) abortion.

Malignant transformation in GTD involving a series of genetic changes including activation of oncogenes and inactivation of tumor suppressor genes. Choriocarcinoma is more likely to spread to organs away from uterus. Rarely choriocarcinoma. Can develop in other parts of the body in both men and women. These are not related to pregnancy. They may develop in the ovaries, testicle, chest (or) abdomen. These nongestational choriocarcinoma tends to be less responsive to chemotherapy and has a less favourable prognosis than gestational choriocarcinoma.

Placental Site Trophoblastic Tumor:

Placental site trophoblastic tumor is an uncommon but important variant of GTN that consists predominantly of intermediate trophoblast and a few syncytial elements. These tumors produce small amounts of HCG and human placental Lactogen relative to their mass, and tend to remain confined to the uterus, metastasizing late in their course. In contrast to other trophoblastic tumors, placental site tumors are relatively insensitive to chemotherapy. High cure rates can be achieved with early diagnosis and surgical resection. Intensive combination chemotherapy may achieve complete remission in patients with metastatic disease, particularly when the interval from the Antecedent pregnancy is less than 4 years.

Persistent Gestational Trophoblastic Tumor:-

Locally invasive GTN develops in 15% of patients after evacuation of a complete mole and infrequently after other gestations. These patients usually present clinically with one (or) more of the following.

1. Irregular vaginal bleedingTheca Lutein cysts
2. Uterus subinvolution (or) asymmetric enlargement
3. Persistently elevated serum HCG levels

After molar evacuation, persistent GTN may exhibit the histologic features of either hydatidiform mole (or) choriocarcinoma. After a non molar pregnancy,however persistent GTN always has the histological pattern of choriocarcinoma.

The current staging system for GTN combines both Anatomic staging and a prognosting scoring system.

Revised FIGO 2000 Staging

Staging of Gestational Trophoblastic Neoplasia

Stage I	Confined to Uterine corpus
Stage II	Metastasis to pelvis & vagina
Stage III	Metastasis to Lung
Stage IV	Distant Metastasis

Scoring system (Revised FIGO) based on Prognostic factors.

	0	**1**	**2**	**4**
Age	<40	≥40	-	-
Antecedent Pregnancy	Mole	Abortion	Term	
Intervel months from index pregnancy	<4	4-6	7-12	≥13
Pretreatment serum HCG (IU / l)	$<10^3$	10^3-$<10^4$	10^4-$<10^5$	$\geq 10^5$
Largest tumor size (including uterus)	-	3cm -<5cm	≥5cm	
Site of metastasis	Lung	Kidney/Spleen	Gastrointestinal liver	Brain
Previous failed chemotherapy	-	-	Single drug	2 (or) more drugs
Number of Metastasis	-	1-4	5-8	>8

In orders to stage and allot a risk factor score – Patient diagnosis is represented by eg. Stage II: 4, Stage IV:9. The stage and score will be allotted for each patients.

The total score <4 – Low risk
5-7 – Middle risk
≥8 – High risk

A prognostic scoring system reliably predicts the potential for resistance to chemotherapy and to assist in selecting appropriate chemotherapy.

REVIEW OF LITERATURE

Gestational trophoblastic disease comprise a group of interrelated disease including complete and partial molar pregnancy, invasive mole, placental site trophoblastic tumor and choriocarcinoma that have varying propensities for local invasion and metastasis (Berkowitz and P.Goldstein)[2].

Gestational trophoblastic disease is among the rare human tumors that can be cured even in the presence of wide spread dissemination (Norak 14th Edition)[38].

Incidence:-

Estimates of the incidence of GTD vary dramatically in different region of the world (Novak 14th edition)[38]. The frequency of molar pregnancy in Asian countries is 7 to 10 times greater than the reported incidence in North American (or) Europe where as hydatidiform mole occurs in Taiwan in one per 125 pregnancies, the incidence of molar gestation in the United States is about one per 1500 live births. (Williams J Hoskins 3rd Edition)[46].

The incidence of disease in higher in the eastern countries than the west (Shaw). It is suggested that GTD occurs especially in rice eaters. (Jeffcoate 5th edition)[30].

As per a study by B.W.L. Tham et al in BJOG June 2003[39], there is little epidemiological data from the Indian subcontinent, with the exception of a reported rate of choriocarcinoma of 19.2 / 1000 pregnancies, from India. But an Indian study by Kumar N et al[29] published in medical science monitor in 2003 October from New Delhi state that the incidence of GTD was 1.31 / 1000 live births and one per 967 pregnancies (including live birth, still birth, spontaneous abortions & MTP).

One study from Japan by Matsui et al states the incidence of hydatidiform mole /1000 live birth was constant from 1974 to 1990, while it decreased significantly after 1991. (chi (2) – test for trend, $P<0.0001$). The incidence of complete mole also decreased.

A reported study by Cheah PL et al from malayasia states that hydatidiform molar pregnancy has the highest prevalence among Indians. A similar finding by B.W.L. Tham et al in BJOG[39] states that Asian women are increased risk of having molar pregnancies.

A Singapore study by Hancock BW et al, the incidence of gestational trophoblastic disease in the Asian Population was 1.95 times

higher than in the Non Asian population. (1/387 live births Vs 1/752 live births).

These regional differences in the frequency of hydatidiform mole have been attributed to genetic and environmental factors, (or) the interaction of both. This under lines the need for region specific epidemiological and etiological study of GTD. Some predisposing factors – such as early Menarche, parity, age at first pregnancy, interval between previous pregnancies, malnutrition and socioeconomic status generally have a geographical specific characters.

On the other hand Asian descent has been reported as a risk factor for GTD. This indicates that emphasis on detailed study of GTD and its follow up in Asian regions may help in revealing its geographical distribution, in a clearer way. (Kumar et al medical science monitor – 2003)[29].

Age:-

Maternal age older than 35 years has consistently been shown to be risk factor for complete mole. Ova from older women may be more susceptible to abnormal fertilization. In one study, the risk for complete mole was increased 2 fold for women older than 35 years and 7.5 fold for women older than 40 years. (Novak 14th Edition)[38].

In a study by Berkowitz et al[24], the risk of having a complete molar pregnancy increases with advanced maternal age, women older than 40 have 5 to 10 fold greater risk of having a complete molar gestation.

A study from clinical Obstetrics Gynaecology 2007, by Donald P. Goldstein et al shows that increasing age is the best established risk factors for complete molar pregnancy, women over 40 years of age having a 5-10 fold higher risk than younger women. Because of the higher number of pregnancies in younger women, however most complete moles occur in women under 35. Maternal age has not been associated with risk of partial molar pregnancy.

The Following are the various studies on maternal age of GTD

Greatest number of GTD in those

Age above 35years (or) under 20 years	-	Talati et al, Karachi[47].
The age specific incidence of Complete mole – Major peak in those of 35 years and over, between 35-39 years – relative risk, 2.5 >40 years – RR was 9.8.	-	Fajardo AM et al, Abu Dhabi
Mean age for Gestational Trophoblastic Disease was 29.2 years	-	Figueira LM et al, Caracas, Venezuela, 2006.
Greatest Number of GTD cases occurred mainly among 20-34 years	-	Shi Y F, Chen XJ et al, China, 2005
The incidence of GTD is higher in Women below 20 years and above 39 years	-	Loukovaara M et al, 2001, Finland[18]
Majority of patients are multipara 40 years of old.	-	CISSE CT et al, Dakar, 2004[17]

Excess of molar pregnancies in the Extreme maternal age group	-	Tham B.W. et al, Singapore, 2003[39]
The mean age for both types of HM Was 28 years	-	Osamor JO et al, Nigeria, 2002[40].
Majority of patients between 20 to 25 years	-	Kumar et al, India, 2003[29].

A study from Milan Italy by DICINTIO E et al show that different frequency in the various classes of age is seen through out the world. This is due to the various ages of maximum fertility in various country (Kumar et al, India). The frequency of malignant complications was remarkably high in age superior (or) equal to 40 years, high multipara (CISSE CT et al – Dakar, 2004)[17].

Antecedent Pregnancy:-

Abortions:-

It is believed that poor obstetric histories associated with increased fetal wastage may increase the risk of GTN (Shakuntala Chhabra et al, India, 2003). Abortion was associated with modest increased risk of GTD

in at least seven studies with relative risk ranging from 1.1 to 3.3 (Andrea Alteeri et al, 2003, Lancet).

The risk of both complete and partial molar pregnancy is increased in women with a history of prior spontaneous abortion (Berkowitz et al)[12] But a study from Vietnam by Hamar et al in 1996 showed a relative risk of 0.3 for a history of induced abortions but no associations for spontaneous abortions.

However the association, if any between the no of abortions & same subtypes of GTD could be due to the fact some previous abortions could have been undiagnosed GTD, that the increased the risk of a subsequent GTD.

Previous Molar Pregnancy:

Women with prior molar gestation have a 1% risk of repeat mole, approximately 10 times the risk of molar pregnancy in the general population (Donald P.Goldstein et al)[42], Seventeen out of 21 invasive moles (80.9%) were found in multiple abortions and mechanical interference in form of check curettage, which probably implicates repeated the mechanical interference in the conversion of a mole in to a invasive mole (Kumar N et al)[29].

When a patient had a molar pregnancy she is at an increased risk of having a molar gestation in subsequent pregnancies. After one molar pregnancy, the risk of having molar disease in a future gestation is about 1%. Therefore for any subsequent pregnancy, it seems prudent to undertake the following approach. (Novaks, 14th edition)[38].

1. Perform pelvic ultrasound examination during the first trimester to confirm normal gestational development.
2. Obtain an HCG measurement 6 weeks after completion of pregnancy to exclude occult trophoblastic neoplasia.

Previous Pregnancies:

The effect of reproductive history on the risk of GTD remains unclear. Atleast three cases control studies in GTD showed a relative risk of between 0.6 and 1 for parous women compared with nulliparous women (Brenton LA et al, La Veechia et al, Parazzini F et al)[41], but two other studies reported no association (Matsuura J et al). A separate Analysis for CHM and PHM showed a decrease in risk with number of births for both diseases, although the trend is reduced risk was only significant for PHM (Parazzini F et al) [41]. With respect to choriocorcinoma a case control study showed a relative risk above unity for parous women, although this association was significant only for more than 5 births/ relative risk 5.2). However, since GTD are strongly

associated with pregnancy, the choice of an adequate comparison group is difficult.

Blood Group:-

Women belonging to blood group – A are susceptible to this disease, but the reason is not known (Shaw 13th edition). But study by Bassaw B et al. The incidence was greatest in patients with blood group O. Women with Group A (or) AB blood seemed to have a high risk for HM compared with women with blood group B (or) O. (Relative Risk 0.9 to 4.8). The data also suggested a higher risk for persistent GTD and for CHM compared with PHM. (La Vecchia C et al, Parazzini F et al) [41], When the combination of different maternal and paternal blood group or considered an increased risk was evident for HM for women with group A blood and men with group O or A compared with all other combinations. (relative risk 1.1 to 2.8 AM. Epidanmol. 1985) [36].

Oral contraceptives:

The study by Costa & Dolyle et al, the risk ratio for oral contraceptive use were 0.69 and 0.71 respectively. Use of oral contraceptives was generally associated with an increased risk of GTD, with a relative risks ranging from 1.1 (La Vecchia C et al)[36] 2.6 (Brenton LA et al). The risk generally increased with duration of use.

In largest case control study on Hydatidiform mole (Parazzini F et al)[41] which included 268 cases the relative risk was 1.7 for 1 year of use (or) longer. A relative risk of about 2 was reported for more than 4 years of use for both CHM (Parazzini F 2002)[41] and PHM (Berkowitz et al)[2]. For choriocarcinoma the relative risk ranged from 2 to 6.4 for ever use compared with never use. Only one study reported a relative risk for long duration of use (2.8 for ≥7years of use, (Palmer JR et al, 1999).

The incidence of post molar GTN has been reported to be increased among patients who used oral contraceptives before gonodotrophin remission. However data from both the NETDC and the Gynaecologic, Oncology group (GOG) indicate that these agents do not increase the risk of post molar trophoblastic disease. In addition the contraceptive method didn't influence the mean HCG regression time. It appears that oral contraceptives may be safely prescribed after molar evcuation during the entire interval of hormonal followup.

Host Related Factors:-

There is limited information on other possible etiological risk factors for GTD such as smoking, alcohol consumption, diet, socioeconomic status.

3 studies showed relative risk greater than 2 for HM and choriocarcinoma in women who smoked, with a trend towards increased risk with longer duration of the habit (relative risk for years 4.2;95%). CI 1.6 – 10.8) (Baltazar JC et al, LA Vecchia C et al)[36]. However two other studies found no association between smoking and GTD (Messerti – ML et al) (or) CHM (Bronton LA et al).

An association between high alcohol intake and GTD was found in a study from the USA (relative risk 2.1 >95%, 1.2-3.9 for >53 drinks / week, Brinton LA et al). But no association was reported in a study on HM from Italy (Parazzini et al)[41].

Diet has also been suggested to have an etiological role owing to the high frequency of GTD in some regions, where malnutrition is common. However the result of most been inconsistent. A protective role of a high betacarotene intake has been suggested in a study from Italy. (Parazzini et al relative risk 0.2) [41]. This evidence was not confirmed in another study on PHM from USA. (Berkowitz RS et al)[12].

Clinical Presentation:-

1. Vaginal Bleeding:-

Vaginal bleeding is the most common symptoms causing patients to seek treatment for complete molar pregnancy, previously it was

reported to occur in 97% of the cases, where as currently it is reported to occur in 84% of patients (17). Because vaginal bleeding may be considerable and prolonged , one half of these patients had anemia (hemoglobin < 10gms / 100ml). Currently anemia is present in only 5% of patients.

2. Excessive Uterine Size:-

Excessive uterine enlargement relative to gestational age is one of the classic signs of complete mole, although it was present in only about one half of patients. Currently excessive uterine size occurs in 28% of patients.

3. Pre-Eclampsia:-

Pre eclampsia was once observed in 27% of patients with a complete mole. Preeclampsia is now reported in only 1 of 74 patients with complete mole at the initial visit (17). Although preeclampsia is associated with hypertension, protinuria and hyperreflexia, eclamptic convulsions rarely occur. Preeclampsia develops almost exclusively in patients with excessive uterine size and markedly elevated HCG levels. Hydatidiform mole should be considered whenever preeclampsia develops early in pregnancy.

4. Hyperemesis Gravidorum:-

Hyperemesis is requiring antiemetic (or) intravenous replacement therapy occurs in one fourth of the women with a complete mole, particularly those with excessive uterine size and markedly elevated HCG levels. Severe electrolyte disturbances may develop and require treatment with parental fluids. Currently only 8 % of the patients have hyperemesis.

5. Hyperthyrodism:-

Clinically evident hyperthyrodism is observed in approximately 7% of patients with a complete molar gestation. Galton et al (13) repored 11 patients whose thyroid function test values were elevated before molar evacuation and the thyroid function test values rapidly returned to normal in all patients after evacuation.

6. Trophoblastic Embolization:-

Respiratory distress developed in 2% of patients with a complete mole in the past, but currently rarely occurs. Respiratory distress is usually diagnosed in patients with excessive uterine size and markedly elevated HCG levels.

7. Theca Lutin Ovarian Cysts:-

Prominent theca lutin ovarian cysts (6cm in dia meter) developing in about one half of patients with complete mole. After molar evacuation theca lutin cysts normally regressed spontaneously within 2 to 4 months.

Partial Hydatidiform Mole:-

Patients with partial hydatidiform mole usually do not have the dramatic clinical features characteristics of complete molar pregnancy. In general these patients have the signs and symptoms of incomplete or missed abortion, and the partial mole can be diagnosed after histological review of the tissue obtained by curettage (Novak 14th edition)[38].

In a survey of 81 patients with a partial mole presented with the following features:-

Vaginal bleeding	-	72.8%
Excessive Uterine enlargement	-	3.7%
Pre eclampsia	-	2.5%

None had theca lutein cysts, hyperemesis (or) hyperthyrodisim. Pre evacuation HCG levels were measured in 30 patients and were higher than 1,00,000 mIU/ml in only 2 patients (6.6%).

Study from India in 2003 patients presented with the following clinical features.

Bleeding PV	–	93.5%
Hyperemesis & Hypertension	–	1%
Asymptomatic	–	<10%

Treatment: (Practical Gynec. Oncology – Jonarthan Berck 4th Edition)[38]

After molar pregnancy is diagnosed, the patient should be evacuated carefully for the presence of associated medical complications, including preclampsia, hyperthyrodisim, electrolyte imbalance and anemia. After the patient has been stabilized, a decision must be made concerning the most appropriate method of evacuations.

Suction Curettage:-

Blood should be transfused if required, Suction Curettage is preferred method of evacuation, regardless of uterine size in patients who desire to preserve fertility. It involves the following steps.

1. Cervical dilation :- Induction of abortion of a molar pregnancy with prostaglandins is effective in dilating the cervix prior to evacuation. Prostaglandin vaginal persary for ripening the cervix (or) cervicalgel 0.5mg denoprossone (PGE2) may be warranted in a few

cases in whom cervical dilation with metal dilator may be undesirable (or) difficult due to tight cervical OS.

2. Oxytocin infusion: This is begin in the operating room before the induction of anesthesia (oxtocin dip of 10-20 units (or) more in 500ml of 5% glucose).
3. Suction Curettage: Within a few minutes of commencing suction curettage, the uterus may decreases dramatically in size and the bleeding is usually well controlled. If the uterus is more than 14 weeks in size, one hand may be placed on top of fundus and the uterus massaged to stimulate uterine contraction and reduced the risk of perforation.
4. Sharp Curettage: When suction evacuation is though to be complete, sharp curettage is performed to remove any residual molar tissue. The specimens obtained on SE and sharp curettage should be submitted separately for pathological review.

   Hysterectomy – if the patient diseases surgical stabilization & above 40 years hysterectomy may be performed with the mole in situ. The ovaries may be preserved at the time of surgery, even though theca lutein cysts are present. Prominent ovarian cysts may be decompressed by aspiration.

Prophylatic Chemotherapy:

The use of prophylatic chemotherapy at the time of evacuation of a complete mole is controversial. The debate conerns the wisdom of exposing all patients to potentially toxic treatment, when only approximately 20% are at risk for development of persistent GTN.

In a study of 247 patients with complete molar pregnancy who received a single course of actinomycin Dprophylactically at the time of evacuation, local uterine invasive subsequently developed in only 10 patients (4%) and in no case did metastasis occur. Prophylatic chemotherapy, therefore, not only prevented metastasis, it reduced the incidence and morbidity of local uterine invasion. Therefore prophylaxis may be particularly useful in the management of high risk complete molar pregnancy, especially when hormonal follow up is unavailable (or) unreliable. But in our instution we are not using prophylactic chemotherapy.

Follow up (Novak 14th Edition)^{38}.

After molar evacuation, patients should be monitored with weekly determinations of B subunit HCG levels, until these levels are normal for 3 consecutive weeks, followed by monthly determinations until the levels are normal for 6 consecutive months. The average time to achieve the first normal HCG level after evacuation is about 9 weeks. At the

completion of follow up, pregnancy may be undertaken. After a patient achieves is non detectable HCG levels, the risk of developing tumor relapse is very low and may approach zero.

It appears that oral contraceptives may be used safely after molar evacuation, during the entire interval of hormonal follow up.

AIM OF THE STUDY

The study aims to analyse the epidemiological factors of molar pregnancy and its varied clinical presentation in the Institute of Obstetrics and Gynaecology, Govt. Hospital for women and children, Egmore, Chennai.

MATERIALS AND METHODS

Place of Study:

The study was conducted in the Department of Medical Oncology and department of Obstetrics and Gynaecology, Government Hospital of Women and Children, Egmore, Chennai.

Period of Study:

The cases registered in the dept of medical oncology from July 2006 – July 2007 were taken up for analysis / study.

Sample Size:

The patients who were studied during this period 110 patients. Normal Deliveries during the same period was taken as control group.

Methods:

This is an observational and a prospective study in patients with vesicular mole. (Symptoms, USG, BHCG level, HPE and Macroscopic specimen appearance). Excluded all cases referred for oncology care to IOG.

The patients under the study were admitted in IOG and undergone suction evacuation in this Institute, and its sister Institute KGH

Triplicane. All were registered and followed up in the Department of Medical Oncology IOG, Chennai.

This study was conducted over a period of one year in the medical oncology department of IOG. The patients were inter viewed, examined and their medical records were checked thoroughly. All relevant factors such as age, parity gravida socioeconomic status, general condition, age of menarche were noted. Apart from this their previous obstetric history like the previous pregnancy and their outcome and previous history of vesicular mole was also noted.

The clinical features that were analysed are bleeding PV, Abdominal pain, hyperemesis, the gestational age at the time of diagnosis and the uterine size in relation to gestational age. Details of complication and abnormal presentation are noted.

Serial estimation of serum BHCG and the time taken for the serum BHCG to normalized to <5 MIU was noted. The ultrasonographic findings lik the status of ovaries (the lutein cysts) and the patients diagnosed asymptomatically with only USG findings were analyzed. The chest x-ray findings were noted. The details of patients follow up at the medical Gyneacology department was noted and combined.

Statistical Analysis:

Statistically the chi squared test was used to define the significance of differences between groups.

OBSERVATION

The observational study is a hospital based one and not population based.

Incidence:

During the study period there was a total of 19,944 deliveries in IOG.

Total no of cases of GTD during this one year is 110 of which 20 cases were treated outside and sent here for oncology care. Hence not included in this study. So total number of cases molar pregnancy works upto 90, shows the distribution of molar pregnancy in the study.

TABLE – 1

Total No of cases of molar pregnancy: 90

Complete hydatidiform mole	**81 (out of this 10 remain as PTD)**
Partial hydatidiform mole	9
Chorio Carcinoma	-
Persistent trophoblastic disease	10

Incidence of Molar Pregnancy in IOG

4.51 / 1000 Deliveries

Above table shows the incidence of molar pregnancy as 4.51 per 1000 deliveries our Institute is a tertiary referral center. The above datas are hospital based and not a population based.

Referral:

20 cases of GTD (PTD and choriocarcinoma and (invasive mole) had undergone suction and evacuation (or) dilation and curettage (or) hysterectomy outside, long time ago and referred for complications.

Of the 20 cases referred 3 were referred as cases of choriocarcinoma with only 2 had HPE report. These patients were not included in the study.

AGE:-

Age distribution of molar pregnancy in IOG is as follows:-

TABLE-3

Age	**No of Cases**	**%**
<20	16	17.78%
21-30	64	71.11%
31-39	10	11.11%

Most of the cases of molar pregnancy presented at IOG were between the Age Group 21-30 years which is about 71.11%, 17.78% of cases were below the age of 20 years. No cases registered were beyond 40 years of age. Only about 10 cases registered between 31-40 years.

ANTECEDENT PREGNANCY:-

TABLE-4

Antecedent Pregnancy	**No of Cases**	**%**
Primi	36	40%
G2 (full term)	20	22.22%
G3 (full term)	9	10%
G4 (full term)	3	3.33%
Abortion	18	20%
Previous Molar Pregnancy (included in gravida)	2	2.22%
G6	2	2.22%

Most of the patients in this study were primi i.e., about 40%. Only 3 cases of fourth gravida and 2 cases of 6^{th} gravida were there in our study. About 20% of patients, molar pregnancy is preceded by abortions. Two patients had history of previous molar pregnancies.

TABLE – 5

BLOOD GROUP:-

Blood Group	No	%
O	31	34.44
B	29	32.22
AB	6	6.67
A	24	26.67

Most of the patients blood group were O about 31 patients (34.44%). 32.22% belonged to Group B. 26.27% belonged to Group A and 6.67% of the patients belonged to Group AB. As the spouses blood group, could not be followed the combination could not be studied.

Host related Factors:-

The patients in this study group belong to all castes and creeds as our institute served the population of not only Tamilnadu but also the adjoining state of AP & Karnataka.

Majority belonged to low socioeconomic status of class IV and V with >90% them being literate.

Patients in this study were either pure vegetarians (<10%) (or) taking mixed diet, i.e. occasional non vegetarian diet once (or) twice in a

week. All of them took less of fruits and vegetables. None of the patients gave history of smoking (or) consuming alcohol. Less than 2% of women gave H/o using OCP.

Hemoglobin:-

More than 60% of the patients had Hb more than 10gms/dl ranging from 6.5 to 13.5 with an average of 10gm/dl. This shows a reduction of patient presenting with Anemia.

Menarche:-

The average age of menarche the patients with molar pregnancy was 13 years, ranging from 11-16 years and most of them i.e. more than 90% had normal menstrual cycles.

Clinical Features:-

TABLE-6

Clinical Presentation:-

Clinical Presentation	No	%
Bleeding PV	65	72.22%
Passing Vesicles	3	3.33%
Spotting	12	13.33%
USG	11	12.22%
Elevated BHCG	2	2.22%
Other Presentation	1 (thyrotoxicosis)	
PIH	2	

This study shows 72.22% presented with bleeding PV and a few 3% had H/o passing vesicles 13.33% of the patients presented with minimal bleeding of just spotting.

Interesting features of the clinical presentation was that 11 patients in our hospital were admitted with no symptoms of molar pregnancy but only with ultrasonographic evidence and elevated βHCG level. They were diagnosed to have molar pregnancy incidentally when they underwent routine USG in their first trimester of pregnancy. In coming

years we are likely to encounter more number of such asymptomatic cases of molar pregnancies.

The prognosis of these asymptomatic cases were excellent, they all had βHCG values less than 1lakh IU unit except one case, and all cases including the one with high βHCG level normalize with in average period of 6 wks and none of them had persistent trophoblastic disease.

Only two cases presented with preclampsia, and one of the patient presented with features of thyrotoxicosis.

Period of Amenorrhoea:

TABLE-7

Period of Amenorrhoea	No	%
2MA	19	21.11%
3MA	31	34.44%
4MA	25	27.80%
5MA	13	14.44%
6MA	2	2.22%

Average no of Weeks: 12.86 weeks

More than 50% of the patients presented at 3 month and 4 months of amenorrhoea and only 2 patients presented at 6 months of amenorrhoea and the average period of amenorrhoea when patients presented was 12.86 weeks.

TABLE-8

Uterine Size in relation to Gestational Weeks

Uterine size	No	%
Corrosponding	30	33.33%
Big (more)	45	50%
Small (less)	15	16.67%

The uterine size corresponds to the period of amenorrhoea in 33.33% of patients. It was bigger than the period of amenorrhoea in 50 % of patients and 16.67% had uterine size smaller than the period of amenorrhoea. Of 45 patients with large uterine size about 14 had BHCG value more than 1Lakh mIU/Lit.

USG:-

TABLE-9

USG	No	%
Theca lutein cyst	24	26.67%
Bilateral Theca lutein cyst	18	75%
Unilateral Theca lutein cyst	6	25%

USG is the gold standard for the diagnosis of vesicular mole with typical “snow storm” appearance. The patients in this study were all subjected to sonographic examination either with symptom (or) Asymptomatically.

24 patients of this study i.e. 26.67% had theca lutein cysts of which 6 were unilateral and 18 had Bilateral lutein cysts. 10 patients who had persistent trophoblastic disease 4 had theca lutein cysts.

One patient was diagnosed to have ? cornual pregnancy (Lt Cornua) with partial molar changes, the patient had bleeding PV on & off for 1 month duration, done suction evacuation – HPE report showed that cornual pregnancy was a partial mole. There was problem in curetting the

uterus because of cornual location, hence injection methotrexate given. Her βHCG value normalized with in 8 weeks.

One of the Patient had twin gestation of which one was a molar pregnancy, patient became symptomatic at 3 months of amenorrhoea with C/o of spotting PV, the USG done and diagnosed of having twin, one of which is vesicular mole, hence pregnancy terminated and she was followed up.

Chest x-ray:-

All patients were subjected to chest x-ray before suction evacuation and none of them had any abnormality like metastasis (or) pulmonary embolism.

Treatment:-

Patients diagnosed to have molar pregnancy were admitted. Basic investigations like Hb, PCV, Urine Analysis, Renal and Hepatic parameters were taken patients blood grouping and Rh typing done for all cases. An USG to confirm diagnosis, Chest X-ray and ECG for Anaesthetic purpose were taken. Patient had their serum βHCG done outside whenever affordable. About 55% of the patients had their preevaluation βHCG done outside.

If the patients had profuse bleeding, on examination the OS was open, they underwent emergency suction evacuation. Others underwent elective suction evacuation. Their cervix was softened and dilated with either misoprostal (PGE1) 200-400 μg vaginal tablets (or) cerviprime gel (PGE2) 0.5mg (or) osmotic dilators like laminaria tents were used.

During the procedure a unit of Blood cross matched and kept ready for transfusion. Whenever need arises depending on the bleeding during the procedure (or) whenever the patients pre evacuation hemoglobin was low, blood transfusion was given. Suction evacuation done under IV sedation. Oxytocin 20 units in 500ml of 5% dextrose started in all cases prior to giving IV Anaesthesia after cervical dilatation. At the end of the procedure 0.2mg of IV methergine given. All Rh negative mothers were given Anti D immunoglobulin depending on the period of Amenorrhoea 150 μg IM.

None of the patients developed any anaesthetic (or) procedural complications like shock, haemorrhage perforation (or) embolism etc.

Follow Up:

TABLE-10

β***HCG Levels:- Follow Up after Evacuation.***

Weeks	No of Cases	%	Average Weeks
<9wks	33	52.38%	6.9wks
9-12wks	20	31.25%	11.15wks
>13-16wks	6	9.52%	15.3wks
>16wks	5	7.93%	18.4wks

83% have average of 7.68 wks for βHCG to normalize, patients were asked to come weekly till their βHCG values normalize for three consecutive weeks and then given monthly follow up for one year. Patients were put on OCP and they were asked to do βHCG level outside. Each time they came for follow up, patients were subject to abdominal examination, sonographic examination, and if needed chest x-ray was taken. If patients could not do βHCG outside, they were subjected to urine βHCG examination in dilution. Serum βHCG value of <5m IU unit was taken as normal.

Only about 71% of the patients had serum βHCG values done outside in their follow up. Another 5% of the patient underwent urine βHCG examination in dilution. In 52% of the cases βHCG normalizes

within average of 6.9 weeks, and 31.25% of cases βHCG normalized within 12 weeks. Only 17% of cases βHCG normalized after 16weeks of followup. 83% of patients studied had their βHCG normalized within average period of 6.9 weeks.

TABLE-11

Persistant Trophoblastic Disease:-

Method of Diagnosis	**No of PTD**	**%**
Plateauing of βHCG	8	80%
Presence of symptoms (irregular vaginal bleeding)	2	20%
Invasive Mole	5	50%

TABLE-12

Persistant Trophoblastic Disease

Drug Taken	Complete Remission	Partial Remission
Methotrexate wkly Cases With Folic acid	7 Cases	3
Actinomycin - D Case	2 Cases	1
Multi Drug Etoposide, Cisplatin	1 Case	

Persistent Trophoblastic Disease:-

Of 90 cases 10 patients went in for persistant trophoblastic disease which is about only 11.1% out of 10 cases of PTD – 8 cases are diagnosed by persistently increased βHCG levels, and 2 cases are diagnosed as PTD due to persistence of symptoms. Out of 10 cases of PTD – five cases are invasive moles.

Out of 10 cases of persistent trophoblastic disease, seven cases the βHCG level normalizes with single agent chemotherapy regimen. (Methotrexate + folic acid weekly) with average of 12.28 weeks.

In the remaining 3 cases, 2 cases βHCG normalized with Actinomycine – D. In one case of PTD diagnosed at 10 weeks after

evacuation due to persistently high βHCG – the Methotrexate regimen started, after 2 weeks of starting Methotrexate – due to plateauing of βHCG – Actinomycin – D added again due to persistence of βHCG – Cisplatin + Etoposide regimen started, after 6 weeks of starting this combination Chemotherapy βHCG normalized.

RESULTS AND ANALYSIS

As our institute is a tertiary referral center, the below data are hospital based data and not a population based.

Incidence:

During the study period there was a total of 19,944 Deliveries in Institute of Obstetrics and Gynaecology.. Total no of Gestational Trophoblastic diseases during this one year is 110 of which 20 cases were referred from outside with complications treated outside. Hence not included in this study. The total number of molar pregnancy hence works upto 90. Table 1 shows the distribution of molar pregnancy in IOG.

TABLE-1

Total No of cases of Molar pregnancy	–	90
Complete Hydatidiform mole	–	81 (out of this 10 remains as PTD)
Partial hydatidiform mole	–	9
Choriocarcinoma	–	-
Persestant trophoblastic Disease	–	10

Incidence of Molar Pregnancy in IOG.

4.51 / 1000 Deliveries

Table 2 shows the incidence of molar pregnancy in IOG during the study period as 4.51 / 1000 deliveries. The study by Kumar et al from New Delhi[29] shows the incidence of 1.31 / 1000 live births. This variation in the incidence rate in molar pregnancy may be due to the differences between reporting population and the hospital based data.

The regional differences in the frequency of hydatidiform mole have been attributed to genetic and environmental factors (or) the interaction of both.

This high incidence when compared to incidence in North America and UK (2 in 1000) can be attributed to the factor that Asian descent and especially Indian's (Cheah PL et al Malaysia, Wales study) are at increased risk for GTD. As it is suggested that GTD occur especially in rice eaters (Jeffcoate)[30]. Hence the increase in incidence of molar pregnancy among our population, whose stable food is rice.

When compared to previous years incidence in IOG – which was about 4.8 in 2004, 5 in 2005, the incidence of molar pregnancy has come down. This is due to literacy, awareness, socioeconomic improvement availability of medical facilities, their easy approachability and also due to increased rate of permanent method of sterilization. This is similar to a Korean study by KIM SJ et al 1998[31] states that Koreas socioeconomic

improvement in recent decades also contributed to decrease in the incidence of GTD and increased survival rates.

Referral:-

As our's was a tertiary referral center, 80% of the cases were diagnosed outside as vesicular mole and referred early without any intervention. These cases subsequently underwent suction evacuation, registered and followed up.

20 cases of GTD (PTD, Choriocarcinoma and invasive mole) who had undergone suction evacuation (or) dilatation and curettage (or) hysterectomy outside and then referred here. Of the 20 cases referred from outside 3 were found to be choriocarcinoma. All these patients were invariably treated with chemotherapy and once remission occurred they were followed up with ocpills. Their morbidity (more days of hospital stay) & mortality was definitely higher compared to the study group.

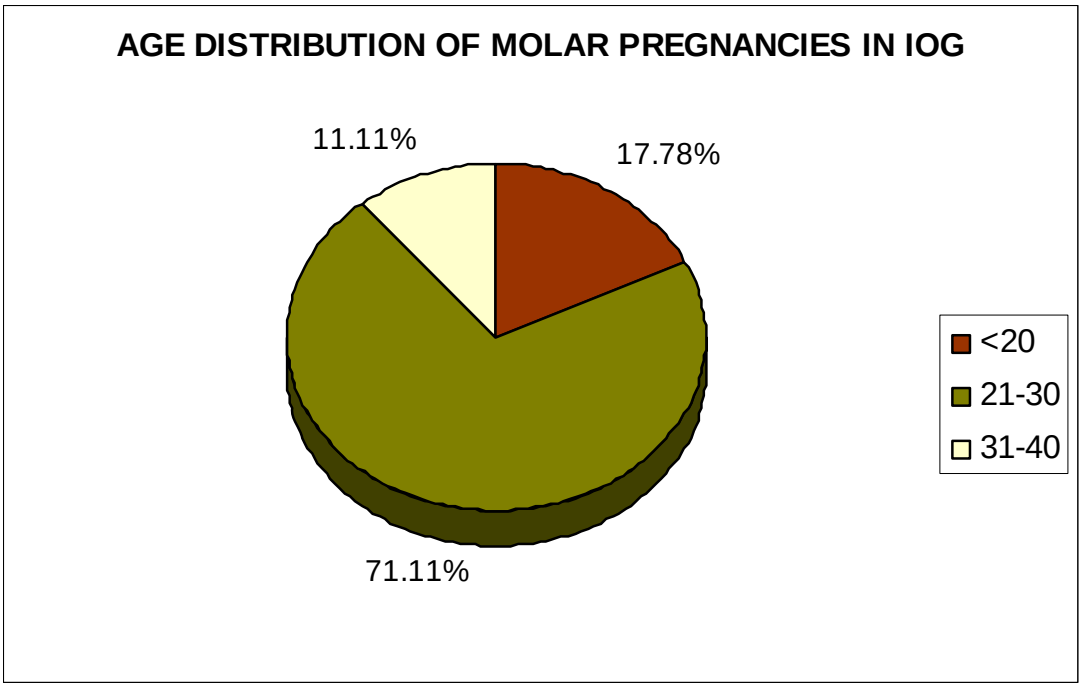
The Age Distribution of molar pregnancy in IOG is as follows.

TABLE-3

Age	No of Cases	%
≤20	16	17.78%
21-30	64	71.11%
31-40	10	11.11%

Most of the cases of molar pregnancy presented at IOG were between the age group of 21-30 years i.e. about 71.11%. And 17.78% of cases presented at earlier age of less than (or) equal to 20 years. No cases registered were beyond the age of 40 years.

The age specific distribution of patients shows most of the patients belongs to age group 21-30 years. Average age was 24.56 years. The fertility at the National level which reaches maximum at 20-25 age group, which was reflected in our data.



Maternal age is a well estabilized risk factor for both HM & Choriocarcinoma with woman younger than 20 and particularly woman older than 40 years.shows stronger risk (Lancet 2003). This study did not have patients above 40 years, but there were 17.8% of cases below the age of 20 years.

TABLE - 4

Age Group in Years	Study Group 90	Control Group 19944	Differences in two groups
≤20 years	14 (15.6%)	4432 (22.22%)	Z1.38 P0.17 NS
21-29 years	67 (74.4%)	14512 (72.76%)	Z0.23 P0.82 NS
> 30 years	9 (10%)	1000 (5%)	Z1.96 P0.05 S

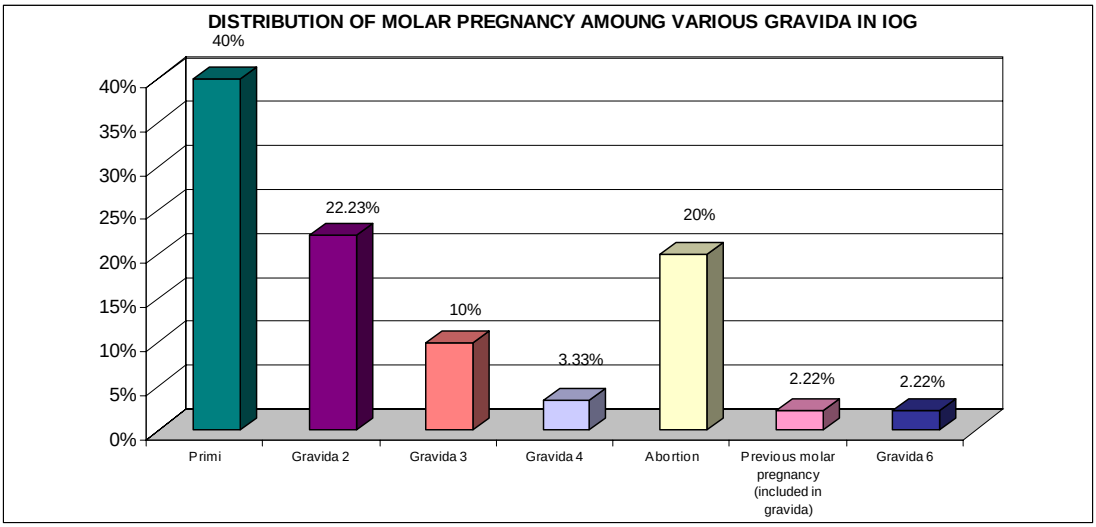
NS – Not Significant
S – Significant

Above table shows significant risk of about 1.96 times was found in women more than 30 years.

Antecedent Pregnancy:-

TABLE - 5

Antecedent Pregnancy	No of Cases	%
Primi	36	40%
Gravida 2	20	22.227%
Gravida 3	9	10%
Gravida 4	3	3.33%
Abortion	18	20%
Previous molar pregnancy (included in gravida)	2	2.22%
Gravida 6	2	2.22%



1. Abortions:-

18 out of 90 cases of molar pregnancy i.e. 20% gave a history of previous abortion. Abortion was associated with a modest increased risk of GTD in at least 7 studies.

Similar finding was seen in the study group from Delhi Where 36.9% of the patients with GTD had previous history of abortion as against 9.3% of the patient who had normal deliveries in their institute.

This shows the likelihood of abnormal oocyte to be fertilized is increased in those woman with previous history of abortions (or) these abortions were actually undiagnosed molar pregnancies.

2. Previous Molar Pregnancy:-

This study revealed that about 2.22% of the patients with molar pregnancy gave history of previous molar pregnancy. A previous history of molar pregnancy is the second best established risk factor (Buckley et al)[17] the risk of Hydatidiform mole in a subsequent conception is about 1% (Buckley JD et al, Matsui et al).

This study also reflects a similar finding of 1-2, increased risk of developing molar pregnancy in patients with history of previous molar pregnancy.

Previous Pregnancy:-

About 40% of the patients in this study were primigravida and 20% of the patients were 2nd gravidas with Antecident term deliveries. The effect of the reproductive history on the risk of GTD remains unclear (Lancet 2003). As GTD are strongly associated with pregnancy the choice of adequate comparison group is difficult. The increase incidence of molar pregnancy in primigravida may be attributable to the younger age of these patients i.e. 20% were below the age of 20 years. Similarly the incidence increased in multiparous may also be attributed to their increasing age, where chances of fertilization of abnormal oocyte is always increased.

TABLE - 6

Distribution of Molar Pregnancy among various Gravidas:

Previous Pregnancy	Study Group 90	Control Group 19944	Differences in P value
Primi	36 (40%)	10218 (51.2%)	Z=2.02, P = 0.04 S
Gravida 2	20 (22.22%)	7326 (36.73%)	Z=2.75, P=0.07 S
Gravida 3	9 (10%)	1902 (9.54%)	Z=0.00, P=1 NS
Gravida 4	3 (3.33%)	402 (2.01%)	Z=0.16, P=0.87 NS
Gravida 5	-	66	-

NS - Not Significant
S - Significant

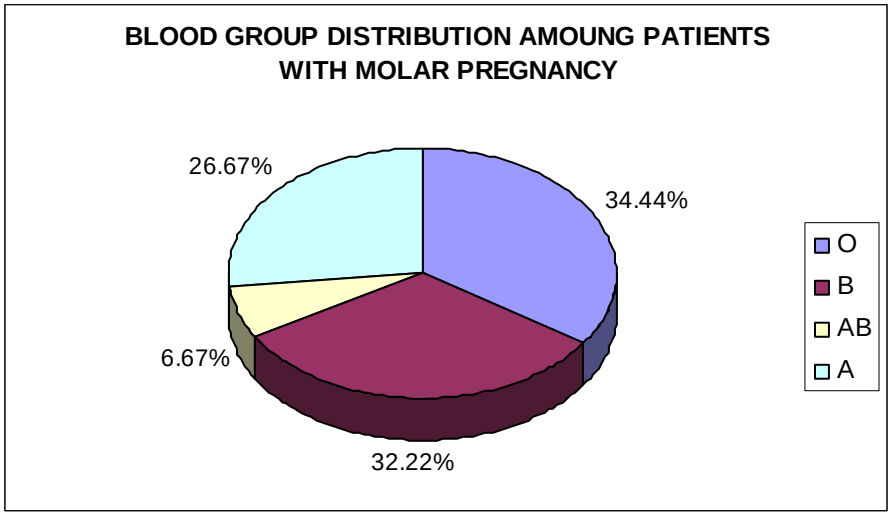
In comparison with control group and the study group, the P value in primigravida is 0.04 which is significant. And also in second gravida study group (22.22%) when compared with control group (36.73%) the P value is 0.07, significant.

Blood group Distribution among patients with molar pregnancy.

TABLE - 7

Blood Group	No	%
O	31	34.44 %
B	29	32.22%
AB	6	6.67%
A	24	26.67%

Most of the patients blood group was O about 31 patients (34.44%). 32.22% belonged to Group B. 26.67% belonged to Group A and 6.67% of the patients belonged to Group AB. As the spouses blood group, could not be followed the combination could not be studied. Hence no conclusive implication of this information could be associated with molar pregnancy.



Host Related Factors:

The Patients in this study group belong to all castes and creeds as our institute served the population of not only Tamilnadu but the adjoining state of AP and Karnataka.

Majority belonged to low socioeconomic status of class IV, V with >90% of them being literate.

Patients in this study were either pure vegetarians (<10%) (or) taking mixed diet i.e. occasional non vegetarian diet once (or) twice in a week. All of them took less of fruits and vegetables. None of the patients gave history of smoking (or) consuming alcohol. Less than 2% of woman gave H/o using oral contraceptive pills.

Haemoglobin:-

More than 60% of the patients had Hemoglobin more than 10gms/dl ranging from 6.5 to 13.5 with an average of 10gms/dl. This shows a reduction of patient presenting with anaemia.

Menarche:-

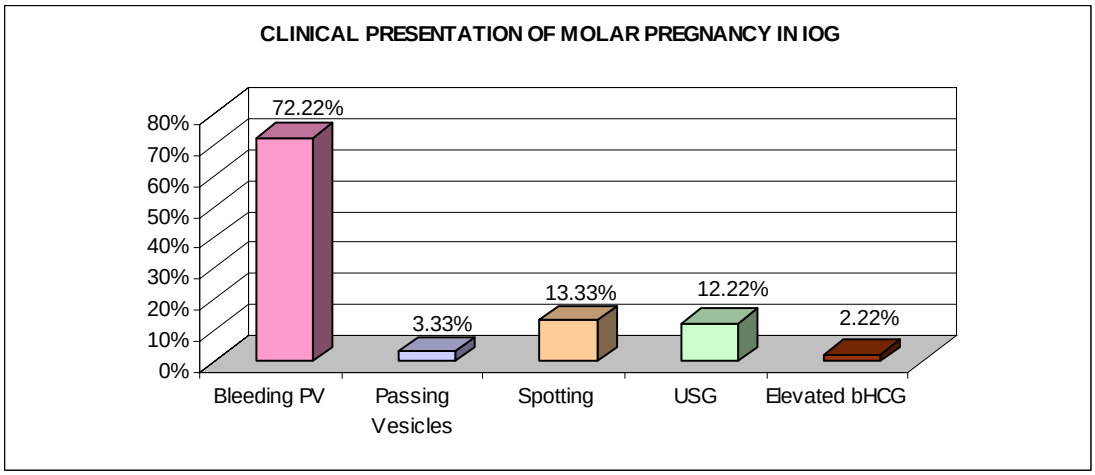
The average age of menarche the patients with molar pregnancy was 13 years, ranging from 11-16 years and most of them i.e. more than 90% had normal menstrual cycles.

TABLE - 8

Clinical Presentation:-

Clinical Presentation	No of Cases	%
Bleeding PV	65	72.22%
Passing Vesicles	3	3.33%
Spotting	12	13.33%
USG	11	12.22%
Elevated βHCG	2	2.22%
Other Presentation	1 (Thyrotoxicosis)	
PIH	2	

This study shows 72.22% presented with bleeding PV and few 3% had H/o passing vesicles 13.33% of the patients presented with minimal bleeding, of just spotting.



Interesting Feature of the clinical presentation was that 11 patients in our hospital were admitted with no symptoms of molar pregnancy but only with ultrasonographic evidence and elevated βHCG level. They were diagnosed to have molar pregnancy incidentally when they underwent routine USG in their first trimester of pregnancy. Incoming years we are likely to encounter more number of such asymptomatic cases of molar pregnancy. The study conducted in USA about 50% of patients presented asymptomatically. (Pennsylvania 1999). A finding from a study by Kumar et al from New Delhi[29], India, Showed about 6.5% of cases which presented without any symptoms.

The Prognosis of these Asymptomatic cases were excellent, they all had βHCG values less than 1 lakh IU unit except one case and all cases including the one with high βHCG level normalized within the

average period of 6 weeks, and none of them had persistent trophoblastic disease.

Only two cases presented with preeclampsia, and one of the patient presented with features of thyrotoxicosis, all the three relieved of symptoms after evacuation. Even the number of patients with Anemia was comparatively less. All these point to the better medical facilities available in a developing country like India.

PERIOD OF AMENORRHEA

TABLE – 7

Period of Amenorrhea	No of Cases	%
2MA	19	21.11%
3MA	31	34.44%
4MA	25	27.80%
5MA	13	14.44%
6MA	2	2.22%

Average No of weeks: 12.86 weeks-

More than 50% of the patient presented at third and fourth month of Amenorrhea and only two patients presented at 6MA. The average period of Amenorrhea when patients presented at IOG with molar pregnancy was 13 weeks (12.86wks).

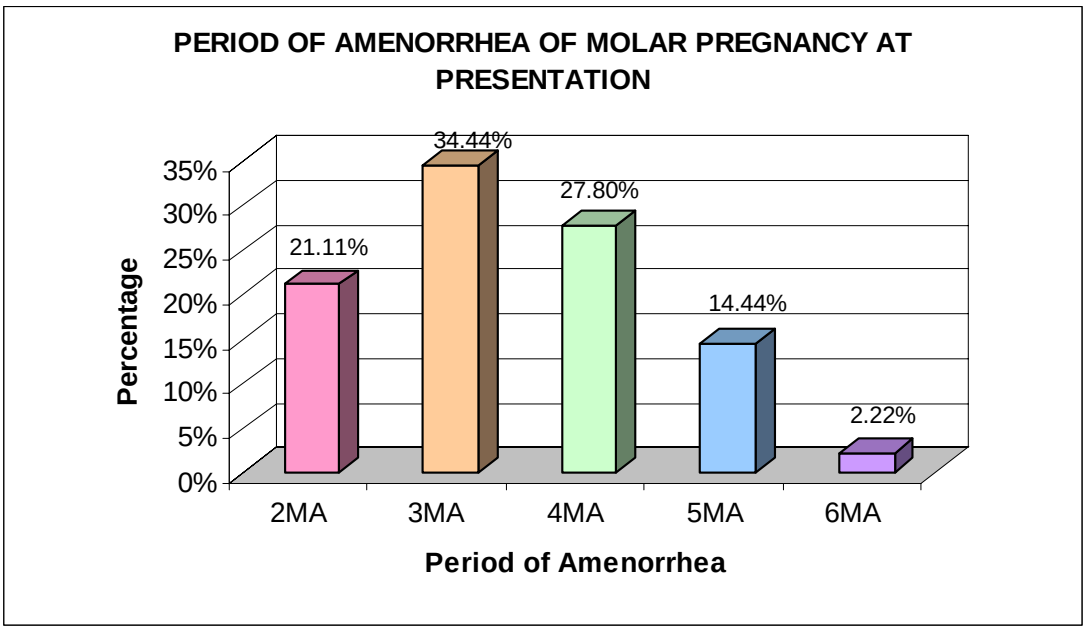

PERIOD OF AMENORRHEA OF MOLAR PREGNANCY AT PRESENTATION
Percentage
35%
30%
25%
20%
15%
10%
5%
0%
21.11%
34.44%
27.80%
14.44%
2.22%
2MA
3MA
4MA
5MA
6MA
Period of Amenorrhea

TABLE - 8

Uterine Size in Relation to the Period of Amenorrhea

Uterine Size	No of Cases	%
Corresponding	30	33.33%
Big (more)	45	50%
Small (less)	15	16.67%

The uterine size corresponds to the period of Amenorrhea in 33.33% of patients. It was bigger than the period of Amenorrhea in 50% of patients and 16.67% of patients had uterine size lesser than the period of Amenorrhea. Of 45 patients with large uterine size about 14 had βHCG value more than 1 lakh mIU/ml. The βHCG was elevated with large uterine size.

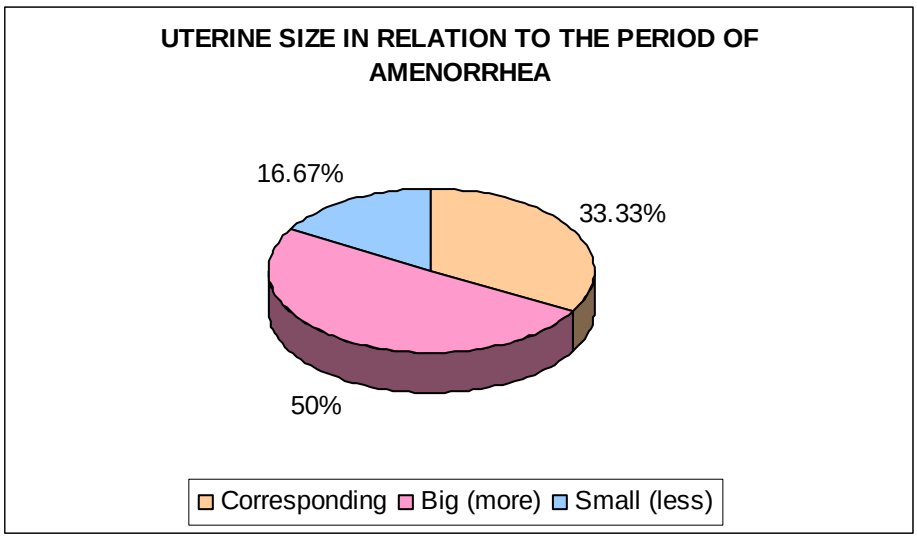


TABLE - 9

USG	No of Cases	%
Theca Lutein Cyst	24	26.67%
Bilateral Theca Lutein Cyst	18	75%
Unilateral Theca Lutein Cyst	6	25%

USG is the gold standard for the diagnosis of vesicular mole with typical “snow storm” appearance.

The patients in this study were all subjected to sonographic examination either with symptoms (or) Asymptomatically.

24 patients of this study i.e. 26.67% had theca lutein cysts of which 6 were unilateral and 18 had bilateral theca lutein cysts. One patient was diagnosed to have corneal pregnancy (left cornual) with partial molar changes, The patient had bleeding PV on & off for 1 month duration, undergone suction evacuation at IOG. HPE report showed that the cornual pregnancy was a partial mole. There was problem in curetting the uterus hence injection Methotrexate given. Her βHCG value normalized with in 8 weeks.

One of the patient had twin gestation of which one was a molar pregnancy. Patient became symptomatic at 3MA with complaints of spotting PV. Hence pregnancy terminated and she was follow up.

Chest X-Ray:-

All patients were subjected to Chest X-ray before suction and evacuation and none of them had any abnormality like metastasis (or) pulmonary embolism.

Treatment:

Patients diagnosed to have molar pregnancy were admitted. Basic investigations like Hb%, PCV, Urine analysis, Renal and Hepatic Parameters were taken. Patients blood was grouped and typed. An USG to confirm diagnosis. Chest X-ray and ECG for anaesthetic purpose were taken. Patients had their serum βHCG done outside whenever affordable. About 55% of the patient had their preevacuation βHCG done outside.

If the patients had profuse bleeding, on examination if the OS was open, they underwent emergency suction evacuation. Others underwent elective suction evacuation. Their cervix was softened and dilated with either Misoprostal (PGE1) 200-400 μg vaginal tables (or) cerviprime gel (PGE2) 0.5mg (or)Osmotic dilators like laminaria tents were used.

During the procedure a unit of blood cross matched and kept ready for transfusion. When ever need arises depending on the bleeding during the procedure (or) whenever the patient preevacuation hemoglobin was low, blood transfusion was given. Suction evacuation done under IV sedation. Oxytocin 20 units in 500ml of 5% dextrose started in all cases prior to giving IV anaesthesia.

At the end of the procedure 0.2mg of IV Methergine given. All Rh negative mothers were given injection Anti D immuno globulin depending upon the period of Amenorrhea (150μgmIM).

None of the patients developed any anaesthetic (or) procedural complications like shock, Haemorrhage perforation (or) embolization etc.

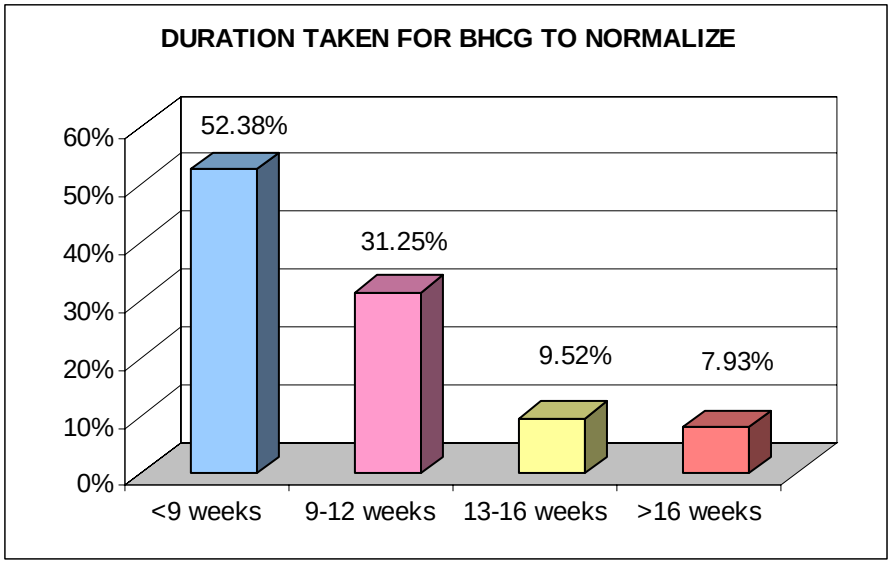
TABLE – 10

Follow Up:-

βHCG – Follow up after Evacuation.

Weeks	No of Cases	%	Average Weeks
<9 weeks	33	52.38%	6.9weeks
9-12 weeks	20	31.25%	11.15 weeks
13-16 weeks	6	9.52%	15.3 weeks
>16 weeks	5	7.93%	18.4 weeks

83% have average of 7.68 weeks for βHCG to normalize, patients were asked to come weekly full their βHCG Values normalize for three consecutive weeks and then given monthly follow up for one year. Patients were put on OCP and they were asked to do βHCG outside. Each time they came for follow-up, patients were subjected to abdominal examination, sonographic examination, and if needed X-ray chest was taken. If the patient could not do βHCG outside they were subjected to urine βHCG examination in dilution. Serum βHCG value of <5mIU/I was taken as normal.



Only about 71% of the patients had serum βHCG values done outside in their follow-up. Another 5% of the patient underwent urine βHCG examination in dilution in 52% of the cases βHCG normalizes within average of 6.9 weeks, and 31.25% of cases βHCG normalized with in 12 weeks. Only 17% of cases βHCG normalized after 16 weeks of follow up. 83% of patients studied had their βHCG normalized within average period of 6.9 weeks.

TABLE – 11

Persistent Trophoblastic Disease:-

Method of Diagnosis	No of PTD	%
Plateauing of βHCG	8	80%
Persistent of Symptoms – Irregular Bleeding PV	2	20%
Invasive Mole	5	50%

TABLE - 12

Total No of Persistent Trophoblastic Disease – 10

Drug Taken	Complete Remission	Partial Remission
Methotrexate wkly Cases With Folic acid	7 Cases	3
Actinomycin – D Case	2 Cases	1
Multi Drug Etoposide, Cisplatin	1 Case	

Persistent Trophoblastic Disease:

In my study, of 90 cases of GTD, 10 patients went in for persistent trophoblastic disease which is about 11.1%. Seckl et al report the incidence of a complete hydatidiform transformed into malignant GTN is 15%. The incidence of PTD in Kumar et al[29] study in India is about 12.12% among GTD cases. Out of 10 cases of persistant trophoblastic disease 2 cases were diagnosed as PTD due to complaints – Irregular bleeding PV and 8 cases are diagnosed due to persistently increased βHCG values. Out of 10 cases of PTD – 5 Cases are invasive moles.

In my study out of 10 cases of persistent trophoblastic disease the complete remission occurred in seven cases with only single agent chemotherapy (Methotrexate + folic acid weekly regimen) with average of 12.28 weeks.

In the remaining 3 cases (30%), 2 cases (20%) complete remission occurred with Actinomycin D. In one case of PTD diagnosed at 10 weeks after evacuation due to persistently high βHCG – Partial response to Methotrexate and due to plateauing of βHCG – Actinomycin added. Again due to persistence of high βHCG – cisplatin + etoposide regimen started, after 6 weeks of starting this combination chemotherapy the patients attained complete remission.

In my study the persistent trophoblastic disease (10 cases – 100%) attained complete remission either with single drug therapy (70%) (or) multidrug therapy (30%). In the study by Kumar et al New Delhi – By early detection and treatment of persistent trophoblastic disease they achieved 95.7% complete response and 6.5% partial response.

SUMMARY

- The incidence of molar pregnancy over past 10 years had definitely come down. The development and improvement of suction curettage, termination of pregnancy, contraceptive techniques, diagnostic imaging, and biochemical testing have been associated not only with a fall in the birth rates, but also with a reduction in the incidence of trophoblastic disease.
- Delayed referral and improper follow up of patients may lead to complications. Hence the need to educate the patients on the risk factors, early signs and symptoms, the need for prompt referral and proper follow up. This will not only bring down the mortality but also the morbidity of GTD.
- In considering the clinical presentation, 12% of the patients were asymptomatic diagnosed during their routine Antenatal USG. These patients had good prognosis. So with the current widespread use of Ist trimester USG, can detect abnormal pregnancy like molar pregnancy earlier.
- The risk of molar pregnancy is more in teenage pregnancy and in old age pregnancy. This can be prevented by improving the female

literacy and adolescent health education. Permanent sterilization after completion of family will bring down the old age pregnancy.

- ❖ Blood grouping did not throw any light about the risk of GTD.
- ❖ Patients with uterine size larger than the period of Amenorrhoea had higher βHCG levels and increased incidence of PTD. By educating the health care providers, and patients about early signs and symptoms, of GTD like hyperemesis, first trimester spotting, early onset PIH, will help in early referral to higher centers.
- ❖ The need for tertiary care for all patients with molar pregnancy will bring down the morbidity of this disease.
- ❖ Careful and reliable Human Chorionic Gonadotrophin monitoring is essential for the early detection of post molar persistent trophoblastic tumor.
- ❖ If PTD diagnosed during follow up and treated earlier, the low risk trophoblastic disease are 100% curable.
- ❖ Gestational trophoblastic tumors have an excellent prognosis if diagnosed and treated in time, and the potential for child bearing can be maintained.

CONCLUSION

- Early pregnancy USG will help in early recognition of abnormal pregnancy like molar pregnancy, this will definitely reduce the morbidity of this curable disease.

- Proper follow up helped in recognizing the cases of persistent trophoblastic disease early.

- If Persistent Trophoblastic Disease diagnosed during follow up and treated earlier, the low risk trophoblastic diseases are 100% curable.

PROFORMA

Name: Age: IP No:

Socioeconomic Status

Literacy

Nutritional History

Menstrual History Menorche Menstrual Cycles

Obstetric History

- ✓ Gravida
- ✓ Abortions
- ✓ Previous molar pregnancies

Blood Group

USG

CXR

Hemoglobin

Pre evacuation βHCG

Gestational age at the time of Diagnosis

Uterine size in relation with gestational age

- ✓ Corresponding Gestational age
- ✓ Large than the Gestational age
- ✓ Small than the Gestational age

Previous history of any contraception

Clinical Presentation

- ✓ Bleeding PV
- ✓ Detected without any complaint

Associated complaints

- ✓ Hyperemesis
- ✓ Hypertension

Follow up

KEY WORDS

GTD	-	Gestational Trophoblastic Disease (CHM, PHM, PTD, Choriocarcinoma and invasive mole)
CHM	-	Complete Hydatidiform Mole
PHM	-	Partial Hydatidiform Mole
PTD	-	Persistent Trophoblastic Disease
Molar Pregnancies	-	Complete hydatidiform mole and partial hydatidiform Mole
IOG	-	Institute of Obstetric and Gynecology
OCP	-	Oral Contraceptive Pills.

BIBLIOGRAPHY

1. Amir.SM, Osathanondh R, Berkowitz RS, Goldstein D.P. Human chorionic gonadotrophin and thyroid function in patients with hydatidiform mole. Am.J Obstet. Gynecol. 1984;150:723-728.

2. Berkowitz RS, Goldstein D.P. The management of Molar pregnancy and gestational trophoblastic tumors. In Knapp RC, Berkowtiz RS, eds Gyneacologic Oncology 2nd edition 1993;328-338.

3. Bagshawe KD. Risks and prognostic factors in trophoblastic Neoplasia Cancer 1976. 38:1373-1385. 1994; 39;155-162.

4. Berkowitz RS, Cramer DW, Bernstein MR, et al risk factors for complete molar pregnancy from a case control study AMJ Obstet. Gynecol. 1985;52:1016-1020.

5. Berkowitz RS, Goldstein D.P., Presentation and management of molar pregnancy. In Haneock BW, Newlands ES, Berkowitz RS, eds Gestational Trophoblastic diseases 1997; 127-142.

6. Berkowitz RS, Goldstein D.P., Marean AR, et al oral contraceptives and post molar trophoblastic disease obstet. Gynecol. 1981; 58: 474-477.

7. Bunholz J, Goldstein D.P, Berkowitz RS, et al. Pelvic ultrasonographic and the management of gestational trophoblastic disease. Gynecol. Oncol. 1983;15:403-412.

8. Bagshawe K.D., Treatment of high risk choriocarcinoma J Reprod Med 1984;29:813-820.

9. Bolis G, Bonazzi C, Landoni F, et al EMA – Co-regimen in high risk gestational trophoblastic tumor. Gynae. Oncol 1988;31:439-444.

10. Bagshawe KD, Dent J, Newlands ES, Begent RHJ, Rustin GIS. The role of low dose methotrexate and folic acid in gestational trophoblastic tumors. Br.J Obstet Gynaecol 1989;96:795.

11. Braken MB. Incidence and etiology of hydatidiform mole an epidemiological review, Br. J obstet Gynecol. 1987;94:1123.

12. Berkowitz RS, Ozturk M, Goldstein DP, Bernstein MR, Hiul Wards JR, Human Chorconic gonadotrophin and free subunits serum levels in patients with partial and complete hydatidiform moles. Obstet gynaecol, 1989;74:212.

13. Benson CB, Genest DR, Beinstein MR, Soto-Wright V. Sonographic appearance of first trimester complete hydatidiform moles Ultrasound. Obstet Gynaecol. 2000;16:188-191.

14. Curry SL, Schlaerth JB, Kohorn EL, Boyce JB, Gosett et al Hormonal contraception and trophoblastic sequelae after hydatidiform mole (a Gynaecol. Oncology group study) AMJ Obstet. Gynecol. 1989;160:805-811.

15. Cole LA, Butler S. Detection of HCG in Trophoblastic disease the USA, HCG reference services experience. J. Reproductive Med 2002;47:433-444.

16. Curry SL, Hermmond CB, Tyrey L, Geasman WT, Parker RT Hydatidiform Mole:- Diagnosis, Management, and long term followup of 347 patients. Obstet. Gynaecol. 1975;45:1-8.

17. Cisse CT. Lon, Moreau JC, et al clinique – de gynecology Dakar, BP – 15, 745.

18. Loukovaara M, Pukkala E et al, Epidemiology of Hydatidiform mole in Finland, 1975; 2001.

19. Daftary SN, Padubidri VG. Trophoblastic diseases: In Padubidri VG, Daftary SN (eds) shows text book of Gynaecology 13th edition New Delhi. Elserver India Ltd 2004;248-259.

20. Fine C, Bundy AL, Berkowitz RS, Bosewell SB et al sonographic diagnosis of partial hydatidiform mole Obstet. Gyanecol. 1989;73:414-418.

21. Feltmate CM, Batorfi J, Fulop.V, Goldstein DP et al Human Chorionic Gonodatrophin followup in patients with molar pregnancy a time for reevaluation. Obstet Gynaecol. 2003;101: 732-736.

22. Feltmate CM, Genest DR, Wise L, Bernstein MR, Goldstein DP placental site trophoblastic tumor. 17 years experience at the new England trophoblastic disease center Gynaecol. Oncol. 2001;82:415-419.

23. Fisher RA, Hodges MD, New Lands ES, Familial recurrent hydatidiform mole, a review J Reprod Med 2004;49:595-601.

24. Goldstein DP, Berkowitz RS, Prophylactic chemotherapy of complete molar pregnancy semin Oncol 1995;22:157-160.

25. Genest DR, Laborde O, Berkowitz RS, et al. A clinicopathological study of 153 cases of complete hydatidiform mole. Obstet. Gynaecol. 1991;78:402-409.

26. Goldenstein DP, Vzanten Przybysz I, Bernstein MR, et al revised FIGO staging system for gestational trophoblastic tumors recommendations regarding therapy J.Reprod Med 1998;43:37-43.

27. Garner EIO, Lepson E, Bernstein MR, et al subsequent pregnancy experience in patients with molar pregnancies and gestational trophoblastic tumor. J.Reprod Med 2002;47:380-386.

28. Garrett AP, Garner EO, Goldstein DP, Berkowitz RS methotrexate infusion and folic acid as primary therapy for nonmetastatic and low risk metastatic gestational trophoblastic tumors, 15 years of experience J Reprod Med 2002;47:355-362.

29. Host and risk factor for gestational trophoblastic diseases a hospital based analysis from India by Kumar N. et al Medical Science Monitor 2003.

30. Jeffcoates test book of Gynecology 5th Edition

31. Kim DS, Moon H, KIM KT, Moon YJ, Hwang YY. Effect of prophylactic chemotherapy for persistent trophoblastic disease in patients with complete hydatidiform mole. Obstet Gynaecol 1986;67:690-694.

32. Kohorn EI, Negotiating a staging and risk factors scoring system for gestational trophoblastic neoplasia a progress report J Reprod Med 2002;47:445-450.

33. Mosher R, Goldstein DP, Berkowitz RS, Bernstein M, Complete hydatidiform mole – Comparison of clinicopathological features, current and past J Reprod Med 1998;43:21-27.

34. Montz FJ Schlerth JB, Morrow CP. The natural history of theca lutein cysts. Obstet Gynaecol 1988;72:247-251.

35. Menczer J. Modan M, Serr DM, Prospective follow up of patients with hydatidiform mole Obstet. Gynaecol 1980;55:346-349.

36. La Vecchia C, Parazzini F, Bolis G et al. Risk factors for gestational trophoblastic disease in Italy. AMJ Epidiomol 1985;121:457-464

37. Mondal NR, Chatterjee T. Gestational trophoblastic tumor at a tertiary level center. A retrospective study J Reprod Med 2006.

38. Novaks & Jonathan Berck, Text Book of Gynecology 14th edition.

39. B.W. Tham, Everard JE, Tidy JA, et al Gestational Trophoblastic disease in the Asian Population BW of Northern England and North Wales. BJOG 2003 Jun 11016:559-590.

40. Osamor JO, Dluwasola AO, Adewole IF, Clinicopathological study of complete and partial hydatidiform moles in Nigerian Population in J Obstet Gynaecol. 2002 July 22(4):423-5.

41. Parazzini F, Cipriani S, Mangili G, Garavaglia E et al. Oral contraceptive and risk of gestational trophoblastic disease. Contraception 2002 June 65 (6):425-7.

42. Soto-Wright V, Bernstein MR, Goldstein DP, et al. The changing clinical presentation of complete molar pregnancy. Obstet. Gynaecol. 1995-86:775-779.

43. TOW WSH – The influence of the primary treatment of hydatidiform mole in its subsequent course J obstet gynaecol Br. Commonio 1966; 73:545-552.

44. Stone M, Dent J, Kardana A, et al relationship of oral contraception to development of trophoblastic tumor after evacuation of a hydatidiform mole. BJOG 1976;83:913-916.

45. Smith HO. Gestational trophoblastic disease epidemiology and trends clin Obstet. Gynaecol. 2003;46:541-556.

46. Soper JT, Lewis JL JR. Hammond CB. Gestational trophoblastic disease. In Hoskins WJ, Perez CA, Young RC, Principles and practice of gynaecology and oncology 2nd edition 1996;P 1039-1077.

47. Talati NJ. The pattern of benign gestational trophoblastic disease in Karachi. J Pakistan Med 1998 ; 48:296-300.

48. Wolfberg A, Feltmate C, Goldstein DP et al. Low risk of relapse after achewing undetectable HCG levels in women with complete molar pregnancy Obstet. Gynaecol. 2004; 104;551 – 554.

49. Walden PAM, Bagshawe KD. Reproductive performance of women successfully treated for gestational trophoblastic tumors. AMJ Obstet gynaecol 1976;125 (8) 1108-1114.

50. Yalcin OT, Tanir HM, Ozalp SS. Hydatidiform mole at extremes ages of reproductive life in developing country. Eur J Gynaecol Oncol 2002; 23(4); 361-2.

Key to Master Chart

SE – Suction Evacuation

CTF – Chemotherapy

MVA – Manual Vaccum Aspiration

V.Mole – Vesicular Mole

PIH – Pregnancy Induced Hypertention

D&E – Dilatation & Curettage

PTD – Persistent trophoblastic disease

RPT Mole – Recurrent Mole