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Histopathologic Patterns of Gestational Trophoblastic Disease in Jimma University Medical Center, Jimma, Southwest Ethiopia: A Three Year Retrospective Study

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A Three Year Retrospective Study

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Abstract

Introduction: Gestational trophoblastic diseases are group of diseases related to abnormal proliferation of trophoblast tissue. They include both benign and malignant forms; hydatidiform mole, Invasive mole, Placental Site Trophoblastic tumor, epithelioid trophoblastic tumor, Choriocarcinoma and trophoblastic nodules.

The incidence of gestational trophoblastic disease has been reported to show racial and geographical variations. Extremities of maternal age and previous history of molar pregnancy are among the risk factors.

Objective: To describe all cases of histologically diagnosed gestational trophoblastic diseases, seen at pathology department of Jimma university medical center.

Methods: : This is hospital based three years retrospective study employing records of histologic diagnosis of all females patients diagnosed with gestational trophoblastic diseases in the pathology department JUMC from September 2015 to august 2018.

Results: There were a total of 231 cases of GTD diagnosed clinically and 226 confirmed histologically from a total of 4802 biopsies done and 17,331 deliveries in JUMC during the study period making the magnitude of GTD to be 13.04 per 1000 deliveries. The mean age of patients was 29.81years, the minimum and maximum age being 15 and 48 years respectively. The peak age for GTD is 35 years. GTD was high in the age group of 20 to 29 with 99(42.9%) cases followed by age group of 30 to 39 with 81(35.1%) cases. Most of the cases were multiparas with greater than five previous deliveries 97(42.4%) and prim gravidas accounts for about 62(27.8%). The mean GA was 15.6 weeks, the minimum and maximum 5wks and 32 weeks respectively. The most common type of hydatidiform mole was complete mole which was diagnosed in 110(47.6%) followed by partial mole 79(34.2) cases.

Conclusion: The prevalence of gestational trophoblastic was high in JUMC, Ethiopia. Complete mole was the most common spectrum of disease diagnosed, followed by partial mole and choriocarcinoma. GTD is high in the third and fourth decade and the peak age was 35 years.

Keywords: histopathology, Gestational trophoblastic disease, molar pregnancy, choriocarcinoma

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Abbreviations/Acronyms

APSN……..Atypical placental site nodule
CHM……Complete Hydatidiform Mole
D & C ……..Dilatation and Curettage
Dx……Diagnosis
ETT ……Epithelioid Trophoblastic Tumour
EPS……..exaggerated placental site
GTD ……...Gestational Trophoblastic Disease
GTN ……...Gestational Trophoblastic Neoplasia
GA ……..Gestational age
H & E ……Hematoxyline and Eosin
HCG ……Human Chorionic Gonadotropin
MP…….Molar pregnancy
HM……Hydatidiform Mole
IM ……invasive mole
HPL …….Human Placental Lactogen
JUMC….. …….Jimma University Medical Center
PHM ……..….Partial Hydatidiform Mole
PX ……pregnancy
PSN…….....Placental site nodule
PSR……..Placental site reaction
PSP……placental site plaques
PSTT ……..….Placental-Site Trophoblastic Tumor
PSPN……placental site plaque and nodule
OBGN……Obstetrics and Gynecology
SPSS……Statistical Package for the Social Science
UAE……United Arab Emirates
USA….. ……..United States of America

yrs……..years

Wks ……weeks

WHO……World Health Organization

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Chapter one: Introduction

1.1: Background

Gestational trophoblastic diseases (GTDs) are group diseases attributed to abnormal proliferative placental conditions which are usually associated with pregnancy. Histologically, it includes the premalignant lesions (molar pregnancies) of partial hydatidiform mole (PHM), complete hydatidiform mole (CHM) and invasive mole, malignant lesions of the choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) and Tumor-like conditions or atypical placental site nodule (APSN) which includes exaggerated placental site, placental site nodule and plaque. The malignant forms of GTDs can arise after any type of pregnancy and are collectively known as Gestational trophoblastic neoplasms (GTN) [**1**].

The World Health Organization (WHO) also classified GTDs as benign conditions like hydatidiform mole (HM), which includes (partial, complete, and invasive mole), tumors (gestational choriocarcinoma, PSTT and ETT) and tumor-like conditions (exaggerated placental site, placental site nodule or plaque)[**2**]. The tumors or malignant forms of the disease are also referred to as Gestational Trophoblastic Neoplasia (GTN). These tumors, depending on the stage have effects on local tissues or on distant organs [**3**].GTN most commonly are a complication of molar pregnancy; however they may also follow other pregnancy events like miscarriages, ectopic pregnancy or term pregnancy [**4**]. Therefore, by virtue of their origin, they are able to produce significant amounts of human chorionic gonadotropin (HCG) which is a reliable tumor marker for diagnosis and monitoring of response to treatment [**4, 5].**

While PSTT, ETT, and APSN have more varied production of the pregnancy hormone HCG, all other forms of GTD produce this hormone very well. Indeed, HCG is an excellent biomarker of disease progression, response, and subsequent post treatment surveillance. Thus, a plateau or rising HCG level enables the early detection of progression of CHM and PHM to GTN that occurs in 15%–20%, and 0.5%–5% of cases, respectively [**6].**

The use of this biomarker together with the development of highly effective therapies has transformed survival outcomes so that today nearly all women affected by GTN can expect to be cured if managed properly **[7].**

A wide global variation in the prevalence of molar pregnancy has been reported, ranging from 12 per 1000 pregnancies in Indonesia, India, and Turkey to one to two per 1000 pregnancies in Japan and China and 0.5 to one per 1000 pregnancies in North America and Europe [**8]**. Likewise, the reported prevalence of choriocarcinoma varies widely worldwide, from a low of two per 100 000 pregnancies in the United States to a high of 202 per 100 000 pregnancies in China **[9]**.Choriocarcinoma have declined over the past 30years in all groups, possibly related to improved economies and diet as well as a decline in the total birth rates [**9, 10].**

The prevalence rates of both HM and PHM are more frequent at the extremes of reproductive age (<15 and >45 years) and pregnancies at these ages are a risk factor for HM. History of a previous molar pregnancy increases the risk to 10 times that for sporadic moles[**11**]. The reported incidence of choriocarcinoma ranges from 1 in 4,0000 pregnancies in North America and Europe, to 9.2 and 3.3 per 4,0000 pregnancies in Southeast Asia and Japan, respectively[**6]**.

Molar pregnancies and GTN's, all take their origin from placental tissue. GTDs results when all or one of trophoblastic tissue cells (syncytiotrophoblast, cytotrophoblast and intermediate) proliferates in uncontrolled manner [**2, 6**].Molar pregnancy appears to be caused by abnormal gametogenesis and fertilization. CHM is usually diploid, and have the 46XX and 46XY karyotypes constituting 90% and 10% approximately. This implies that the chromosomes are purely paternal in a complete hydatidiform mole. PHM have a triploid karyotypes usually 69 XXY. The chromosomes are both paternally and maternally derived. Histopathologically, PHM demonstrates identifiable fetal or embryonic tissue [**12**].

The invasive mole is a tumor which arises from myometrial invasion of a hydatidiform mole via direct extension through tissue or venous channels. [**6, 12]**

Choriocarcinoma is a malignant disease characterized by abnormal trophoblastic hyperplasia and neoplasia, absence of chorionic villi, hemorrhage and necrosis, with direct invasion into the myometrium, vascular invasion and spread to distant sites.50% are said to arise from hydatidiform moles, although only 2-3% of the moles progress to choriocarcinoma**[13].**

These are rare disease which arises from the placental implantation site, and consists predominantly of mononuclear intermediate trophoblast without chorionic villi formation infiltrating in sheets or cords between myometrial fibers. Immunohistochemically, diffuse

presence of cytokeratin and human placental lactogen (HPL) staining are demonstrated, while the HCG staining is only focal areas for those tumors **[6, 2, and 13].**

A diagnostic criterion for each GTD type depends on different microscopic features in H&E stain; Lesions are diagnosed as CHM if they have marked variation in sizes of the villi, with many abnormally distended chorionic villi, absence of villous capillaries in the core of the chorionic villi and circular trophoblast hyperplasia around the villi. Lesions are diagnosed as PHM if they have variable sizes and shape of chorionic villi, focal edema, and scalloping in the villous cores, functioning villous circulation in the core of the villi and focal trophoblast hyperplasia with only mild atypia. Lesions are diagnosed as invasive mole if the villi are invading the myometrium. Lesions are diagnosed as choriocarcinoma if they have abnormal trophoblast hyperplasia, anaplasia necrosis and hemorrhage in the absence of chorionic villi. Lesions are diagnosed as placental-site trophoblastic tumor if have proliferating intermediate or extra villous trophoblast in the form of sheets, nests and cords in the absence of chorionic villi [**6, 12 and 13**].

Post molar GTN is usually diagnosed by HCG surveillance without symptoms. Only about 50% of GTN follows molar pregnancy, the rest can occur after a spontaneous abortion, ectopic pregnancy, or a term pregnancy. Other clinical presentations can include bleeding from metastatic sites such as the liver, intestines, lung, or brain; pulmonary symptoms; and neurological signs from spine or brain metastasis [**14].**

A recent study however revealed that with increasing early diagnosis of molar pregnancies with imaging, fewer women now present with these classical symptoms [**15**]. The overall clinical features of GTDs however depend on the histological type of the specific GTD and extent of the disease at presentation [**16**].

Suction evacuation and curettage is the preferred method of evacuation of a molar pregnancy independent of uterine size if maintenance of fertility is desired and hysterectomy is an alternative to if childbearing is complete [**17].** In both of the management options patients should be followed with serum HCG for possible progression to GTN and Treatment of GTN is generally by chemotherapy after histological confirmation of the diagnosis [**18].**

One characteristic of GTDs that makes them unique is their significant response to chemotherapy and a cure rate exceeding 90%.This allows affected women who are within child bearing age to achieve their reproductive potential after treatment. Currently apart from cure rate the other big issue of GTD management is preservation of fertility which has

significant influence in patient's psychology and in fact this is dependent on early treatment of the disease [**10**].

Following treatment for GTDs, follow up with serial measurements of HCG is important. Unfortunately, this is a problem in resource poor settings where studies conducted reported high rates of loss to follow-up. This is significant and is a major contributing factor to the pattern of presentation and outcome in these areas **[19, 20].**

1.2 Statement of the problem

There seems to be regional variations in the incidence of GTD worldwide. This is exemplified by the low rate of 23 per 100,000 pregnancies reported in Paraguay in contrast to high rate of 1,299 per 100,000 pregnancies in Indonesia [**21**]. The highest reports of GTDs are from Asian countries and a relatively higher risk is also documented for black women [**22**].Some studies reported that 50% or more of cases of GTDs had antecedent history of molar pregnancy while about 25% were seen to follow miscarriages or tubal pregnancy, and another 25% term or preterm pregnancy [**22-25].**

Significant risk factors for the development of GTD are the age of the patient [**23].** The risk of GTDs appears to be more at the extremes of reproductive age [**17, 26**]. Women who are less than 16 years of age are six times more likely to develop the disease than women who fall within the 16-40years age range. Furthermore, there is a 17% risk of molar gestation in women who become pregnant at 50 years or more [**23, 26**]. Previous diagnoses with HM confer a 1% risk of recurrence in subsequent pregnancies. This escalates to approximately 25% with more than one prior HM [**19**]. Other factors that have been linked to development of GTD's include low economic status, deficiency of vitamin A, protein, folic acid and carotene [**24**, **27**] and use of oral contraceptives and parity [**24, 26**]**.**

Low literacy levels, poor socio economic status, and lack of antenatal care have been documented as major contributory factors to late presentation, as well as the inability to understand the importance of follow up in the Asian region of Pakistan [**22**]. Owing to the unique challenges of health care system in developing countries, patients mostly present late though they are quite potentially curable [**19**]. This may not be far from the situation in our own environment, which would have informed the need for the index study to a large extent.

The diagnosis of cancer in general and GTDs in particular is late with poor outcome in developing countries due to the fact that many patients present late in the stage of the disease when outcome is not so favorable. The reasons for this late presentation may be due to patient

and health system factors, including poor health seeking behavior and unavailability of diagnostic tools in the health system [**22, 28**]. This situation is different from what is obtainable in advanced settings where cancer management and survival rates have greatly improved **[28**].

The importance of early diagnosis, prompt institution of treatment, and monitoring the effects of therapy, by using serial determination of serum HCG are advocated as GTDs are curable. However, HCG secretion is by no means restricted to gestational choriocarcinoma, or other forms of trophoblastic diseases. It can occur also in non-trophoblastic disorders such as non-gestational choriocarcinoma, ovarian and testicular germ cell tumors, melanoma, and some carcinomas. Therefore final diagnosis of GTDs requires Histopathologic examination and classification accordingly [**22**]. So one importance of this study is to show the gaps of clinically diagnosed GTDs Histologically confirmed ones.

So the wide variation in incidence of GTDs, difference in the risk factors, special dependence of outcome of the disease in early presentation and poor awareness of the disease in developing countries were some of the main reasons to undertake this research in our setup.

1.3 Significance of the study

Although GTDs affect mainly reproductive age group with significant effect in maternal fertility and psychology, the overall works done in our setup to halt GTDs are not rewarding, And different researches show that there is significant variation in GTD distribution in different geographic areas of the world. However researches done in our setup on GTD are scarce, so this research is a good supplementary material for different clinical practices and baseline for other researches hoping that this research shows histologically confirmed distribution of different patterns of GTDs in different age groups, gestational ages and parity.

The information obtained is helpful in guiding formation of policies and establishment of protocols and feature similar further studies which are geared towards improving the morbidity and mortality associated with this disorder in our environment.

Chapter 2: Literature review

2.1 General over view of GTDs

GTD as a group are a relatively rare condition, especially in the western world, where a modest amount of work has been done and documented on it. Again, as with most other conditions, data from Africa on GTD has been relatively scarce [**26**]. But from available

studies, it is found to be more common or prevalent among Asian and black women. To confirm diagnosis, or make primary diagnosis of unsuspected cases of molar gestation, histopathological examination of uterine evacuation specimens is important, but in a particular study done in Nigeria only 28.0% of patients seen had histopathology reports on their specimens [**29]**.

There are both clinical and histopathological modes of classification GTDs [**16**]. The system of classifying gestational trophoblastic diseases adopted here is the modified world health organization histopathological classification of gestational trophoblastic diseases 2010 as this research is mainly focusing on the histopathological patterns of GTDs which is more important for management of the disease [**2**]. Different researches show that there are regional variations in the incidence of GTDs worldwide. One research show low rate of 23 per 100,000 pregnancies reported in Paraguay in contrast to high rate of 1,299 per 100,000 pregnancies in Indonesia [**21**]. Overall, about two third of these cases are attributed to molar pregnancy while the remaining one third are due to malignant forms of the disease [**3**, **27**]. These differences in the prevalence rates of GTDs have been attributed to use of different criteria for classification of GTDs, clinical diagnosis and research methods [**17, 30**]

2.2 Distribution of GTDs by histopathologic patterns

There are three main forms in which GTDs occur, hydatidiform moles (CHM, PHM, locally invasive moles), GTNs (choriocarcinoma, PSTT and ETT), and APSN [**3**]. In a review of cases of GTDs by Moore and Hernandez, reported frequencies range from 1 in 100 pregnancies in Indonesia to 1 in 200 pregnancies in Mexico, and 1 in 5000 pregnancies in Paraguay [**21**]. In another review, the incidence in USA was about 1 in 2000 deliveries, which was said to be influenced by socioeconomic status and race [**9**]. The incidence of GTDs in the UK was 1.5 per 1000 pregnancies, in Japan it was 2 per 1000 pregnancies, and in Nigeria it was 2.4 per 1000 pregnancies [**31**].

2.2.1 Complete Hydatidiform Mole

As was earlier highlighted from published literature, complete hydatidiform mole is the most common form of GTD. A study in the Asian region in Abu Dhabi reported that Gulf Arabs have the highest risk of developing CM. Maternal ethnic-specific incidences per 1000 births in different regions, for complete hydatidiform mole are as follows: Gulf Arabs 3.29, UAE Arabs 1.90, Asians 1.58, British women 0.55, and 2.14 for African women [**22**].

The reported prevalence of complete hydatidiform mole from an East African review in Mulago hospital, Kampala Uganda was 3.42 per 1000 deliveries. The conclusion from this study was that complete hydatidiform mole is a common condition in the region [**32**]. The study in Zaria, Nigeria revealed that CHM occurs more frequently than the partial hydatidiform mole, with thirty-four (34) cases reported as CHM out of fifty-six (56) molar lesions (60.7% of cases studied were CHM)[**5**].

2.2.2 Partial Hydatidiform Mole

In the multicenter study by Nggada which analyzed cases drawn from three tertiary hospitals in Maiduguri, Ilorin and Nnewi, the conclusion reached was that partial hydatidiform mole was the most frequent (64.50% of total cases) histopathological pattern of gestational trophoblastic diseases ,Whereas twenty cases (35.70%) were reported as PHM[**33**]. out of the 56 cases of molar gestations studied in Zaria Nigeria, making it less frequent than complete hydatidiform mole, this is in keeping with data of published literature[**5**].

2.2.3 Invasive Mole

In Latin America, an eight-year study at the Hospital Universitario de Caracas revealed out of twenty five (25) patients diagnosed with and characterized as cases of gestational trophoblastic neoplasia, 4.0% had invasive mole. Of the GTD cases studied in East Africa, from two teaching hospitals in Addis Ababa, Ethiopia 12.90% were invasive mole [**19**]. Cases of invasive mole encountered in the multicenter study by Nggada, accounted for just around 1.10% of all GTD lesions characterize [**33**].

2.2.4 Choriocarcinoma

It is reported that in Europe and North America, choriocarcinoma affects approximately 1 in 40,000 pregnancies, and 1 in 40 hydatidiform moles, while in South-east Asia and Japan; the rates are higher at 9.20 and 3.30 per 40,000 pregnancies respectively [**21, 22**].The incidence rates for both hydatidiform moles and choriocarcinoma are said to have declined in all populations over the past thirty (30) years [**9,**]. From East Africa, in the Addis Ababa, Ethiopia series, choriocarcinoma was the second most common morphological pattern of GTD, accounting for 15.0%34 [**19**]

The Zaria, Nigeria series reported by Mayun showed that out of 56 molar gestations, 37.0% (43 cases) of the GTDs were choriocarcinoma. Choriocarcinoma also accounted for 57.7% of malignant tumors of the female genital tract, in a separate series in Zaria, North-Western Nigeria [**5**]. In the Nnewi, South-eastern Nigeria series, the conclusion reached was that a high prevalence of GTD exists, notably of choriocarcinoma, with associated high mortality. It accounted for 66.7% of the cases of GTD studied [**23**].

2.3 Distributions of GTDs by maternal age, gestational age and parity

A case-controlled study from Baltimore (USA , shows that the factors associated with gestational trophoblastic diseases included, history of prior spontaneous abortions and the mean number of months from the last pregnancy to the index pregnancy. Furthermore, the highest incidences of GTD are observed among women with the following demographic characteristics; Extremes of reproductive age, i.e. greater than 45 years, and less than 15 years, whereas a significantly lower incidence was seen in women at 20 to 29 years of age in a study by this group [**14**]. Some of the certain specific factors for choriocarcinoma are prior CHM in which Choriocarcinoma is approximately one thousand times more likely after CHM than after another normal pregnancy event and advancing maternal age[**15,22**].

In another USA study, GTN is diagnosed in 15 to 20% of patients with prior complete hydatidiform mole and in 2 to 3% of patients with PHM, while lung metastases were found in 4 to 5% of patients with a CHM.HM is more common at the extremes of reproductive age; the most at-risk women are in their early teenage and/or premenopausal years. Women older than thirty-five (35) years have a 2-fold increase in risk and those older than forty (40) years have a 5 to 10-fold increase in risk compared to younger women [**34**]. Though most choriocarcinoma follow the evacuation of a HM, 25% accompany spontaneous miscarriages or ectopic pregnancies; the remaining quarter (25%) occur, following term delivery, and any GTD that occurs following a normal (uneventful) pregnancy and delivery is invariably a choriocarcinoma[**15 ,34**].

In a study done in South Korea in which the medical records of 370,117 from a total of 4,476,495 patients from 2009 to 2011, GTD was identified in 372 among women with an average age of 35.4 years, and 31.1years for those without GTD. The incidence rate of GTD between 2009 and 2015 was 130 ± 10 cases per 100,000 pregnancies, which included HM, invasive HM, and malignant neoplasm of the placenta (110 ± 10, 20 ± 0, and 10 ± 0 cases per 100,000 pregnancies, respectively. The lowest incidence of GTD occurred in patients in their

late 20's and early 30's and the highest in patients in their late 40's and beyond. HM accounted for 80.3% of all GTD cases, followed by invasive HM (13.1%), and malignant neoplasm of the placenta (6.6%). It shows overall incidence rates of GTD and HM of 1.3 and 1.1 per 1,000 pregnancies, respectively [**35**].

Research in tertiary care hospital in India where 18345 deliveries reported; out of which 77 cases were diagnosed as GTD. Almost 97.40% cases were of HM, 1.30% cases of choriocarcinoma and 1.30% cases of PSTT. Among the cases of HM 57.34% were complete mole and 41.33% cases were of partial mole. The blood group A was most commonly observed in patient (49.35%). In majority of cases beta HCG levels were between 50,000 and 100,000 mIU/ml. The correlation between beta HCG level and GTD were done [**36**].

Another study done in Nigeria, Abuja from 2009 to 2016 (hospital based retrospective descriptive study) shows, 51 cases of GTD from 12,517 total numbers of deliveries. There were 30(58.8%) cases of molar pregnancy (26 CHM, 4PHM) and 21 (41.2) %) cases of choriocarcinoma. The prevalence of GTDs was 0.44% or 4.4 per 1000 deliveries while the prevalence of molar pregnancy and choriocarcinoma were 2.4 and 1.6 per thousand deliveries [(1 in 416) and (1 in 625)] respectively. Most of the patients with GTD were within the age group 25-29 years {18(35.3%)}. This was followed by 12(23.5%) patients who were aged 40 years and above. The lowest number of cases {5(9.8%)} were in the 30-34 year age group. The highest numbers of patients (36.7%) with molar pregnancy were in the 25-29 year age group while the highest numbers with choriocarcinoma (38.1%) were in the age group of 40 years and above. The parity distribution of the most (49%) of cases were Para 1-4, followed by nulliparous women which most of them were Christians (64.7%), married (90.2%) and housewives (37.3%). The antecedent pregnancy events reported include miscarriage, live birth and molar pregnancy, seen in 38(74.5%), 12(23.5%) and 1(2%) of patients respectively [**37].**

A cross-sectional study carried out from November 2016 to February 2017 to determine the prevalence and clinical factors associated with hydatidiform mole at Regional Referral Teaching Hospital in Uganda show prevalence of HM 6.1% (11/181). All detected moles were CHM, and there were no diagnosed PHM. Clinical diagnosis of molar pregnancy was suspected in 13 patients, but only 69.2% (9/13) were confirmed as molar pregnancies histologically. Two cases were clinically unsuspected. Factors that had a significant

relationship with CHM included maternal age of 35 years and above, gestational age beyond the first trimester at the time of uterine evacuation and history of previous abortion [**38**].

A six years retrospective study done in Ethiopia, Addis Ababa, from 1994 to 1999 found 33, 438 deliveries conducted in both Tikur Anbessa and St. Paul's millennium medical college and GTDs was diagnosed in 105 women of whom the complete medical records of 93 patients were obtained with a coverage rate of 88.6%. The median age and the mean of patients were 34.5 years and 30.9 (±6.5) years, respectively. The youngest and the oldest patient were 14 and 53 years old. The median gravidity was 4.Fifteen (16.1%) were prim gravidas. Forty seven (50.5%) had five or more pregnancies, Forty two (45.2%) were grand multiparas and Thirty five (37.6%) had experienced at least one abortion [**19**].

Histopathologic result was available in 72 (77.4%) of the patients. Accordingly, the magnitude of GTD was 2.8 per 1000 deliveries. Those with five or more pregnancies and patients with history of two or more abortions tend to have a significant increase in the disease prevalence Sixty seven (72.0%) were diagnosed to have HM, 14 (15.1%) choriocarcinoma and 12 (12%) invasive mole [**19**].

Chapter three: Objectives

3.1 General objective

- To describe histopathologic patterns of gestational trophoblastic disease in JUMC, Jimma, South west Ethiopia from September 2015 to august 2018

3.2 Specific objectives

- To describe the distributions of GTDs by specific histologic types
- To determine the distributions of GTDs by residence, maternal age,number of previous pregnancy and Gestational age
- To find out the relationship of maternal age , number of previous pregnancy and Gestational age to GTDs

Chapter four: Method's and materials

4.1 Study area and period

The study was conducted in Jimma university medical center [JUMC] which is found in Jimma town, Oromia regional state. Jimma town is located in Southwest part of Ethiopia which is 352 KM away from Addis Ababa. JUMC is the only teaching university hospital serving as a specialized referral hospital for most of south western Ethiopia including

Jimma town.

Estimated catchment area of the hospital is 17,500{km with 15 million people is believed to get the service. The pathology department is among the most actively functioning department with staff profile of 5 pathologists, 15 practicing pathology residents, two general practitioners, 2 histopathologists and 7 technical assistant workers. The department activities are subdivided in to Histopathology, hematopathology and cytopathology units. The Histopathologic services is the area where this research is focusing uses the routine Hematoxylin and Eosin stain without any additional ancillary techniques having average annual patient flow of 1500 to 1800. The study period for conducting this research was from July to August 2019 G.C

4.2 Study Design

Facility based retrospective cross-sectional study designs was used in this study

4.3 Populations

4.3.1 Target population:

All female patients of south west ethiopia

4.3.2 Source population:

All female patients for whom biopsy was summated to JUMC department of pathology for histopathologic diagnosis from September 2015 to august 2018

4.3.3 Study population

All female patients with the clinical diagnosis of GTD for whom biopsy was summated to JUMC department of pathology for histopathologic diagnosis from September 2015 to august 2018

4.4 Inclusion and exclusion criteria

4.4.1 Inclusion criteria:

All biopsy reports of female Patients with the diagnosis of GTD which are done from September 2015 to august 2018

4.4.2 Exclusion criteria:

Biopsy reports which do not have diagnosis or two of the following variables: patient age, gestational age, number of previous pregnancy and residence

4.5 Sample size and sampling technique

All the biopsy reports with the diagnosis of GTD in the time frame of the study period that fulfill the inclusion and exclusion criteria were included in the research. Non-probability convenient sampling technique was employed

4.6 Data collection procedure:

All biopsy reports of GTD containing age, residence, gestational age and diagnosis were retrieved and recorded from pathology department data archive. OB/GYN registry book were referred for any missed variables. Checklist that contained the study variables was prepared. The data were collected by three selected technical assistant staffs. The completeness of the data was checked. Cases were categorized in to three diagnostic categories: molar pregnancy (partial mole, complete mole and invasive mole), malignant lesions (choriocarcinoma, PSTT and ETT) reactive lesions (exaggerated placental site, placental nodule and plaques)

4.7 Variables

4.7.1 In dependent variable

- Age
- Residence
- Number of previous pregnancy
- Gestational age
- Clinical Diagnosis

4.7.2 dependent variable

- Histopathologic Diagnosis

4.8 Data processing and analysis

Immediately after the data collection was completed, data was coded and entered into computer software of EPI Data version 3.1 Data was cleaned, edited, compiled and described. Descriptive analyses using SPSS were done to describe variables in the study. Results were presented using tables and graphs.

4.9 Data quality control

Two days training were given to the data collectors on how to locate, retrieve, categorize and record the data. The principal investigator [Medical Doctor] were following and supervising while the technical assistants are retrieving and recording the biopsy results from pathology department using check lists. Consultations by senior pathologist were sought at time of technical difficulties. The collected data was rechecked for completeness and accuracy by the principal investigator according to their specific accession number and study identification number.

4.10 Ethical consideration

Ethical clearance was obtained from Institutional Review Board of Jimma University. Permission to conduct the study was also obtained from pathology department.

4.11 Limitation of the study

Final confirmatory test (immunohistochemistry and karyotypes) for GTD were not used in this research.

4.12 Dissemination plan

The results of this study will be presented to Jimma University, Regional health bureau, departments of Pathology, department of OBGN and other concerned bodies. The study findings will also be disseminated through reports and publication on an appropriate journal will be considered.

4.13 operational definitions

Number of deliveries: refers to all deliveries including abortions, intrauterine fetal deaths, GTDs, preterm, post term and term deliveries

Previous pregnancy: all pregnancies excluding the one with the current presentation

Urban: is defined as those who came from Jimma town

Rural: those who came from out of Jimma town within the catchment area

Chapter five: Result

There were 226 histologically confirmed cases of GTD in the study period in pathology department. Two hundred thirty one cases were initially diagnosed as GTD clinically and from those only 222(96.1%) cases were confirmed with histologic examination the remaining 9(3.89%) cases had other histologic diagnosis. Four had other clinical diagnosis initially

which was later confirmed as GTD in histologic study. These accounts 4.70% for the histologically confirmed GTDs of all the surgical pathology specimens received and processed in pathology department in the study period, which were a total of 4802 specimens within the study period. All of the cases of GTDs in this hospital were from uterine. The total number of deliveries registered at the Obstetrics and Gynecology Department were totally 17,331 which were 5,384, in 2008 E.C, 6,069 in 2009 E.C. and 5,878 in 2010 E.C respectively. The 226 histologically confirmed cases of GTD translate to a frequency of **13.04 cases per 1,000** deliveries. Table 1.1 shows number of GTDs with regard to year, number of deliveries and total biopsy done.

Table 1 year of biopsy done, number of biopsy, clinical diagnosis, histologic diagnosis of GTD, in JUMC from sep 2015 to aug 2018,n=226

Year	Number of deliveries	Number of biopsy done	Clinically diagnosed GTD	histologically confirmed GTD
2015/2016	5,384	1319	59	59(26.1%)
2016/2017	6,069	1636	68	64(28.32%)
2017/2018	5,878	1847	104	103(45.57%)
Total	17,331	4802	231	226(100%)

The three years trend of GTD in JUMC shows increment from 2015/2018 which was 59 to 103 cases in 2017/2018.

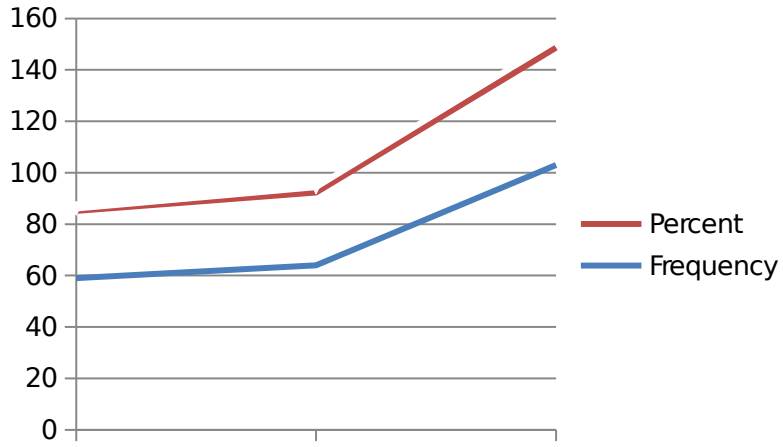


Figure 1 patterns of GTD in three years JUMC, from sep2015 to sep2018, n=226

5.1 Distribution of GTD in sociodemographic status

Among the 226 cases 9(4.0%) had no registration of residency and from the remaining 222 cases 141(62.4%) were from rural and 76(33.6%) from urban areas. there is no association between residency and diagnosis of GTD with P value of 0.509.

The ages of the patients in this research ranged from 15 to 48 years, with a mean age of 29.8±7.9 years and the peak age for histologically confirmed GTD was in the 35 years with 32(14.2%) cases. GTD is high in the age group of 20 to 29 accounting for 95 cases (42.0%) followed by the age group of 30 to 39 years which account 80cases(35.4%) and the least age group is seen in less than 20 years which accounts 17 cases (7.5%). There is also significant association between age of the patient and histologic diagnosis of GTD with P value of 0.007.

5.2 Disruption by Gestational age and number of previous pregnancy

The distribution of GTD in number of previous pregnancy shows the average number of previous pregnancy was 3.6±2.9, the minimum zero (prim gravidas) which account for 62(28.4%) cases and maximum 12 previous pregnancies which account only one case (0.4%). GTD was high in those who had five or more previous pregnancies accounting for 96(44.03%) and 8(4%) cases had no record of number of previous pregnancies. There is no significant association between number of pregnancy and occurrence of GTD with P value of 0.290.

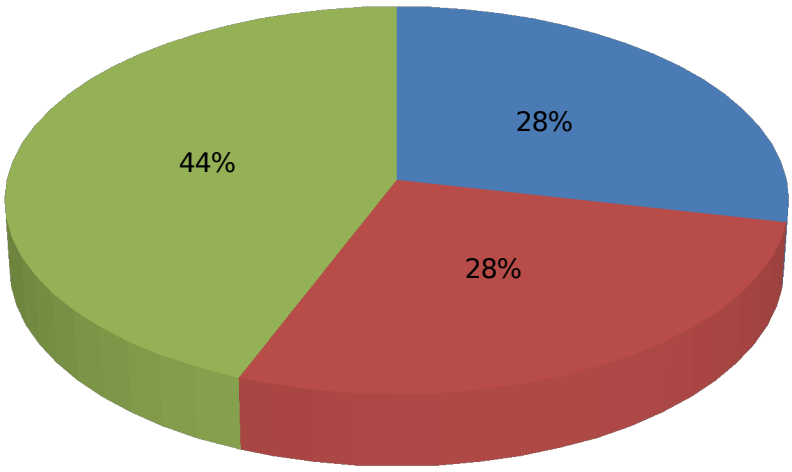


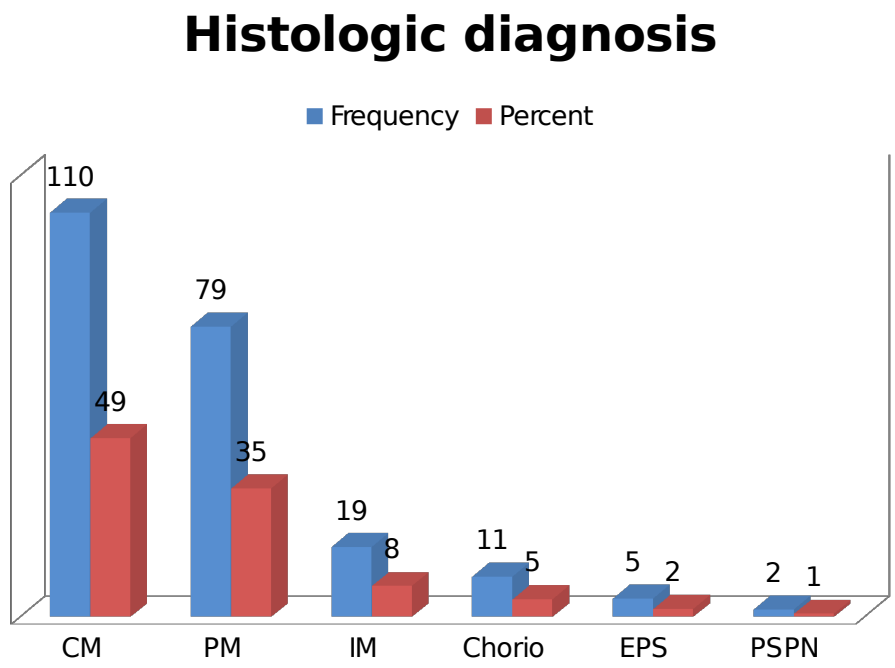
Figure 2 Distribution of GTD with Number of previous pregnancy in JUMC from September 2015 to sep2018, N=218

Distribution of GTD with regard to gestational age (GA) at presentation shows that the mean GA at presentation was 15.7±4.9 week (wks), the maximum and minimum was 5wks and 32 wks respectively. The peak GA for GTD was 16 wks which account for 53(23.8%) cases and GTD was high is in second trimester pregnancy with 143(63.8%) cases, followed by first trimester with75(33.5%) and third trimester with6 (2.7%)cases. 2(0.94%) cases had no record of GA.

5.3 Distribution of GTD in histological diagnosis

From the 226 histologically diagnosed cases, 110 (48.7%) cases were diagnosed as complete hydatidiform mole, 79(35.0%) were diagnosed as partial hydatidiform mole, 19 (8.4%) cases were invasive mole, 11 cases (4.9%) were choriocarcinoma.

For CHM, mean age was 28.4±3.9 years and peak age was 35 years accounting for 14(12.72%). Most of the cases of CHM were seen in those patients who had no previous pregnancy accounting for 36(32.7 %) cases. The GA ranges from 5 wks to 28 wks. The peak GA was 16 wks accounting for about 28(25.4%) cases. This is followed by partial hydatidiform mole 79 (35.0 %) cases with a mean age at 31.04 ±4.7 years and the age ranges from 18 years to 46 years and the peak age was 35 years which account for 9(11.4%) cases. The GA for PHM range from6 to 32 wks the peak GA was 16 wks accounting for 16(20.3%) cases. Most of patients with PHM had no previous pregnancy accounting for 21 (26.5% cases.



- **KEY**

CM: complete mole

PM: partial mole

IM: invasive mole

Chorio: choriocarcinoma

EPS: exaggerated placental site

PSPN: placental site plaque and nodule

Figure 3 Distribution of GTD with specific histologic diagnosis, in JUMC from September 2015 to August 2018, N=226

Overall molar pregnancy accounts for 208(92.0%) cases, GTN for 11(4.9%) and non-molar non neoplastic reactive proliferations for about 7(3.1%) of the cases respectively.

The distribution of specific histologic diagnosis with age category shows that CM &PM are higher in age group of 20 to 29 accounting for 47 and 35 cases, whereas the age group of 30 to 39 accounts for about 29 and 27 cases of CM and PM respectively. There were only 2 cases of PSNP which were in the age group of 30 to 39. There is association of age with specific histologic diagnosis with P value of 0.007.

Table 3 Cross tabulation of age category and histologic diagnosis in JUMC, from seb 2015 to aug 2018,n=226

age category	CM	PM	IM	Chorio	EPS	Total
<20 years	11	6	0	0	0	17
20-29 years	50	37	4	3	1	95
30-39 years	32	29	11	3	3	78
40-49 years	17	7	4	5	1	34
Total	110	79	19	11	5	224

Key

CM: complete mole EPS: exaggerated placental site

PM: partial mole PSPN: placental site plaque and nodule

IM: invasive mole chorio: choriocarcinoma

Maternal age category has association with GTN and molar pregnancy but not with CHM and PHM with P values of 0.032 and 0.438 respectively. Number Previous pregnancies also have association with GTN and MP but not with CHM and PHM with P values of 0.039 and 0.220 whereas GA at presentation (in trimesters) has association with CHM and PHM but not with MP or GTN with P values of 0.030 and 0.454 respectively. There is no association between residency with CHM, PHM and GTN with P values of 0.96 and 0.710.

Table 2 cross tabulation of different variables with CHM, PHM, MP and GTN in JUMC from Sep 2015 -Aug 2018 ,n=226

		CM	PM	Chi-squre	MP	GTN	Chi -squre
Residency	Urban	43	24	X^2 =1.90	76	3	X^2=0.138
	Rural	59	51	P=0.96	124	8	P=0.710
Age	<20 yrs	11	6		17	0	X^2 = 8.82
	20 -29yrs	50	37	X^2 = 2.72	91	3	**P= 0.032**
	30-39 yrs	32	29		72	3	
	40- 49 yrs	17	7	P = 0.438	28	5	
Previous PX	0	36	21	X^2 = 3.03	59	1	X^2 = 6.50
	1-4	22	24	P = 0.220	57	1	**P= 0.039**
	>5	41	25		86	9	
GA	1st trimester	30	31	X^2 = 6.99	69	2	X^2 = 1.58
	2nd trimester	78	43	**P= 0.030**	132	9	P= 0.454

	3rd trimester	1	4		6	0	

Chapter six: Discussion

The total burden of GTD in our series was 226cases which are histologically confirmed that translate to a frequency of 1.3% or 13.04 cases in 1000 deliveries. Study done in Ethiopia, Addis Ababa, the magnitude of GTD was 2.8 per 1000 deliveries [**19**]. Another study done in Nigeria, Abuja show the prevalence of GTD is 0.44% or 4.4 per 1ooo deliveries [**35**]. The GTD frequency reported in Ebonyi by Anuma and Co-workers is 3.58 per 1000 deliveries [**25**]. A study done in South Korea the incidence of GTD was 1.30 per 1000 deliveries and the anther study done in India show that the magnitude of GTD was 4.19 per 1000 deliveries [35, 36]. In the United Kingdom (UK) and Japan, GTD had frequencies of 1.5 and 2.0 in 1000 pregnancies respectively [20]. In a review of cases of GTDs by Moore and Hernandez, reported frequencies range from 1 in 100 pregnancies in Indonesia to 1 in 200 pregnancies in Mexico [**21**].Compared to the others the observation in our study shows the magnitude of GTD in Jimma university specialized hospital is higher except to that of the Indonesia and Mexico which is relatively comparable. This may be due to the reason that GTDs come as referral cases though the most deliveries are done in nearby hospitals and health centers.

The ages of the patients in this research ranged from 15 to 48 years, with a mean age of 29.8±7.9 years and the peak age for histologically confirmed GTD was in the 35 years with 32(14.2%) cases. GTD is high in the age group of 20 to 29 accounting for 99 cases (42.9%) followed by the age group of 30 to 39 years which account 81cases (35.1%) and the least age group is seen in less than 20 years which intern accounts 17 cases(7.4%). The age range is nearly similar to that of the Gombe Nigeria, which has an age range of 15 to 44 years for all cases of GTDs. The peak age of occurrence of GTD in Gombe was noted in the second decade and third decade which is similar to ours in JUMC [**5**]. Whereas report in Ebonyi, by Anuma and Coworkers, show an age range of 19 to 55 years and a mean age of 30.4±7.4 years which have relatively a wider range but the mean age almost similar[**25**]. The age range in our study is also similar to that observed at Nnewi, which is put at 15 to 46 years. The mean age of patients reviewed in the index study reported to be 29.81 years is slightly lower than 33.4 years in Ebonyi, but is comparable to 31.0±8.6 years reported in Nnewi [**23**].Study done in Ethiopia, in both Tikur Anbessa and St. Paul's millennium medical college the mean age was 30.9±6.5 years, and the median age was 34.5 years while the ages of the patients were in the range 14 to 53years. These are approximately comparable to the observations

made in the JUMC [**19**]. The mean age of patients in the index study population of 29.81 years is comparably higher than that observed by Nggadaet al37 put at 27.7 years [**33**]. Slight variations noted may be due to the different sample sizes used in the different studies. However the mean ages were all observed within the second and third decade of life which is compatible with reproductive life. These differences in frequency and age characteristics between our local studies and those done in Western countries might be explained by the availability of and access to healthcare facilities and service delivery in the Western world and females become pregnant at late age the developed world.

The gravidity distribution in this research shows that the peak for GTD is in prim gravida which accounts for about 62 (27.8%) cases. whereas those with five or above pregnancies accounts for 97(43.5%) and those with gravidity one to four accounts 64(28.7)cases .This finding is similar to the finding of the study done in Pakistan in which more than one third of GTDs were in prim gravida [22]. But there is slight variance with that of other the study done in Ethiopia, adds Ababa and Ebonyi which report that more than 50% of cases were seen in women who were Para 5 and above[19,25].in another study done in Nigeria, Abuja the parity distribution of the most 29 (49%) of cases were Para 1-4, followed by nulliparous women17(33.4)cases and those who have above five parity it was only 9(17.6%) cases. over all though there is slight variation most reports show GTDs are common in prim gravida and those with greater than five or more previous pregnancies[**8,21,24and37**].this maybe cue to the pathogenesis of the disease.

The distribution of GTD in this research with regard to gestational age shows that the mean GA was 15.6 wks, the peak GA for GTD was 16 wks and over all ranges from 5 weeks to 32 weeks. The higher GA category for GTD was 14 to 26 wks accounting for 145(63.3%), followed by on those less than 14 wks around 78(34.1%) cases and on those GA above 27 weeks there were only 6(2.6%) cases. a research done in Nigeria by Nyengidiki shows the common GA for GTDs were in second trimester accounting for 23(60.5%), followed by first trimester accounting for about 9(23.7%) and third trimester of 6(15.8) cases[24]. this is pretty similar to our finding in this research. in another report from Uganda the prevalence of GTD in first and second trimester is similar which accounts 75 and 81 cases each respectively. this is slightly different from our finding in which most of them was in first trimester. The possible reasons for this difference may be attributed to the quality of health service, patient awareness and health seeking behavior in different setups.

In this research the specific histologic diagnosis distribution shows that one hundred ten cases (47.8%) were diagnosed as complete hydatidiform mole, seventy nine (34.3%) were diagnosed as partial hydatidiform mole, nineteen (8.3%) cases were invasive mole, eleven cases (4.8%) were choriocarcinoma, five cases were diagnosed as exaggerated placental site accounting for 2. 2%, this is followed by two cases of placental site trophoblastic nodule, accounting for approximately 0.9% of GTDs and 4(%1.7)cases have other histologic diagnosis though they were diagnosed as GTD clinically. this finding is more or less consistent with most of published literatures, standard texts of histopathology and gynecologic pathology so far [**4,12,17,35 and 37**].

The histopathologic pattern of gestational trophoblastic diseases observed in our study also exhibited similarity to that reported by reported by Mayun et al in a separate study in Zaria, where complete hydatidiform mole was the commonest type with a proportion of 60.7%, followed by choriocarcinoma making a proportion of 37%, while PHM and invasive mole, each accounted for 35.7% and 3.6% respectively of all the GTD cases seen except mild variation in the proportion of choriocarcinoma and invasive mole[**5**].

In contrast to most researches one report in Nigeria by Nggadaet al37, PHM was the commonest histological type of GTD seen, accounting for 64.5%, followed by choriocarcinoma which accounted for 21.5% of cases. The complete hydatidiform mole (CHM) made 12.9% of cases, while invasive mole accounted for 1.1% of all GTDs reviewed, but there was no case of placental site trophoblastic tumor (PSTT) seen in their series[33].

In Ethiopia, Addis Ababa reported by Negussie et al, choriocarcinoma was reported to have accounted for 15.1% of the cases analyzed, invasive mole accounted for 13.9% and HM was diagnosed in 72% of cases, making it the most common histologic subtype. However no cases were recorded of partial hydatidiform mole or placental site trophoblastic tumor [19].this is also similar with ours except relatively high (15.1%) of choriocarcinoma as compared to our finding which was only 4.8%.

Chapter seven: Conclusion and recommendation

7.1 Conclusion

In conclusion this study has found gestational trophoblastic diseases to be a common condition in JUMC as compared to other researches. Complete hydatidiform mole in particular was found to be the commonest histologic subtype, closely followed by PHM and

choriocarcinoma. While the molar lesions peaked in the third and fourth decades, choriocarcinoma peaked in the fifth decade of life. The peak age for GTD was 35years and the mean age was 29.81±7.9 years. GTD is high in those of who don't have previous pregnancies and grand multiparas with five and above deliveries and the mean GA was 15.6 ±4.9 wks. There is association of occurrence of GTD with maternal age but not with previous number of pregnancy or GA at presentation.

7.2 Recommendations

1. Awareness programs should be extended to all women of the reproductive age group to report and register all pregnancy-like and pregnancy events at the nearest facility for proper follow-up.
2. Clinician should have high index of suspicion for GTD as early treatment and follow up will change the prognosis and out came of the disease
3. Detailed studies with wider sample size to determine risk factors, management outcomes and patient follow up should be done to further characterize the disease.
4. The study recommends the use of immunohistochemistry markers and some aspects of cytogenetic to comfortably diagnose the disease.

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Annex

Checklist

No.	Variables		Choice
1	Biopsy No.		
2	**Year**	A. 2008 B. 2009 C. 2010 D. Year not recorded	
3	Sex	**A. Female(F)**	
4	Age	A. < 20 B. 20 - 29 C. 30 -39 D. 40- 49 **E.** ≥ 50 **F.** Age not recorded	
5	Residence	A. Urban B. Rural C. Residency not recorded	
6	Gestational age at presentation	A. <14 weeks B. 14 -26 weeks C. >27 weeks D. Gestational age not recorded	
7	Numbers of previous pregnancy	A. O B. 1- 4 C. >5 D. Number of pregnancy not recorded	
8	Anatomic site	**A.** Uterus **B.** Ectopic pregnancy site C. Other	

9	The Histopathologic diagnosis	A. Complete Hydatidiform Mole B. Partial Hydatidiform Mole C. Invasive mole D. Choriocarcinoma E. Placental Site Trophoblastic Tumor F. Epithelioid Trophoblastic Tumor G. Placental site reaction H. Placental site nodule and plaque I. Histologic diagnosis not recorded	