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Gestational Trophoblastic Disease in Malta

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Abstract

Background: Gestational trophoblastic disease (GTD) is a group of uncommon conditions associated with pregnancy and includes a spectrum of premalignant to malignant disorders. The aim of this study is to determine the local incidence of GTD and to analyses the management that is being offered to patients with GTD in Mater Dei Hospital.

Methodology: All patients diagnosed with GTD from 1st January 2015 till 31st December 2020 were studied. The list of patients with GTD was obtained from the Pathology Department and data was collected from medical records, iSOFT and electronic discharge summaries.

Results: In this 6-year study period, 83 cases of GTD were identified. 79.5% of patients had partial hydatidiform mole and 16.9% had complete mole. 3.6% were cases of gestational trophoblastic neoplasia. 55.4% of patients received medical treatment with vaginal misoprostol and 27.7% had immediately surgical management. Their follow-up was studied; 21.7% had 3 out-patients visits or less, 33.7% had between 4 to 6 visits and 19.3% had 7 to 15 outpatients visits. 7.2% had extra oncology out-patients visits. 40% of patients had a follow-up that lasted for 7 months or more.

Conclusion: GTD in Mater Dei Hospital appears to be an uncommon disease, but the local incidence was noted to be as high as 1 per 319 living births. This study demonstrated that a large number of patients were medically treated and the follow-up received was noted to be inconsistent. The care of these patients can be highly optimized by the set-up of a small dedicated clinic.

Keywords: Gestational Trophoblastic Disease; Hydatidiform Mole; Pregnancy; Malta

Abbreviations: GTD: Gestational Trophoblastic Disease; PSTT: Placental Site Trophoblastic Tumour; ETT: Epithelioid Trophoblastic Tumour; GTN: Gestational Trophoblastic Neoplasia; ERPC: Evacuation of Retained Products of Conception; FIGO: Federation of Gynaecology and Obstetrics; FSRH: Faculty of Sexual Health and Reproductive Health; IUC: Intrauterine Contraception; GTN: Gestational Trophoblastic Neoplasia.

Introduction

Gestational trophoblastic disease (GTD) is a group of uncommon conditions associated with pregnancy. GTD arises from abnormal placenta and it includes a spectrum of premalignant to malignant disorders. Histologically, GTD includes the pre-malignant partial hydatidiform mole and complete mole, as well as the malignant invasive mole, choriocarcinoma, placental site trophoblastic tumour

(PSTT) and epithelioid trophoblastic tumour (ETT). The last three forms can arise after any type of pregnancy and are collectively known as gestational trophoblastic neoplasia (GTN) [1]. The GTD spectrum has now been expanded to also include the atypical placental site trophoblastic nodule as 10 – 15% may coexist with or develop into PSTT or ETT [2].

Different epidemiological studies have reported wide variations in the incidence of GTD [3]. Estimates from different studies carried out in Australia, New Zealand, North America, and Europe have shown that the incidence of hydatidiform mole ranges from 0.57 – 1.1 per 1000 pregnancies, whereas studies in Southeast Asia and Japan have reported an incidence as high the as 2.0 per 1000 pregnancies [4]. Up to the current knowledge, the local incidence of GTD in Malta is not known. The aim of this research is to determine the local incidence of GTD and also to analyze the management that is being offered to patients with GTD in Mater Dei Hospital. In this research local practice will be studied and compared to the RCOG Green-top Guideline number 38 – Management of Gestational Trophoblastic Disease last updated in June 2020 [5].

Methodology

All patients diagnosed with GTD in Mater Dei Hospital from 1st January 2015 till 31st December 2020 were studied. The list of patients with GTD was obtained from the Pathology Department of Mater Dei Hospital and data was collected from the medical records, iSOFT and electronic discharge summaries. For this research the permission of the Head of Department of Obstetrics & Gynaecology and the permission of the Data Protection Officer of Mater Dei Hospital were obtained. All data was anonymized and no direct interaction with patients was required.

Results

In this 6-year study period, 83 cases of GTD were identified at Mater Dei Hospital. Table 1 represents the different types of GTD identified. The mean age of these women was 32.3 years with a range of 18 years to 51 years. 18% of these women with GTD were women of 40 years and over. 73.5% (61 patients) were Maltese and 26.5% (22 patients) were non-Maltese. 38.6% (32 patients) were nulliparous and 33.7% (28 patients) had previous miscarriages, ectopic pregnancies or termination of pregnancies. Only one patient was found to have twice partial hydatidiform mole in this study period, and none of the other patients had a history of previous GTD outside the study period.

Type of Gestational Trophoblastic Disease	Number of Cases	Percentage
Partial Hydatidiform Mole	66	79.50%
Complete Hydatidiform Mole	14	16.90%
Invasive Mole	1	1.20%
Choriocarcinoma	1	1.20%
Epithelioid Trophoblastic Tumour	1	1.20%

Table 1: The different types of GTD identified in this 6-year study period.

The number of cases of GTD according to the year of presentation is shown in Table 2. The highest percentages are noted to be in the last 3 years with the highest cases being detected in 2020. The clinical presentation was also studied. The most common presentation was vaginal bleeding and abdominal pain (50.6%). Table 3 represents the clinical presentation of these GTD cases. 4 patients had no medical notes available. 16 patients were diagnosed with GTD prior to treatment. 57.1% (6) of patients with complete molar pregnancy were diagnosed from the ultrasound scan carried out prior to treatment. In this study population, 55.4% (46 patients) received medical treatment with vaginal misoprostol. Out of these patients, 73.9% (34 patients) had an evacuation of retained products of conception (ERPC) after the medical management. 27.7% (23 patients) had immediately surgical management by ERPC. 64.9% of patients (37 patients) who underwent an ERPC were given intravenous syntocinon during the procedure. 28.1% (16 patients) did not receive intravenous syntocinon and 7% of patients (4 patients) had no medical notes available. In addition, 1 patient had uterine artery embolization treatment prior to the ERPC for a complete molar pregnancy, while another patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy for ETT.

Year of Presentation	Number of Cases	Percentage
2015	14	16.90%
2016	9	10.80%
2017	10	12%
2018	17	20.50%
2019	15	18.10%
2020	18	21.70%

Table 2: The number of GTD cases according to the year of presentation.

Clinical Presentation	Number of Cases	Percentage
Vaginal Bleeding and Abdominal Pain	42	50.60%
Silent Miscarriage on routine scan	27	32.50%
Molar pregnancy on ultrasound	3	3.60%
Incomplete Miscarriage on ultrasound	2	2.40%
Hyperemesis	1	1.20%
Fainting episode	1	1.20%
Haemoptysis and Coughing	1	1.20%
Uterine mass on CT scan	1	1.20%
High hCG levels	1	1.20%

Table 3: Clinical presentation of GTD cases.

The further treatment needed was then studied. 6 patients (7.2%) required additional treatment. 3 patients who had complete molar pregnancy, who were treated only with ERPC, required methotrexate. The other 3 patients who required a combination of chemotherapy were the patients with invasive mole, choriocarcinoma and ETT.

The follow-up that these patients with GTD received was studied. 15 patients (18.1%) had private follow-up or did not attend to the gynaecology out-patients department. 18 patients (21.7%) had 3 out-patients visits or less, 28 patients (33.7%) had between 4 to 6 visits, 16 patients (19.3%) had between 7 to 15 outpatients visits. 6 patients (7.2%) had extra oncology out-patients visits. 6 patients (7.2%) of our study population still have on-going follow-up up to the current date. Out of the 65 patients who came for their follow-up at the gynaecology out-patients, 15 patients (23.1%) had follow-up for 2 months or less, 8 patients (12.3%) had follow-up for 3 to 4 months, 13 patients (20%) had follow-up for 5 to 6 months, 16 patients (24.6%) had follow-up for 7 to 9 months and 10 patients (15.4%) had follow-up for 10 months or more.

Discussion

GTD is a spectrum of interrelated disease processes originating from the placenta. GTN neoplasia refers to lesions that have the potential for local invasion or metastasis [6]. The average incidence of GTD in Mater Dei Hospital was found to be 1 per 319 live births. Up to the current knowledge, this is the first incidence of GTD that was determined in Malta and when compared to other countries this incidence is quite high. In fact, the calculated incidence of GTD in the United Kingdom is that of 1 in 714 live births, while that of Asian women is 1 in 387 live births [5]. The latter are known to have high incidence, and our local incidence is even higher. This high incidence of GTD in Mater Dei Hospital could be contributed to multiple factors. Some of these potential contributing factors could be the following. First of all, in Mater Dei all products of conception are sent to the pathology lab for histological analysis and this is not a common practice in every international hospital. Also, in Malta we have noticed an increase in non-Maltese women including Asian patients and these could be further contributing to the rise in the number of GTD in Malta. Another contributing factor could be that 13 cases of the partial moles were reported as cases of suspicious of partial moles. This was further discussed with the pathology department and was advised to include them with the partial moles as the histological diagnosis of partial moles can be quite challenging. And so, the lack of specialized center in Malta and lack of specialized pathologist might contribute to the over diagnosis of partial moles.

Hydatidiform Moles

Hydatidiform moles are the most common type of GTD. Hydatidiform moles are most commonly diagnosed in the first half of pregnancy [6] and in this study period all cases were diagnosed in the first trimester of pregnancy. Only 3.6% of patients were noted to have molar pregnancy on ultrasound without any other symptoms. Overall, 19.3% (16 patients) of cases had ultrasound diagnosis of GTD prior to treatment and 80.7% (67 patients) were diagnosed only from the histology result. Hydatidiform moles are divided into partial and complete moles. In both these two conditions, the placental villi become oedematous and this is caused through a defect in gametogenesis or fertilization [6,7]. Table 4 represents the different features of partial and complete mole. Despite the differences mentioned in this table, their management is similar. In our study 27.7% had suction curettage under general anaesthesia in theatre, 14.5% had medical treatment only with vaginal misoprostol and 41% had first medical management which was followed by surgical evacuation in theatre. The RCOG Green-top guideline states that suction curettage is the method of choice for the removal of complete molar pregnancies. In complete molar pregnancies there will be no foetal parts, so suction removal is the method of choice irrespective of the uterine size [5]. Suction curettage is also the method of choice for partial moles except when the size of fetal parts deters the use of suction curettage and then medical removal is preferred [5]. In this study, high number of patients with partial moles, 39 cases out of the 66 partial moles (59.1%) where treated with vaginal misoprostol.

Features	Partial Mole	Complete Mole
Karyotype	69 XXX or 69 XXY (2/3 paternal, 1/3 maternal origin)	46 XX or 46 XY(paternal origin)
Evidence of foetus	May be present	Absent
Villous oedema	Variable	Diffuse
Trophoblastic proliferation	Focal	Diffuse
p57 staining	Present	Absent
Clinical diagnosis	Missed spontaneous abortion	Molar gestation or missed spontaneous abortion
Theca lutein cysts	Rare	9 – 25%
Medical Complications	Rare	6 – 20%
Post-molar GTN	2.5 – 7.5%	7 – 30%

Table 4: Different features of partial and complete moles [6].

The medical management of complete molar pregnancy should be avoided. In a study of more than 4000 women with GTD, it was found that the risk of developing GTN and requiring chemotherapy was 16-fold higher when the medical methods of removal were used compared with the surgical removal [8]. In this study population, 4 out of the 14 cases (28.6%) of complete moles received medical management, however none of them had any complications and they did not require further treatment such as chemotherapy. The 3 cases of complete moles that required additional chemotherapy had immediate surgical treatment with suction curettage. The International Federation of Gynaecology and Obstetrics (FIGO) add that hysterectomy can be an alternative to suction curettage if child-bearing is complete. It is stated that by performing a hysterectomy one would provide permanent sterilization and also decreases the need for subsequent chemotherapy by eliminating the risk of local myometrial invasion as a cause of persistent disease [9].

Case reports on uterine artery embolization as part of the treatment for GTD have been reported Carlini L, et al. [10,11]. This modality has been used in cases of persistent GTD and selective uterine artery embolization was carried out instead of invasive surgery and they managed to achieve both the control of the hemorrhage and also the control of the disease [10]. This modality of treatment can also be used for GTN [11]. In this study population, we had one case in October 2020 of complete molar pregnancy who had uterine artery embolization prior to ERPC. The patient is still being followed up but did not require any further treatment such as chemotherapy. In this 6-year study period, there were no cases of twin pregnancies with one viable foetus and the other molar pregnancy. In such rare cases, women should be counselled about the potential increased risk of perinatal morbidity. Sebire, et al. [12] published a study in 2002 on the outcome of 77 mothers with twin pregnancies who had complete mole and healthy co-twin. They concluded that although there is high risk of spontaneous abortion, they had 40% live births and no significant increase in persistent GTD.

The optimum follow–up care was changed in the last updated Green-top guideline. Before the latest update of September 2020, the follow-up for complete and partial moles were the same [13]. In the latest Green-top guideline, the follow–up for partial moles was changed. For complete mole, if the HCG level has reverted to normal values within 56 days of the pregnancy event, then follow-up will be for 6 months from the date of uterine removal [5]. On the other hand, if hCG level has not returned to normal values within 56 days of the pregnancy event, then follow-up will be for 6 months from the normalisation of the hCG level [5]. The new follow-up for partial moles is now shorter. The follow-up is concluded once the HCG level has returned to normal values on two samples, at least 4 weeks a part [5]. Also, it is now clearly stated that women who have not received chemotherapy for GTD no longer need to have hCG measured after any subsequent pregnancy even, as the incidence of GTD in a subsequent pregnancy event in these women is very low [14]. In this study we noted that the follow-up that the patients received was inconsistent and did not follow any regular protocols, with 19.3% of patients who came for follow-up at Mater Dei Hospital had between 7 to 15 hospital visits. These were mainly out-patients visits just for the HCG results and these were visits that were carried out in the same antenatal clinic with other pregnant mothers.

The Faculty of Sexual Health and Reproductive Health (FSRH) Guideline also recommends that after complete molar pregnancy, women are advised to avoid subsequent pregnancy for at least 6 months to allow hCG monitoring for ongoing GTD [15]. And after partial molar pregnancy, women are advised to avoid pregnancy until two consecutive

monthly HCG levels are normal [15]. Women are advised that most methods of contraception can be safely used after treatment for GTD and can be started immediately after uterine evacuation, with the exception of intrauterine contraception (IUC). The IUC should not be inserted in women with persistently elevated HCG levels or malignant disease.

Gestational Trophoblastic Neoplasia

Gestational trophoblastic neoplasia (GTN) is malignant lesions that arise from placental villous and extra-villous trophoblast [16]. GTN occurs in 1 every 40,000 pregnancies and is also more common in Asia than it is in Europe or North America. It mainly consists of 4 different pathological conditions: the invasive mole that follows either after a complete mole or a partial mole, choriocarcinoma, PSTT and ETT [16]. Each of these 4 conditions can penetrate the uterine wall, metastasize and can even lead to death if left untreated. In our 6-year study period we had only 3 cases of GTN out of the 83 total cases of GTD. The process of specifying the aetiological risk factors which could cause GTN progression is not easy [17]. Pregnancy after 40 years and abnormal forms of hydatidiform moles are the main aetiological risk factors of complete mole progression [18]. The development of invasive mole happens when the molar villi exceed the uterine myocytes. Nearly about 15% of complete moles would cause local tumor invasion, and 5% of complete moles will metastases commonly into the vagina or lungs [17]. On the other hand, the progression of local tumor invasion after partial moles happens is about 0.5% of patients, while the occurrence rate of metastatic disease is much less [17].

Approximately 50% of cases of GTN arise from molar pregnancy, 25% from miscarriage or tubal pregnancy, and 25% from term or preterm pregnancy [19]. Invasive mole and choriocarcinoma, which make up the vast majority of these tumors, always produce substantial amounts of HCG and are highly responsive to chemotherapy with an overall cure rate of over 90%, making it usually possible to achieve cure while also preserving fertility [19]. In contrast, PSTT and ETT, which rarely occur, produce very little amounts of HCG and are relatively resistant to chemotherapy [19]. Because PSTTs and epithelioid tumours are not much sensitive to chemotherapy, their mortality rate is higher than that of a choriocarcinoma [17].

Women with GTN are now assessed using the FIGO 2000 scoring system before chemotherapy treatment [5]. Table 5 shows this FIGO 2000 scoring system adapted from the RCOG Green-top guideline. Women with scores of 6 or less are considered as low risk and are treated with single-agent intramuscular methotrexate, alternating daily with folinic acid for 1 week followed by 6 rest days [5]. Women with scores of 7 or greater are considered as high risk and are most commonly treated with intravenous multi-agent chemotherapy, which includes combinations of methotrexate, dactinomycin, etoposide, cyclophosphamide and vincristine. However, the best combination of chemotherapy for GTN was not established in the Cochrane database review that was published in 2016 by Izzam, et al. [5,9,20].

FIGO Scoring	0	1	2	4
Age (years)	< 40	≥ 40	----	----
Antecedent Pregnancy	mole	Abortion (including miscarriage)	Birth	----
Interval months from end of index pregnancy to treatment	< 4	4 to < 7	7 to < 13	≥ 13
Pretreatment serum hCG (IU/L)	$< 10^3$	10^3 to $< 10^4$	10^4 to $< 10^5$	$\geq 10^5$
Large tumour size, including uterus (cm)	< 3	3 to < 5	≥ 5	----
Size of metastases	Lung	Spleen, Kidney	Gastrointestinal	Liver, Brain
Number of metastases	----	4-Jan	5 – 8	> 8
Previous failed chemotherapy	----	----	Single Drug	2 or more drugs

Table 5: The FIGO 2000 scoring system adapted from the RCOG Green-top Guideline [5].

Recommendations

FIGO recommends that the optimal care of rare diseases like GTD is centralized care [9]. Without some type of centralization, treatment decisions and follow-up will be inconsistent. In this study population it was clearly demonstrated that the management and even more the follow-up that these patients received was completely haphazard. The care of these patients can be greatly optimized if the treatment and follow-up is regulated by simple local

protocols and carried out by a small group of dedicated doctors. As the numbers of GTD in Mater Dei Hospital are approximately only 14 cases each year, these patients can be easily be seen and followed-up in an afternoon clinic at the Gynaecology out-patients department with other mothers who have suffered a miscarriage. Currently, patients with GTD and unfortunately even patients suffering from a miscarriage are being followed-up at the same out-patient clinic with other antenatal mothers. And this is not right! Most of the patients studied had multiple hospital visits for just the HCG result. These could have been easily be avoided by simple telephone consultations. Appendix 1 is a simple management protocol for patients with hydatidiform moles that can be used in the absence of a dedicated clinic. This can help trainees and other senior staff in regulating the treatment and follow-up of patients with GTD.

Conclusion

GTD in Mater Dei Hospital appears to be an uncommon disease, but when compared to other countries our local incidence was noted to be as high as 1 per 319 living births. This study also demonstrated that a large number of patients received medical treatment instead of the surgical treatment, but only 6 patients out of the 83 studied requiring further chemotherapy. In addition, the follow-up that these patients received was noted to be inconsistent and impractical. The care of patients with GTD can be highly optimized by the set-up of a small dedicated clinic in Mater Dei Hospital.

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