GESTATIONAL TROPHOBLASTIC DISEASE IN HOSPITAL USM: A RETROSPECTIVE REVIEW

BY

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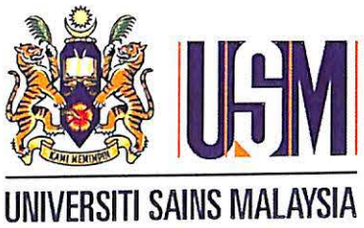

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ABSTRACT

Introduction - Gestational trophoblastic disease (GTD) forms a group of disorders spanning the conditions of complete and partial molar pregnancies through to the malignant conditions of invasive mole, choriocarcinoma and the very rare placental site trophoblastic tumour (PSTT). The World Health Organization classification divides Trophoblastic Disease into the Pre malignant condition which is Partial Hydratirform moles, Complete hydatidiform moles and malignant condition such as Persistant Trophoblastic Disease, Invasive Mole, Choriocarcinoma, Placental Site Tumours. Molar pregnancies can be subdivided into complete (CM) and partial moles (PM) based on genetic and histopathological features. GTD is a rare event in the Europe, with a calculated incidence of 1/714 live births.

Objectives – To determine prevalence of different types of Gestational Trophoblastic diseases, assess the associated factors of malignant condition compared to pre malignant condition and to determine the outcome of the chemotherapy treatment for patient with GTD.

Methodology – A retrospective review was conducted on all GTD cases over the 10 year period between January 2002 and December 2011. The diagnosis and staging was classified using FIGO anatomical staging (Appendix A) and had histopathological confirmation of the disease, data was compiled through a clinical research form for analysis and data analysis was carried out with SPSS version 22.

Results - Total of 123 cases were diagnosed with GTD within ten years span, there were 98 cases of Benign form GTD and 25 cases of malignant form of GTD. Among the benign form of GTD there were 53(43.1%) patients with partial hydatidiform mole and 45(36.6%) with complete hydatidiform mole diagnosed clinically and conformed by histopathological evaluation. Malignant form of GTD accounted for total of 25(20.3%) patients, among which persistant trophoblastic disease (PTD) consist of 22 patients (17.9%) and 3(2.4%) patients with choriocarcinoma. Among the associated factors of malignant disease studied was age, ethnicity, pre treatment hCG level, parity, child birth spacing, size of the uterus, size of molar tissue, history of molar pregnancy, previous usage of oral contraceptive pills and presence of thecal luthean cyst. Among the risk factors, age was strongly associated with malignant GTD, it was noted that with increase in every year of age the odds of developing malignant GTD was increased by 5%, The outcome of two major treatment group namely MTX regimen and EMACO regimen was studied, total of 22 patients received MTX as a single agent therapy, all of them were diagnosed with PTD and 19 patients had FIGO stage I disease and one patient with FIGO stage II disease and each one patients in stage III and stage IV disease, the patients in stage II and III needed second line chemotherapy with Actinomycin D and achieved full recovery, 19 patients in stage I received single agent MTX and complete recovery was achieved in 12 patients resulting in a success rate of 63% when used a single agent in stage I disease. There were 7 patients with stage I disease who failed to achieve satisfactory response with MTX alone and eventually requiring Actinomycin D (37%) achieved complete recovery from the disease. In this study 3 patients received EMA-CO regime as treatment, all of them were diagnosed with choriocarcinoma, two patients had stage I disease. One of them had hysterectomy

done prior to treatment with EMA-CO and another received only EMA-CO after evacuation. Another one patient had stage IV disease with brain and liver metastasis, she was primarily started on EMA-CO and eventually succumbed to death. The remaining 2 patient had complete remission after treatment with EMA-CO, The success rate of EMA-CO in high risk patients at our center remains good as seen in previous studies.

Conclusion - In this study the was no major changes in term of the epidemiology of the disease, it was well within the generally accepted prevalence for GTD. Perhaps the one of the most interesting finding in this study was the associated risk factors to develop malignant disease, in this study factors which had high association were age, high parity, and long interval of last child birth. Most patients had FIGO stage I disease, the response to single agent MTX treatment achieved an acceptable outcome, while the rest of the patients who received second line therapy also had a complete recovery. Patients who were in stage II and III had complete recovery with EMA-CO regime.MTX remains as our first line treatment in low risk patients while the usage of Actinomycin also proved beneficial in cases of resistant. For the patients in high risk category this study supports the use of EMA-CO.

ABSTRAK

Pengenalan - Penyakit kandungan Mola atau lebih dikenali sebagai Gestational trophoblastic disease (GTD) adalah suatu kumpulan penyakit yang merangkumi kandugan molar penuh dan molar separa, hinggalah ke penyakit barah tropoblastik seperti invasif mol, khoriokarsinoma dan juga barah tropoblastik daripada uri.klasifikasi Pertubuhan kesihatan sedunia telah mebahagikan penyakit tropoblastik kepada dua kumpulan besar ia itu kumpulan Pra barah seperti hidatidifom mol separa dan hidatidifom mol penuh dan kumpulan penyakit barah seperti penyakit tropoblastik kekal, invasive mol,koriokarsinoma dan barah tropoblastik daripada uri.. Penyakit kandungan tropoblastik ialah suatu penyakit yang jarang dilihat di benua europa dengan kadar kejadian sekitar 1/714 kelahiran hidup. Terdapat bukti variasi etnik dalam kejadian GTD, dengan wanita dari Asia yang mempunyai kadar yang lebih tinggi berbanding dengan wanita bukan Asia (1/387 berbanding 1/752 kelahiran hidup).

Objektif - Menentukan kelaziman jenis penyakit kandugan tropoblastik, menilai faktor-faktor yang berkaitan dengan kumpulan penyakit tropoblastik barah berbanding dengan kumpulan penyakit pra barah dan menentukan hasil rawatan kemoterapi pada pesakit dengan penyakit tropoblastic barah yang dirawat di HUSM.

Kaedah - Satu kajian retrospektif telah dijalankan ke atas semua kes GTD bagi tempoh 10 tahun antara Januari 2002 dan Disember 2011,Diagnosis dan tahap penyakit diklasifikasikan menggunakan klasifikasi Tahap penyakit yang diiktiraf oleh FIGO (Lampiran A) dan mempunyai pengesahan histopatologi terhadap penyakit ini, data telah dipungut mengunakan borang pungutan data untuk tujuan analisis dan analisis data dijalankan dengan SPSS versi 22.

Keputusan - Kajian ini meliputi keseluruhan pesakit dengan sebarang bentuk penyakit gestasi Tropoblastik sepanjang tempoh sepuluh tahun, dari Januari 2002 hingga Disember 2011. Sejumlah 123 rekod pesakit telah dipilih, dikaji dan di analisis, terdapat 98 kes GTD berbentuk bukan barah dan 25 kes berbentuk barah. Antara kes berbentuk bukan barah daripada GTD adalah 53 (43.1%) pesakit dengan hidatidifom mol separa dan 45 (36.6%) dengan hidatiform lengkap yang disahkan secara klinikal dan penilaian histopatologi. Bentuk barah daripada GTD menyumbang sebanyak 25 (20.3%) pesakit, antaranya ialah penyakit tropoblastik kekal (PTD) terdiri daripada 22 pesakit (17.9%) dan 3 (2.4%) pesakit dengan koriokarsinoma. Antara faktor-faktor yang berkaitan dengan penyakit GTD jenis barah yang dikaji adalah umur,kumpulan etnik, tahap hormon hCG sebelum rawatan, bilangan kelahiran, Jarak kelahiran, saiz rahim, saiz tisu molar, sejarah kehamilan molar, penggunaan pil perancang keluarga dan kewujudan lutheal cista. Antara faktor-faktor risiko dikaji, umur telah didapati berkait rapat dengan kejadian GTD jenis barah, berdasarkan keputusan kajian ia dilihat bahawa dengan peningkatan setiap tahun umur kemungkinan seseorang menghidap penyakit GTD jenis barah meningkat sebanyak

5%,. Hasil daripada dua kumpulan rawatan utama iaitu rejimen MTX dan rejimen EMACO telah dikaji, sejumlah 22 pesakit menerima MTX sebagai rawatan ejen tunggal, semua daripada mereka disahkan dengan PTD dan 19 pesakit mempunyai penyakit diperingkat tahap FIGO I dan seorang pesakit dengan tahap FIGO II penyakit dan seorang pesakit masing masing di peringkat III dan peringkat IV, pesakit dalam peringkat II dan III telah memerlukan kemoterapi pilihan kedua dengan Actinomycin D dan telah mencapai kadar pemulihan sepenuhnya, 19 pesakit di peringkat FIGO I telah menerima ejen tunggal MTX dan kadar pemulihan yang lengkap telah dicapai dalam 12 pesakit justeru menghasilkan dalam kadar kejayaan 63% apabila digunakan sebagai agen kemoterapi tunggal kepada pesakit di peringkat FIGO I. Terdapat 7 pesakit dengan penyakit peringkat FIGO I yang gagal mencapai kadar pemulihan yang memuaskan dengan MTX sahaja dan akhirnya memerlukan Actinomycin D (37%) dan telah pulih sepenuhnya. Dalam kajian ini 3 pesakit telah menerima rawatan rejimen EMA-CO, kesemua mereka telah disahkan dengan koriokarsinoma, dua pesakit mempunyai penyakit tahap FIGO I.Salah seorang daripada mereka telah mejalani histerektomi atau pembedahan mengeluarkan rahim sebelum rawatan dengan EMA-CO dan satu lagi hanya menerima EMA-CO selepas menjalani prosedur mencuci rahim. Seorang lagi pesakit mempunyai tahap penyakit IV yang telah merebak ke otak dan hati, beliau di rawat dengan rejimen EMA-CO dan akhirnya telah meninggal dunia. Baki dua pesakit telah pulih sepenuhnya selepas rawatan dengan EMA-CO, Kadar kejayaan EMA-CO pada pesakit yang berisiko tinggi di pusat kami masih baik seperti yang dilihat dalam kajian-kajian sebelum ini.

Kesimpulan - Dalam kajian ini tidak ada perubahan besar dari segi epidemiologi penyakit ini, ia masih berada pada kelaziman yang diterima umum untuk GTD. Salah satu daripada penemuan yang paling menarik dalam kajian ini adalah faktor-faktor risiko yang menyumbang kepada penyakit malignan GTD,berdasarkan kajian ini faktor yang berkait rapat termasuklah faktor usia,bilangan kelahiran anak yang ramai, dan jarak kelahiran yang lama.Umur merupakan faktor utama yang menyumbang kepada penyakit malignan berbanding faktor-faktor risiko yang lain, Kebanyakan pesakit didapati berada di tahap penyakit FIGO peringkat I,rawatan dengan MTX telah mencapai hasil yang memuaskan, manakala pesakit lain yang menerima rawatan tahap kedua juga telah pulih sepenuhnya. Pesakit yang berada dalam FIGO peringkat II dan III telah pulih sepenuhnya dengan rawatan rejimen EMACO.MTX kekal sebagai rawatan tahap pertama kami untuk pesakit berisiko rendah manakala penggunaan Actinomycin juga terbukti bermanfaat dalam rawatan untuk pesakit yang kebal kepada MTX . Bagi pesakit yang tergolong dalam kategori berisiko tinggi kajian ini menyokong penggunaan EMA-CO.

ABBREVIATIONS

CHAMOMA	Methotrexate, Folinic acid, Hydroxyurea, Dactinomycin, Vincristine, Melphalan and Doxorubicin
CM	Complete Mole
CNS	Central Nervous System
EMA-CO	Ethoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, vincristine / Oncovine
FIGO	International Federation of Gynaecological Oncology
GTD	Gestational Trophoblastic Disease
GTN	Gestational Trophoblastic Neoplasia
HCG	Human Chorionic Gonadotrophin
HPE	Histopathological Examination

HUSM	Hospital University Sains Malaysia
MAC	Methotrexate / Leucovorin, Actinomycin-D, and Cyclophosphamide or Chlorambucil
MTX	Methotrexate
OCP	Oral Contraceptive Pill
PTD	Persistent Trophoblastic Disease
RCOG	Royal College of Obstetricians and Gynaecologists
S & C	Suction and Curettage
SD	Standard Deviation
T3	Triiodothyronine
T4	Free Thyroxine
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization
>	Value More
<	Value less

INTRODUCTION

1.0 Introduction

Gestational trophoblastic disease (GTD) forms a group of disorders spanning the conditions of complete and partial molar pregnancies to the malignant conditions such as invasive mole, choriocarcinoma and the very rare placental site trophoblastic tumor (PSTT). There are reports of neoplastic transformation of atypical placental site nodules to placental site trophoblastic tumor.

The World Health Organization classification divides Trophoblastic Disease into the Pre malignant conditions which are Partial Hydatidiform moles, Complete hydatidiform moles and malignant conditions such as Persistent Trophoblastic Disease, Invasive Mole, Choriocarcinoma, Placental Site Tumours.(Altieri, Franceschi et al. 2003)

Molar pregnancies can be subdivided into complete (CM) and partial moles (PM) based on genetic and histopathological features. Complete moles are diploid and androgenic in origin, with no evidence of fetal tissue. Complete moles usually (75–80%) arise as a consequence of duplication of a single sperm following fertilization of an 'empty' ovum. Some complete moles (20–25%) can arise after dispermic fertilization of an 'empty' ovum. Partial moles are usually (90%) triploid in origin, with two sets of paternal haploid genes and one set of maternal haploid genes. Partial moles occur, in almost all cases, following dispermic fertilization of an ovum. Ten percent of partial moles represent tetraploid or mosaic conceptions. In a partial mole, there is usually evidence of a fetus or fetal red blood cells.(Soper, Mutch et al. 2004)

Among the risk factors identified for GTD are Women in young age group less than 15 years old and women older than 50 years old, nulliparous women, low socioeconomic background, dietary protein and carotene deficiency. While association with previous molar pregnancy with risk increased by 20 to 40 times, the overall recurrence rates stands at the range of 5% .(Savage, Williams et al. 2009).

GTD (hydatidiform mole, invasive mole, choriocarcinoma, placental-site trophoblastic tumour) is a rare event in the UK, with a calculated incidence of 1/714 live births. While a recorded rate of 0.2 to 1.5 per 1000 live birth in the Europe and north American region. There is evidence of ethnic variation in the incidence of GTD in the UK, with women from Asia having a higher incidence compared with non-Asian women (1/387 versus 1/752 live births). However, these figures may under represent the true incidence of the disease because of problems with reporting, particularly in regard to partial moles. (Savage, Williams et al. 2009)

GTN may develop after a molar pregnancy, a non-molar pregnancy or a live birth. The incidence after a live birth is estimated at 1/50 000. Because of the rarity of the problem, an average consultant obstetrician and gynecologist may deal with only one new case of molar pregnancy every second year. (Sebire and Seckl 2008)

It is now more frequent to diagnose GTD (particularly hydatidiform mole) in the first trimester as a result of hCG determinations and/or sonography (particularly transvaginal). Indeed, these

two tests (beta subunit hCG and sonography) are invaluable in diagnosis, management, and follow-up of GTD tumors. Levels of hCG in urine or serum correspond to the number of viable tumor cells.

The treatment in GTD is based on subtype of the disease, based on clinical examination, HPE report of the Product of conception.

In general the prognosis in majority of patients with any form of GTD remains excellent, most patients require only primary treatment for non malignant conditions, however managing patients with malignant condition of GTD could pose a challenge for the gynecologists , despite the good prognosis and wide range of treatment , it needs long term follow up and careful close monitoring of patients for relapse of the disease, an advanced disease could be difficult treat and may carry a poor prognosis.

LITERATURE

REVIEW

2.0 Literature review

Gestational trophoblastic disease has long history dating back to 400BC, however it was not well understood until year 1895 the modern approach for the understanding, diagnosis and treatment of the GTD discovered. In recent years the understanding and management of trophoblastic disease found a significant improvement in the prognosis of the disease which was previously invariably fatal disease.

Gestational trophoblastic disease is spectrum of disorder which is pregnancy related ranging from benign condition such as hydatidiform mole to malignant condition of invasive mole.

The incidence of GTD varies according to different regions and greatly differ in people with different ethnic background, Asian population appear to have higher rates of GTN, Malaysian population with an average incidence of 2.8 in 1000 pregnancy which almost triple the incidence of European and American counterpart, while similar rates were observed in Singapore (1in 500), Japan (1 in 294) ,Iran(1 in 314). (Cheah, Looi et al. 1993, Nirmala, Nor Azlin et al. 2013)

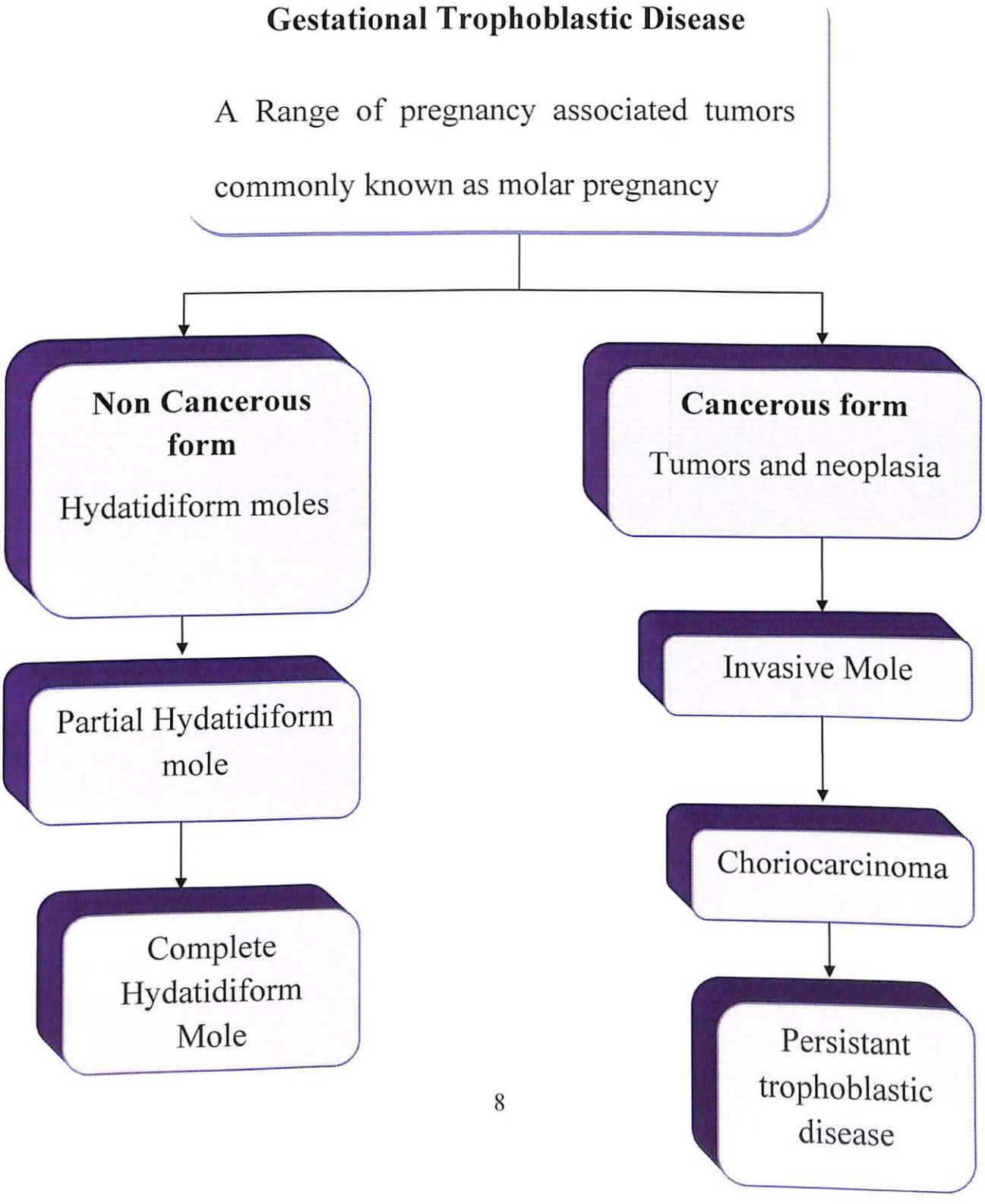
There are many classifications for GTD, however WHO classification (2003) is the most commonly used by many authors. The classification plays an important role in determining the mode of treatment and subsequent monitoring.

With the development of effective chemotherapy and development of accurate tumor marker in the form of human chorionic gonadotrophin for the purpose of diagnosis and monitoring has further improved patient outcome.

GTD (Gestational Trophoblastic Disease) is classified in to 2 main categories which are the Benign and Malignant forms, based on WHO (2003) classification (Figure 1). The benign form includes complete and partial hydatidiform mole ,this diagnosis is usually made upon the histopathological confirmation of the product of conception.

The malignant form or Gestational trophoblastic Neoplasia consists of choriocarcinoma, persistent trophoblastic disease and placental site tumors. Choriocarcinoma is extremely rare. The diagnosis of choriocarcinoma is also achieved by histopathological examination of the product of conception. Persistent trophoblastic disease is a clinical diagnosis unlike other forms of malignant tumors. It is usually a sequel of either partial or a complete mole, when the disease is persistent after initial treatment with suction and curettage and requires chemotherapy as an additional treatment when the patient is diagnosed as Persistent trophoblastic disease (PTD). The disease is identified as persistent during follow up, using the serum hCG level to recognize any plateuing or deviation from normal regression pattern and ultrasound assessment of the uterus together with assessment of sign and symptoms such as per vaginal bleeding. The PTD is diagnosed according to RCOG Criteria for diagnosis of Persistent Trophoblastic Disease (Table 2.0).

Figure 1: The World Health Organization (WHO) Classification of Gestational Throphoblastic Disease (2003) (Altieri, Franceschi et al. 2003)



2.1 Etiology and Pathogenesis:

All Gestational trophoblastic diseases originate from placental source. A complete hydatidiform mole arises as a result of fertilization of an empty ovum or ovum without any maternal chromosomes by a single sperm which then duplicates its chromosome to form a 46XX which Is completely paternal in origin. Rarely the complete hydatidiform mole is 46XY,which happens when an empty ovum is fertilized by 2 spermatozoa.

A partial hydatidiform mean while are almost always triploid, It is the result from fertilization of an normal ovum by two sperms which gives rise to a triploid containing 69 XXY,XXX and sometimes XYY.

The main difference between the partial mole and complete mole is the presence of maternal DNA on immunostaining for partial mole with others features including presence of fetal or embryonic tissue on histopathological examination.

Persistent gestational trophoblastic tumour is a locally invasive diease develops approximately in 15% of the patients following partial or complete hydatidiform mole.(Berkowitz and Goldstein 1996). The presenting symptoms are irregular vaginal bleeding, enlarged uterine size, large theca lutein cyst and occasionally presenting with metastasis to the lungs (80%), liver (4%), vagina (5-16%) and brain (10%). (Evans Jr, Soper et al. 1995)

The term persistent trophoblastic disease is addressed to patients who presents with plateauing or rising level of beta hCG even after complete evacuation. The diagnostic criteria of the persistent trophoblastic gestational disease according to FIGO 2000 criteria(Ngan 2004) includes a rise in hCG levels of 10% or greater over two weeks, a plateau more than four values of hCG for at least three weeks, serum hCG concentration of more than 20, 000 IU/L for four weeks or more, raised hCG concentration 6 months post evacuation even if it is decreasing in trend, heavy vaginal bleeding or evidence gastrointestinal or intraperitoneal hemorrhage.

Choriocarcinoma is an extremely rare malignant tumor. It is the most severe form of molar disease. The distinct difference with molar disease is the characteristically absence chorionic villi. They usually invade myometrium and endometrium, however they tend to have early blood borne metastasis. Prolonged vaginal bleeding is the most common symptom(Soper, Mutch et al. 2004). Due to this any abnormal vaginal bleeding more than six weeks following any pregnancy should be evaluated with beta hCG. The mortality rate is 14 percent for patients who was diagnosed with choriocarcinoma following a term pregnancy.(Lok, Ansink et al. 2006). More than half of them presented with brain metastasis or placental site tumors.(Feltmate, Genest et al. 2001).

2.2 Risk factors:

The risk of developing gestational trophoblastic disease is mainly associated with the extremes of maternal age. It is the maternal age that appears to be the most significant risk factor associated with molar pregnancy. Women who are at increased risk are those younger than 15 years old and older than 45 years old in particular over the age of 50. (Savage, Williams et al. 2009).Women who are 40 year old or more have five to ten fold higher risk of developing hydatidiform mole , it is estimated that almost one third of pregnant women at age greater than 50 year old results in molar pregnancy.

Other risk factors include geographic location and ethnicity, the incidence of gestational trophoblastic diease is higher in Asian population. While a recorded rate of 0.2 to 1.5 per 1000 live birth in the Europe and north American region. There is evidence of ethnic variation in the incidence of GTD in the UK, with women from Asia having a higher incidence compared with non-Asian women 1/387 versus 1/752 live births. (Savage, Williams et al. 2009). However as rare as it sounds in the European population it is more common in Malaysian population with an average of 2.8 in 1000 pregnancy almost triple the incidence compared to European and American counterpart, while similar rates were observed in Singapore (1in 500), Japan (1 in 294),Iran(1 in 314) . (Nirmala, Nor Azlin et al. 2013). (Cheah, Looi et al. 1993)

Other main identified risk factor are previous molar pregnancy, women following one molar pregnancy the risk developing of further molar is less than two percent, however following two molar pregnancies the risk is increased up to one in six and following a third molar pregnancy

the risk may be as high as fifty percent. Apart from this, other factors which appear to be increasing risk for molar pregnancy are carotene deficiency diet and low dietary intake of animal fat and very rarely family clusters has been associated. The use of oral contraceptive pill is associated with an increased risk of GTD with the relative risk of 1.1 to 2.6.(Palmer, Driscoll et al. 1999).

Mean while factors increasing the risk of Persistent Trophoblastic Disease (PTD) are pre-evacuation hCG level more than 100 000 IU/L, uterine size larger than gestational age, thecal lutein cyst larger than 6cm, maternal age more than forty year old, oral contraceptive before hCG falls to undetectable levels.(Berkowitz, Goldstein et al. 1981).The risk of developing PTD after evacuation of a complete hydatidiform mole is as high as 20% compared to partial hydatidiform mole which is around 5%.(Bagshawe 1976).

Table 1.0: Risk of molar pregnancy compared to number of viable conceptions for women in different age groups.

Age	Percent Partial moles of viable conceptions	Percent complete moles of viable conceptions	Overall risk of molar pregnancy
13	0.08	0.32	1 in 250
14	0.07	0.20	1 in 370
15	0.04	0.21	1 in 400
20	0.05	0.06	1 in 909
25	0.09	0.06	1 in 666
30	0.11	0.05	1 in 625
35	0.11	0.05	1 in 625
40	0.18	0.09	1 in 370
45	0.29	0.75	1 in 96
50+	0.59	16.2	1 in 6

(Savage, Williams et al. 2009)

2.3 Presentation and Diagnosis:

The main presenting complaint for GTD is vaginal bleeding up to in 95% of cases with majority of them presenting in the first trimester, however as a result of early recognition through ultrasound and hCG measurement, vaginal bleeding is reported in 84% of patients only compared to 30 years ago which was in 95% of them.(Goldstein and Berkowitz 1994).In rare cases the bleeding maybe severe and life threatening (Chun, Braga et al. 1964).Excessive uterine enlargement relative to gestational age is one the classic signs of hydatidiform mole, approximately 28% of cases are complete hydatidiform mole while less than 10% in partial hydatidiform mole.(Ma, Wong et al. 1990)

Excessive vomiting occurs in about 25% of molar pregnancy (Goldstein and Berkowitz 1982), hydatidiform mole should be particularly looked for in those presents together with excessive uterine size,with high levels of hCG. Pre eclampsia was previously observed in 27% of patients with a complete hydatidiform mole, currently it is reported in only 1 in 74 patients with complete mole on a first visit.(Goldstein and Berkowitz 1994).

Hyperthyroidism was seen more commonly in patients with very high hCG levels, it was observed in approximately 7% of women with complete hydatidiform mole, in severe cases goiter, fine tremor, weight loss were observed (Twiggs 1984). Despite the strong link between hCG and total T_4(thyroxin) and T_3 (tri-iodothyronine) levels , in one study no significant correlation was found linking hCG and T_4 and T_3 (Amir, Osathanondh et al. 1984) .

Another common presentation is theca luthein ovarian cyst, it is a direct result of ovarian hyper stimulation by high level of hCG (Osathanondh, Berkowitz et al. 1986), prominent thecal lutein cyst are more than 6 cm in size and may be up to 20 cm in size. It is found in approximately in 25% patients with complete mole (Berkowitz and Goldstein 1997), the risk of torsion is 2.3%. After evacuation of molar the cyst usually regress spontaneously in within 2 to 4 months.

Trophoblastic embolization with respiratory distress is very rare currently, in the past it was at the range of 2%, patients usually presented with dyspnea, chest pain and tachycardia. Main attributing factors of respiratory distress in molar pregnancy are molar tissue embolization, cardiovascular complication of thyroid storm, cardiovascular complication of pre eclampsia. Respiratory distress usually resolves within 72 hours with cardiopulmonary support, in a very rare occasion disseminated intravascular coagulation may develop.

Patients with partial hydatidiform mole usually do not have prominent clinical features characteristics of a complete hydatidiform mole, in a survey of 81 patient with partial mole, none of them had theca lutein cyst, hyperemesis or hyperthyroidism, the initial clinical diagnosis was incomplete or missed abortion in 91% patients but only 6.2% patients were diagnosed with hydatidiform mole (Berkowitz, Goldstein et al. 1985).

Today the presentation of Hydatidiform mole has changed dramatically over the past decades owed to the easy access to health care facility thus rendering patient to present early and high detection rates via widespread use of ultrasound and measurement of hCG levels.

The diagnosis of Hydatidiform mole and choriocarcinoma is confirmed by histopathological examination of the product of conception, however the mainstay of early diagnosis is ultrasound examination and hCG level measurements ,The use of ultrasound and hCG gaining wide speared popularity due to its non invasive features with minimal adverse effect ,readily available and cost effective method thus becoming choice of many institutions and practitioners.

Ultrasonography is reliable and sensitive method to diagnose Hydatidiform mole, with the introduction of high resolution ultrasound scans it has been a major advantage since the reliable and accurate diagnosis can be made early in the pregnancy, the positive predictive value of ultrasound is as high as 90% (Fine, Bundy et al. 1989). Among the notable ultrasound features for complete mole are placental tissue demonstrating the classical snowstorm appearance representing a hyperechoic endometrial echo complex with multiple hypoechoic space which contains blood between hydropic villi and enlarged uterus while features of partial hydatidiform mole includes focal cystic changes of placenta, increase in transverse diameter of gestational sac and presence of fetal part or growth restricted fetus with focally hydropic placenta. The differential diagnosis of hydatidiform mole is degenerated missed abortion, degenerating fibroid, adenomyosis and rarely uterine malignancy.

The trophoblastic diease is virtually unique in that it produces beta hCG, a specific marker which can be measured in urine or blood and reflects the diease precisely. hCG is a glycoprotein produced by syncytiotrophoblasts, it is composed of alpha and beta subunit with the beta subunit being unique for hCG. In normal singleton pregnancy serum hCG level unlikely to be more than

200 000 IU/L. Higher than 200 000 IU/L of hCG is usually suggestive of molar pregnancy. It may do so in multiple gestation which may lead to diagnostic difficulities. Levels with partial mole are only infrequently above the level for nomal pregnancy in view of that as a diagnostic marker, hCG measurement has a limited value.

Apart from it's role in diagnosing molar pregnancy, beta hCG can be effectively used to assess the response of treatment, recurrence or persistence of the disease.

The diagnosis of persistent trophoblastic disease is made according strict criteria. The RCOG guideline recommends that plateuing or rising hCG level as four or more times for at least three weeks and rising as two consecutive increases in hCG concentration of 10% after evacuation, heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal hemorrhage, serum hCG concentration of 20 000 IU/L or more in four weeks or more after evacuation, raised hCG concentration six months after evacuation even when it is decreasing in trend. Any one of this criteria is enough to make a diagnosis of persistant trophoblastic disease.(Berkowitz and Goldstein 1996)

Table 2.0: RCOG Criteria for diagnosis of Persistent Trophoblastic Disease.

1	Serum beta hCG $\geq$ 20 000 IU/L more than 4 weeks post evacuation
2.	Raised beta hCG six months after evacuation even if still falling levels
3.	Histological diagnosis of choriocarcinoma
4.	Evidence of metastasis in liver, brain, GIT or radiological opacities >2cm on chest radiograph
5.	Heavy vaginal bleeding or evidence of gastrointestinal or intra peritoneal hemorrhage
6.	Plateuing or rising hCG level as four or more times for at least three weeks and rising as two consecutive increases in hCG concentration of 10% after evacuation

(Berkowitz and Goldstein 1996)

2.4 Staging:

Staging system for GTN (Gestational Trophoblastic Neoplasia) has undergone many changes and improvement over the decades, efforts has been directed to produce an effective anatomical and prognostic staging system in order to facilitate the choice of treatment. In 2009 the Collaboration between WHO(World Health Organization) and FIGO (International Federation of Obstetrics and Gynaecology) along with other agencies has produced current anatomical staging and prognostic scoring system.

The prognostic scoring is particularly is helpful in predicting the likelihood of drug resistant and to assist in selection of appropriate treatment regime. The staging system is thought to encourage the objective comparison of data from various centers (Kohorn 2002).

The FIGO anatomical staging of GTN (2009) (Appendix A) (Committee 2002, FCoG 2009) divides the Stages into stage I, II, III and IV.

In stage I, the disease is confined to the uterus and includes all patients with persistently elevated hCG levels, stage II disease is defined when GTN extends outside of the uterus but limited to the genital and pelvic structures such as adnexa, vagina and broad ligament. Stage III is when GTN extends to the lungs with or without known genital tract or pelvic organ involvement, the diagnosis is usually made based on the rising hCG level in the presence of pulmonary lesions viewed best by radiography. Stage IV is patients with advanced disease and involvement of the

brain, liver and kidneys and gastrointestinal tract. Stage IV patients are in the high risk category because they are most likely to be chemotherapy resistant.

2.5 Treatment:

Suction and curettage is the treatment of choice for the evacuation of complete molar pregnancies (Sebire and Seckl 2008). Sharp curettage is not generally recommended due to the risk of uterine perforation and the risk of Asherman's syndrome. Medical termination should be avoided when possible; the use oxytocic therapy may be commenced after evacuation is complete unless there is significant bleeding prior or during evacuation. There is a theoretical concern that oxytocic agents may force trophoblastic tissues into venous space of placental bed and disseminating the disease to the lungs. Whenever the evacuation involves a patient with large gestation precaution need to taken if in case of massive hemorrhage a laparotomy setup should be available for emergency hysterectomy or bilateral internal iliac artery ligation.

All patient with Rh-negative should receive Anti D immunoglobulin after the completion of the evacuation.

The treatment of Gestational trophoblastic neoplasia (GTN) is initiated based on the risk assessment of a particular patient who has met the criteria set for the diagnosis of GTN (Table2).

The WHO & FIGO prognostic scoring system on prognostic factors is used to identify the risk group the patient belongs in order to initiate appropriate treatment.(Appendix B).The group of patients can be divided in to low risk group and high risk group.

Among the components of this scoring system is age in which patient who are more than 40 years old having higher risk , Antecedent pregnancy which highest risk would be for a term pregnancy followed by abortion and mole, interval months from index pregnancy in which time longer than 4 months to 12 months carrying a risk point ,pre treatment serum hCG with level more than 10,000 iu/l to more than 1 million having a increased risk followed by largest tumor size, 3cm or more at risk ,sites of metastasis except for lung carries risk, number of metastases and previously failed chemotherapy. A score of 7 or more is considered as high risk and a score of less than 7 is considered low risk (Appendix B).

Most patients who require additional treatment following their initial evacuation fall into low risk group. The role of repeat suction in these patients has been controversial. Studies suggesting that repeated evacuation in patients with rising or static hCG levels following their initial evacuation is rarely curative (van Trommel, Massuger et al. 2005).Based on these data repeated evacuation is only recommended if the hCG level is less than 5000 IU/L and tissue is seen in uterine cavity on ultrasound examination.

2.5.1 Treatment of Low Risk GTN:

Single agent chemotherapy, Methotrexate (MTX) is treatment of choice for low risk patients,the widely used regime is 50mg intramuscular methotrexate on days 1,3,5, and 7 along with folinic acid on days 2,4,6,and 8 repeated every 2 weeks .Methotrexate is usually well tolerated,it does not cause alopecia or significant nausea and vomiting or myelosuppression, most frequent side effect are mucositis, pleural inflammation and mild elevation liver function test. Patients who develop methotrexate resistant can be switched to Actinomycin D. Single agent MTX chemotherapy achieved complete remission in 90.2% of patients with stage I GTN AND 68.2% in low risk stage II and III GTN (Berkowitz, Goldstein et al. 1986).

The use of MTX and Actinomycin D as single agent chemotherapy in low risk GTN produced similar efficacy according to several studies(Osborne, Filiaci et al. 2011), however MTX has gained popularity because of its easy intramuscular administration compared to intravenous administration of Actinomycin D and MTX is less toxic and well tolerated compared to Actinomycin D ,overall MTX is less toxic, better tolerability and more convenient for patients (Kang, Choi et al. 2010) .

The treatment is continued until normalization of serum hCG levels ,Patients are monitored with serial serum hCG 1 to 2 weekly to assess the response to treatment ,further 3 more courses will be given to ensure eradication of any residual disease after the hCG return to normal level (<2IU/L), the additional chemotherapy given after normalization of serum hCG have reduced recurrence rate to less than 5% (Mutch, Soper et al. 1990).

Those patient who develop resistance to single agent chemotherapy can be subjected to combined or multi agent chemotherapy with either Etoposide, MTX, Actinomycin D, Cyclophosphamide and Oncovin (EMA-CO) or the combination of MTX, Actinomycin D, Cyclophosphamide (MAC).MAC is preferred to EMA-CO regimen is some centers because of the associated risk of secondary tumor ,risk of leukemia (1%) due to Etoposide in EMA-CO regimen (Berkowitz and Goldstein 1996).Actinomycin D can be given in patient with resistance to single agent MTX provided their hCG level is <100 IU/L at the time of commencement of Actinomycin D, if levels are > 100 IU/L either EMA-CO or MAC regime should be considered (Ngan, Chan et al. 2006).Approximately 25% patient will require second line chemotherapy due to single agent chemotherapy resistance however the cure rate is as high almost 100%.

Hysterectomy as a primary treatment is obsolete nowadays, it is no longer an acceptable treatment in women with low risk GTN, with the advancement of chemotherapy drugs and easily available monitoring tool such as hCG less radical approach is favored these days, additionally hysterectomy does not appear to improve the outcome in women with high risk metastatic disease (Lurain 2010)

2.5.2 Treatment of High Risk GTN:

Patients with high risk GTN should be treated with primary multi-agent chemotherapy, latest data indicates that a cure rate of 85-90% in high risk patients treated using multi-agent chemotherapy such as EMACO (Bower, Newlands et al. 1997) (Escobar, Lurain et al. 2003).Historical data from treatment prior to introduction of multi agent chemotherapy

demonstrated that less than one third of high risk patients would be cured with single agent therapy (Bagshawe, Dent et al. 1989).Generally EMACO regimen is well tolerated and serious life threatening toxicity is rare, the major side effects of EMACO are mucositis, pleuritis, alopecia, liver enzyme derangement ,myelosuppression.

Among the other multi agent chemotherapy includes combination of cyclophospamide, hydroxyurea, actinomycin D, MTX, vincristine, melphalan and doxorubicin (CHAMOMA), MTX, etoposide, actinomycin D (MEA), Etoposide, MTX, Actinomycin D, Cyclophosphamide with Platinum based agent ,Cispaltin (EMA-EP).

The relapse rate of high risk GTN is around 7 to 10%,approximately 17% patients develop resistance to multi agent chemotherapy namely EMACO, in this patients second line regimen such as EMA-EP can be used. Despite the recurrence disease the five year survival rate is approximately 85% .Patients with poorest prognosis are those with liver and brain metastases, long term survival rate for liver metastases is 27% and 70% for patients with brain metastases and for patients with both brain and liver metastases is only 10% .

Approximately 4% patients have cerebral metastases at the time of diagnosis, Central nervous system (CNS) or brain metastases may require multimodality treatment comprising radiotherapy with whole brain irradiation, chemotherapy or surgical resection of localized lesion. Generally high dose chemotherapy is given to improve the penetration of the drug into the CNS, Multiagent chemotheraphy when combined with intrathecal methotrexate administration, has a cure rate of