European Journal of Obstetrics & Gynecology and Reproductive Biology 257 (2021) 95–99

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Curative effect of second curettage for treatment of gestational trophoblastic disease - Results of the Belgian registry for gestational trophoblastic disease

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ARTICLE INFO

Article history:
Received 13 July 2020
Received in revised form 30 November 2020
Accepted 3 December 2020

Keywords:
Molar pregnancy
Gestational trophoblastic neoplasia
Second curettage

ABSTRACT

Objective: We assessed the curative effect of a second curettage in patients with persistent hCG serum levels after first curettage for a gestational trophoblastic disease (GTD).
Study Design: This prospective observational study used the data of the Belgian register for GTD between July 2012 and January 2017. We analysed the data of patients who underwent a second curettage. We included 313 patients in the database. Primary endpoints were need for second curettage and chemotherapy.
Results: Thirty-seven patients of the study population (12 %) underwent a second curettage. 20 had persistent human chorionic gonadotropin hormone (hCG) elevation before second curettage. Of them, 9 patients (45 %) needed no further treatment afterwards. Eleven patients (55 %) needed further chemotherapy. Nine (82 %) were cured with single-agent chemotherapy and 2 patients (18 %) needed multi-agent chemotherapy.
Of the 37 patients, patients with hCG levels below 5000 IU/L undergoing a second curettage were cured without chemotherapy in 65 % versus 45 % of patients with hCG level more than 5000 IU/L. Of the ten patients with a hCG level below 1000 IU/L, eight were cured without chemotherapy.
Conclusions: Patients with post-mole gestational trophoblastic neoplasia can benefit from a second curettage to avoid chemotherapy, especially when the hCG level is lower than 5000 IU/L.

Introduction

Gestational trophoblastic disease (GTD) represents a spectrum of different premalignant and malignant diseases. The premalignant diseases are subdivided in complete (CM) and partial hydatidiform mole (PM). Invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) represent the malignant part [1–3]. The malignant diseases, also known as' gestational trophoblastic neoplasia (GTN)', can arise after any type of pregnancy [4].

The prevalence of gestational trophoblastic disease is about 1 in 1 000 pregnancies for CM and 3 in 1 000 pregnancies for PM [2]. CM has a 15–20 % risk of becoming malignant [2,3,5]. Less than 1 % of the PM become malignant [2,6–9]. With a cure rate of almost 100 %, low risk GTN are among the best prognostic solid cancers [2]. Fatal cases due to severe bleeding at the onset of the disease, late presentation, incorrect risk classification, drug resistance or drug complications are becoming very rare [2,4].

The diagnosis of molar pregnancy is made after careful pathologic examination of curettage material [2,3]. Afterwards, human chorionic gonadotropin hormone (hCG) monitoring is essential for early detection of malignant transformation [3,10]. In case of post-mole neoplasia, the main treatment options are chemotherapy or surgery. Indications for treatment with chemotherapy are: a plateaued or rising hCG, histological diagnosis of choriocarcinoma, [2,3].

Currently, the benefit of a second curettage in patients with post-mole gestational trophoblastic neoplasia remains controversial. In a recent study of Osborne et al., a second curettage showed

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https://doi.org/10.1016/j.ejogrb.2020.12.001
0301-2115/

therapeutic effect and allowed to omit the need for chemotherapy in about 40 % of the patients with low-risk, non-metastatic post mole GTN [11].

The aim of this study is to investigate the curative effect of a second curettage after molar pregnancy (with and without progression to GTN and their need for chemotherapy).

Materials and methods

Belgian register for trophoblastic diseases

A Belgian National register for gestational trophoblastic diseases [12] was initiated in July 2012 (Belgian Register for Trophoblastic Diseases (www.mole-chorio-bgog.eu)), and hosted by the Belgian Gynaecological Oncology Group (BGOG).

The aim of this prospective registration study is twofold. First to register patients diagnosed with gestational trophoblastic disease; and second to offer central pathology review and advise about the treatment and follow-up of these patients. Improving the diagnosis, treatment and outcome of patients with GTN is the ultimate goal and has proven useful in other countries [2,5].

Two reference centres were initiated: one for the French-speaking part of Belgium (Centre Hospitalier Universitaire de Liège) and one for the Flemish-speaking part (University Hospitals Leuven). All patients with a diagnosis of gestational trophoblastic disease (after pathology confirmation) are eligible. The local practitioner contacts a reference centre when a molar pregnancy is diagnosed and remains treating physician. Patient referral to the reference centre is not mandatory. The patient is asked to sign an informed consent and to complete a questionnaire on medical history and demographic data. The tumour sample, mostly obtained by curettage, is revised by one of the central pathologists: Dr. Delbecque and Pr. Delvenne (University Hospital of Liège, Liège), Pr. Marbaix (University Hospital Saint-Luc, Brussels), Pr. Noel (Erasmus Hospital, Brussels); Pr. Moerman and Pr Van Rompuy (University Hospitals Leuven, KU Leuven, Leuven). After central confirmation of molar pregnancy, weekly serum hCG (IU/L) is monitored with supervision by the reference centre for early detection of abnormal evolution. The reference centre advises on treatment or follow-up. hCG normalisation curves of this dataset were published previously [13].

When abnormal evolution is observed, the local practitioner is contacted. The hCG level needs to be analysed weekly till the level is normalised ($\leq$ 2.0 IU/L) for 2 consecutive weeks for patients with partial and complete mole. The follow-up for patients with complete mole is extended for a period of 6 months (monthly hCG). Follow-up is shorter for patients with partial mole because the risk for subsequent GTN is less than 1:3000 [14]. Serum hCG levels were determined by the β subunit radioimmunoassay method. The assay used is made according to local laboratory preferences. Persistent hCG elevation was defined as plateauing hCG levels (four values, three weeks of interval) or rising hCG levels (three values, two weeks of interval) according to the FIGO criteria [2].

For the current analysis, we included all women who underwent second curettage. The treating physician decided whether or not a second curettage was performed. For this study we assessed: indications of second curettage, hCG levels at the moment of the second curettage, complications and subsequent treatment. The pathology reports of the first and second curettage were also compared.

Summary statistics of these patients are expressed descriptively or as a percentage.

Results

Between July 2012 and January 2017, 330 patients were registered. After review, 17 patients were excluded for various reasons (no pathology report, no information about treatment or lost to follow-up). Table 1 shows our results after review of pathology. There were 24 pathology slides without review, 5 inconclusive results and 27 missing data. Fig. 1 shows overall need for second curettage and chemotherapy. The overall need for chemotherapy was 22 % (69 patients) in our population.

Table 1
Pathology results after review.

Diagnosis	Number of patients
Partial mole	85
Complete mole	147
Choriocarcinoma	10
Invasive mole	3
PSTT	2
ETT	2
Simple miscarriage	25
No central review	24
Inconclusive results	5
Missing data	27
Total	330

A total of 37 women underwent second curettage. Mean time between the first and second curettage was 49 days (range: 1–217 days). In Fig. 2 outcome of second curettage was shown.

20 patients had persistent hCG elevation, of them 55 % needed chemotherapy after the second curettage. 45 % was cured without chemotherapy. Eight patients received their chemotherapy after the second curettage, three before. There was no reason mentioned for giving the chemotherapy before the second curettage. There were also five patients who received chemotherapy without notion of persistent hCG elevation. Three patients had a complete or

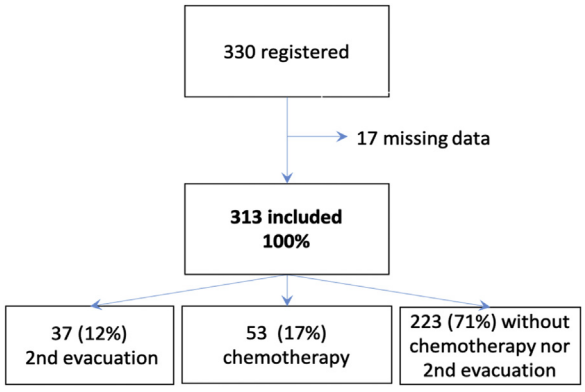

Fig. 1. Outcome of patients registered with gestational trophoblastic disease.

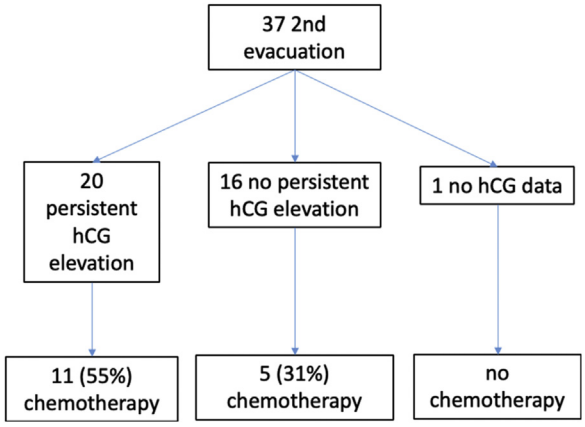

Fig. 2. Outcome of patients with second curettage.

partial mole, one patient had a choriocarinoma, the other a PSTT. Three were treated with methotrexate, the other two received multi-agent chemotherapy.

Eleven patients (55 %) needed further chemotherapy after their second curettage.

Of them, 9 (82 %) were cured with single-agent chemotherapy (low dose methotrexate or dactinomycin) and 2 patients (18 %) needed multi-agent chemotherapy. The pathology report of the patients who needed multi-agent chemotherapys showed one invasive mole and one PSTT.

Fifteen women underwent a second curettage for residual molar tissue in the uterus (40 %). Other reasons for second curettage were: persistent high hCG whether or not with residual molar tissue (n = 12; 32 %); persistent vaginal bleeding (n = 4; 11 %), other (n = 3; 8%) and missing data (n = 3; 8%).

Complications were reported for 2 patients. One patient suffered from a uterine infection with ARDS (acute respiratory distress syndrome), another patient had a haemorrhage (grade of seriousness not mentioned). No uterine perforation was mentioned.

Fig. 3 shows the comparison of the pathology reports after first and second curettage. Twenty-two patients (59 %) had same results in both curettages. For three patients (8 %), there was an upgrading (e.g. CM to choriocarcinoma), in four patients (11 %) we found a downgrading (e.g. PM to benign pathology). In 16 % there were missing data or unknown pathology report of the first curettage.

The mean hCG normalisation time of our overall study population was 12.6 weeks (range: 3–66 weeks). We found a serum hCG normalisation of 17 % within 6 weeks, 60 % within 11 weeks and 93 % within 25 weeks after the first evacuation. When we investigated our population without chemotherapy or second curettage (low-risk), mean hCG normalisation time was 10 weeks. Women who underwent a second curettage and did not need chemotherapy thereafter had a mean hCG normalisation time of 14.5 weeks. With chemotherapy, this mean normalisation time increased to an average of 19 weeks.

Median hCG level at the moment of the second curettage was 3 432 IU/L (range 37–86 062 IU/L; missing data n = 9). Women who needed chemotherapy after their second curettage had a median hCG of 3 400 IU/L (range 37–80 192 IU/L). Eleven patients had a hCG level >5 000 IU/L, 17 patients had a hCG level <5 000 IU/L. In the first group, 5 patients were cured without chemotherapy (45 %) whereas patients with hCG levels <5 000 IU/L undergoing a second curettage were cured without chemotherapy in 65 % (11 patients). Of the ten patients with a hCG level below 1 000 IU/L, eight patients were cured without chemotherapy.

Centralisation

Based on birth rates in Belgium and based on epidemiological date for European countries, there is an estimated prevalence of 100–150 molar pregnancies a year [15]. A retrospective study of the

Fig. 3. Inner circle: first curettage pathology report, outer circle: second curettage pathology report. Legend: PM (partial mole), CM (complete mole), Chorioca (choriocarcinoma), PSTT (placental site trophoblastic tumour), Benign (trophoblastic rest or exaggerated placental site and secretory endometrium).

Belgian registration of molar pregnancies found 174 patients registered between 2005 and 2007 [15]. Since epidemiologically the incidence of PM is three times the incidence of the CM, it is noteworthy that in our database, we found more CM (147) than PM (85). This could be due to a referral bias linked to the fact that PM are considered as more' benign' and less harmful than CM and hence are less signed up to the Belgian Registry. Besides, the histopathological diagnosis of partial mole is difficult, often confused with hydropic abortion and other chromosomic abnormalities.

An objective of this registry was to investigate the beneficial effect of centralisation of this rare and specific disease in Belgium, which has never been done before. Nevertheless, centralisation has proven its significance in other countries. The Department of Health and the Royal College of Obstetrics and Gynaecology established a registration and follow-up system in the UK in 1972. Since then patients with GTD are nationally registered and screened within the following three centres (Charing Cross Hospital in London, Weston Park Hospital in Sheffield and Ninewells Hospital in Dundee) [16–20]. In the Netherlands, there were 2 122 patients registered in the Dutch Central Registry for Hydatidiform Moles Radboud University Nijmegen Medical Centre) between 1987 and 2003 [5]. In France, Le Centre de Référence des Maladies trophoblastiques was established in 1999 in Lyon [21].

Second curettage

In this study, we evaluated the effect of a second curettage. We investigated the need for chemotherapy after a second evacuation and its eventual debulking effect.

In the literature, there is no consensus about a second curettage. Cure rate of a second curettage in the literature varies from 9.4%–83% (Table 2) [5,11,18,22]. Van Trommel et al. performed a retrospective cohort survey in a group of 294 patients with PTD (persistent trophoblastic disease). Eighty-five patients underwent a second curettage, 209 patients were considered as control group. They found a significant difference between the two groups. 9.4 % of patients with PTD needed no further chemotherapy after their second curettage, whereas 100 % of the control group needed chemotherapy. They also found a debulking effect in patients who required further chemotherapy. These women needed less cycles of chemotherapy. The indication for repeat curettage was vaginal bleeding only in 60 % of patients and abnormal hCG levels or evidence of retained tissue in 37.6 % of patients [5]. In their study, a second curettage had a major complication rate (uterine perforation or bleeding) of 4.8 % [5]. In the study of Pezeshki et al., 4 075 patients were registered, and 544 patients had a second evacuation performed. 21 % required chemotherapy thereafter. The indication for the second curettage varied, mainly for vaginal bleeding. Pezeshki et al. found in their prospective study that 68 % of the patients with PTD based on elevated hCG levels only, were cured with a second curettage. Need for chemotherapy was more likely in patients with hCG > 1 500 IU/L and histological evidence of PTD [18]. Osborne et al. as well performed a recent study about second curettage in low-risk GTN patients. Of their study population of 60 women, there was no need for additional chemotherapy in 40 %. Nevertheless, a complication rate of 10 % was noted with one uterine perforation and five uterine haemorrhages [11]. In the small study by Yarandi et al., there was a cure rate of 83 % after second curettage [22].

Our study population with persistent hCG elevation had a cure rate of 45 % after second curettage, meaning that 9 patients possibly evaded treatment with chemotherapy, associated side effects and toxicity. Patients who needed chemotherapy, were cured with single agent chemotherapy in 82 % of cases. Because of this small number of patients and different treatment schemes, this outcome cannot be easily assigned as a debulking effect. As this was a descriptive study, we did not interfere with the treatment and we could not measure the implications of doing a second curettage in patients only with persistent high hCG compared to a control group. We should consider the fact that a second curettage could be done for a few' wrong' reasons. Some patients received their second curettage before they were registered and thus without advice of the referral centre. In our study, the main indication for second curettage was residual molar tissue and not persistent high hCG. Also, vaginal bleeding was a main reason to do a second curettage. For twelve patients, persistent high hCG was specifically mentioned as main reason for second curettage. There is no mention of performed ultrasound examination after the first curettage (completeness of evacuation). Our range of hCG level was wide (37 IU/L to 86 062 IU/L) and often a lot more than the proposed upper limit of 5 000 IU/L for a second curettage [2].

As a recent study of Osborne et al. proved, surgical cure rate was higher with lower hCG levels. They found a response rate of 53 % in patients with hCG levels between 100 and 1 500 IU/L and 0 % in patients with hCG levels above 100 000 IU/L [11]. Patients in our study with a hCG level less than 5 000 IU/L had a cure rate of 65 % without chemotherapy after their second curettage versus 45 % when hCG was higher than 5 000 IU/L [2]. Of the ten patients with a hCG level below 1 000 IU/L, eight were cured without chemotherapy. A study at the Sheffield Gestational Trophoblastic Disease Center between 1991 and 1993 set the cut-off of the hCG level at 5 000 IU/L, with more chance of surgical cure in patients with hCG level of less than 5 000 IU/L [18].

More recent studies talk about cut-off rates of 1 500 IU/L (urinary) [18]. Savage et al. recommend a second curettage only when there is a proven residual mass in the uterus, hCG is less than 5 000 IU/L and patients are well informed about relative risks and benefit of the procedure [23]. Chance of needing chemotherapy after second curettage was more than 50 % [2,23] when the hCG level exceeds 5 000 IU/L.

Taylor et al. found, in a small study (35 patients), a spontaneous normalisation of hCG level in 86 % of patients with molar pregnancy and raised but falling hCG level after six months [24]. Can we just wait with our low risk patients? We also should put the risks of a curettage (e.g. infection, haemorrhage, uterine perforation) together with the high cure rate and safety of chemotherapy [2]. Women with gestational trophoblastic disease are generally young and have fertility wish. Is a second curettage compromising their fertility and slowing down their child wish because the delay of chemotherapy thereafter? We want to

Table 2
Cure rate of 2nd curettage as reported in the literature. Cure is defined as no additional chemotherapy needed.

Study	N second curettage	Percentage of cured patients after second curettage
van Trommel et al. [5]	85	9.4 %
Pezeshki et al. [18]	544	67.6 %
Osborne et al. [11]	60	40 %
Yarandi et al. [22]	12	83 %
Current study	37	57 %

emphasize the importance of selecting the right patients for a treatment with a second curettage.

What is the ratio of patients with initial GTD (mole) that meets the criteria of post-mole GTN that have been cured with a second curettage instead of receiving chemotherapy?

Indeed, What is a persistent GTD?

- Is it a mole that has not been incompletely evacuated during the first curettage?
- Is it a post mole GTN with rising HCG that occurs after a complete evacuation (assessed by US after the first curettage).
- A mixed of both?

Patients with post-mole gestational trophoblastic neoplasia with persistent hCG level can benefit from a second curettage to avoid chemotherapy, especially when hCG level is lower than 5 000 IU/L and even more if hCG is below 1 000 IU/L. Randomised controlled studies are needed to confirm this observation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We want to thank every specialist who registered their patients for the Belgian Register and every patient who acceded this register.

References

[1] Froeling FE, Seckl MJ. Gestational trophoblastic tumours: an update for 2014. Curr Oncol Rep 2014;16(11):408.
[2] FIGO Oncology Committee. FIGO staging for gestational trophoblastic neoplasia 2000. FIGO Oncology Committee. Int J Gynaecol Obstet 2002;77:285–7.
[3] Ngan HY, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynaecol Obstet 2015;131(Suppl 2):S123–6.
[4] Lybol C, Centen DW, Thomas CM, ten Kate-Booij MJ, Verheijen RH, Sweep FC, et al. Fatal cases of gestational trophoblastic neoplasia over four decades in the Netherlands: a retrospective cohort study. Bjog 2012;119(12):1465–72.
[5] van Trommel NE, Massuger LF, Verheijen RH, Sweep FC, Thomas CM. The curative effect of a second curettage in persistent trophoblastic disease: a retrospective cohort survey. Gynecol Oncol 2005;99(1):6–13.
[6] Bagshawe KD, Lawler SD, Paradinas FJ, Dent J, Brown P, Boxer GM. Gestational trophoblastic tumours following initial diagnosis of partial hydatidiform mole. Lancet 1990;335(8697):1074–6.
[7] Berkowitz RS, Goldstein DP, Bernstein MR. Natural history of partial molar pregnancy. Obstet Gynecol 1985;66(5):677–81.
[8] Rice LW, Berkowitz RS, Lage JM, Goldstein DP, Bernstein MR. Persistent gestational trophoblastic tumor after partial hydatidiform mole. Gynecol Oncol 1990;36(3):358–62.
[9] Ngan S, Seckl MJ. Gestational trophoblastic neoplasia management: an update. Curr Opin Oncol 2007;19(5):486–91.
[10] Bolze PA, Attia J, Massardier J, Seckl MJ, Massuger L, van Trommel N, et al. Formalised consensus of the European Organisation for Treatment of Trophoblastic Diseases on management of gestational trophoblastic diseases. Eur J Cancer 2015;51(13):1725–31.
[11] Osborne RJ, Filiaci VL, Schink JC, Mannel RS, Behbakht K, Hoffman JS, et al. Second curettage for low-risk nonmetastatic gestational trophoblastic neoplasia. Obstet Gynecol 2016;128(3):535–42.
[12] Delcominette S, Timmermans M, Delbecque K, Delvenne P, Marbaix E, Noel JC, et al. Belgian register and reference centers for gestational trophoblastic diseases. Rev Med Liege 2015;70(11):550–6.
[13] Delattre S, Han S, Moerman P, Billen J, Goffin F, Scharpe K, et al. Human chorionic gonadotropin regression curves after partial or complete molar pregnancy in flanders: are they different from regression curves from the eighties? Gynecol Obstet Invest 2017.
[14] Mangili Giorgia, Lorusso Domenica, Brown Jubilee, Pfisterer Jacobus, Massuger Leon, Vaughan Michelle, et al. Trophoblastic disease review for diagnosis and management. Int J Gynecol Cancer 2014;24:S109–16.
[15] Han SN, Van Belle S, Peeters M, Goffin F, Verbrugghe M, Vergote I. Evaluatie van een versnelde registratie door het College voor Oncologie van gestationele trofoblastziekten in België. Tijdschr. voor Geneeskunde 2014;70(16).
[16] Kendall A, Gillmore R, Newlands E. Chemotherapy for trophoblastic disease: current standards. Expert Rev Anticancer Ther 2003;3(1):48–54.
[17] Goldstein DP, Garner EI, Feltmate CM, Berkowitz RS. The role of repeat uterine evacuation in the management of persistent gestational trophoblastic disease. Gynecol Oncol 2004;95:421–2 United States.
[18] Pezeshki M, Hancock BW, Silcocks P, Everard JE, Coleman J, Gillespie AM, et al. The role of repeat uterine evacuation in the management of persistent gestational trophoblastic disease. Gynecol Oncol 2004;95(3):423–9.
[19] Sebire NJ, Rees H, Paradinas F, Seckl M, Newlands E. The diagnostic implications of routine ultrasound examination in histologically confirmed early molar pregnancies. Ultrasound Obstet Gynecol 2001;18(6):662–5.
[20] Paradinas FJ. The diagnosis and prognosis of molar pregnancy: the experience of the National Referral Centre in London. Int J Gynaecol Obstet 1998;60(Suppl 1):S57–64.
[21] Golfier F, Clerc J, Hajri T, Massardier J, Frappart L, Duvillard P, et al. Contribution of referent pathologists to the quality of trophoblastic diseases diagnosis. Hum Reprod 2011;26(10):2651–7.
[22] Yarandi F, Jafari F, Shojaei H, Izadi-Mood N. Clinical response to a second uterine curettage in patients with low-risk gestational trophoblastic disease: a pilot study. J Reprod Med 2014;59(11–12):566–70.
[23] Savage P, Seckl MJ. The role of repeat uterine evacuation in trophoblast disease. Gynecol Oncol 2005;99:251–2 United States author reply 2-3.
[24] Taylor F, Short D, Harvey R, Winter MC, Tidy J, Hancock BW, et al. Late spontaneous resolution of persistent molar pregnancy. BJOG 2016;123(7):1175–81.