In Brief
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Repeat Curettage In the Management of Low-Risk Gestational Trophoblastic Neoplasia (GTN)

Soheila Aminimoghaddam[1,2], Shahla Chaichian[2], Mahdis Kashian[1], Arash Mohazzab[3,4], Roghayeh Pourali[1]*

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In Brief

Gestational trophoblastic neoplasia (GTN) refers to a group of malignant neoplasms that consist of abnormal proliferation of trophoblastic tissue and may follow a hydatidiform mole or a non-molar pregnancy. Despite their malignant nature, these neoplasms are curable, especially in the low-risk group. Patients with low-risk GTN have an overall excellent prognosis with survival rates of 100 percent after treatment using six cycles of methotrexate or actinomycin injection on average (1, 2). Second curettage may be considered an alternative therapeutic method to reduce the burden of chemotherapy or the length of medication (3) and many oncologists tend to try this intervention instead of chemotherapy, especially in patients who presented with vaginal bleeding and retained products of conception. Due to the low incidence of GTN, the design of a standard, a single-center comparative study between treatment methods looks problematic. This brief report describes the characteristics of 16 repeat curettage of GTN patients in comparison with chemotherapy in a gynecologic oncologic referral center.

This retrospective cross-sectional study represents the clinical and para-clinical characteristics of 32 women with low-risk GTN which have been treated using two different therapeutic methods, including hysteroscopic guided re-curettage and single-agent chemotherapy between 2014 and 2018 in Firoozgar hospital, Tehran, Iran (Figure 1). Patients who needed hysterectomy because of emergent conditions or did not desire to preserve their fertility and those with contraindications for chemotherapy were excluded.from the study. Moreover, the data was used in a matched analysis to compare the outcome and its correlated factors between these two treatment methods. Patients' medical records were used to obtain all required clinical and laboratory information. All patients had signed the informed consent allowing access to their medical records for research purposes. The ethical committee of the Iran University of medical science approved the study (Approval Code: IR.IUMS.REC.1397.475.)

Corresponding author: *Dr Roghayeh Pourali, Roghayehpourali@ymail.com*

1. Department of Obstetrics and Gynecology, school of medicine , Firoozgar Hospital, Iran University of Medical Sciences,Tehran, Iran
2. Endometriosis Research Center, Iran University of Medical Sciences, Tehran, Iran
3. School of Public Health, Iran University of Medical Science, Tehran, Iran
4. Reproductive Biotechnology Research Center, Avicenna Research Institute Tehran, ACECR, Tehran, Iran

↑What is "already known" in this topic:
Gestational trophoblastic neoplasia (GTN) is a group of malignant neoplasms that consist of abnormal proliferation of trophoblastic tissue. Despite their malignant nature, these neoplasms are curable. Patients with low-risk GTN have an overall excellent prognosis with survival rates of 100 percent after treatment with chemotherapy.

→What this article adds:
Repeat curettage can be considered as an alternative treatment for low-risk GTN with a reasonable success rate. Repeat curettage will be beneficial in patients with lower serum βhCG. GTN surgical treatment leads to a faster βhCG drop and a shorter duration of medical interventions.

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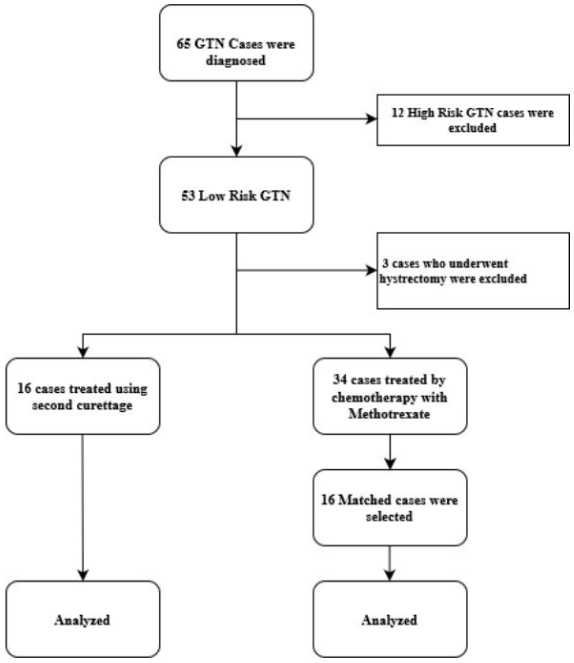

Figure 1. Patients' flowchart

GTN is diagnosed based on these criteria: 1) a rise in the βhCG assay of 3 consecutive measurements, or longer over at least a period of 2 weeks or more; days, 1, 7, 14"; or 2) "a plateau in the βhCG assay for four consecutive weekly levels over three weeks or longer; that is, days 1, 7, 14, 21"; or 3) the βhCG level remains detectable for six months or longer; or 4) histological diagnosis of choriocarcinoma.

Low-risk GTN is defined by the FIGO/WHO staging and risk scoring (risk score of less than 7). Pretreatment evaluation by standard physical examination, chest X-ray, and abdominopelvic ultrasound was performed for all patients to define risk score and stage of the disease. We excluded the patients with any evidence of choriocarcinoma, extrauterine disease, or metastasis. An initial βhCG level was obtained at the time of admission. For patients needing cervical preparation, we prescribed 400 micrograms of misoprostol sublingually 2 hours before the procedure.

Hysteroscopic re-curettage was performed under general anesthesia by the same gynecologist oncologist in all patients, and the same pathologist reviewed all the curettage materials from both the first and second curettage. Serum βHCG levels were measured 48 hours and one week after re-curettage and then weekly until the βHCG levels were normal for three consecutive weeks, then monthly for up to 6 months. All patients used an accepted method of contraception for the duration of the study for six months (oral contraceptives or barrier methods). Surgical failure was defined as any evidence of choriocarcinoma/ PSTT/ ETT diagnosed in second curettage or failure to maintain normal βHCG levels or rise or plateau in the βHCG levels. These patients have been treated with chemotherapy.

A single-agent chemotherapy regimen with 0.4 mg/Kg methotrexate (maximum 25 mg daily) for five days was used for medical treatment. Chemotherapy was implemented every 14 days and followed by three consolidation therapy after negative βhCG achievement.

Patients' characteristic which was considered for evaluation in this study includes low-risk GTN based on WHO score(score<7), Stage 1, being in the first trimester, and also being treated by one of the mentioned methods. During the study period, of 203 patients admitted with GTD impression, 50 patients were eligible according to the study criteria and their medical information such as maternal and gestational age, serum βhCG in various sections of patients' follow-up, ultrasound reports, and histopathologic findings of first and second (If applicable) curettage of patients was extracted. Since the main goal of this study was to evaluate the efficacy of re-curettage for GTN treatment, all 16 patients who were treated using this method were included in the study, and 16 patients treated with chemotherapy were selected and matched with re-curettage patients based on three factors of age (utmost ± 5 years), admission time βhCG after GTN diagnosis (utmost ±10%) and also WHO score (±2 score).

After data extraction, the analysis was performed using SPSS software version 24. Selected variables were compared between two groups of treatment using the Wilcoxon test for quantitative variables. The percentage of completely cured patients and the trend of βhCG before the treatments were compared between two groups of the study using the Sign test.

Many comparisons were made between completely cured and failed re-curettage cases to evaluate factors affecting this therapeutic modality's success. To reach this goal, the Mann-Whitney test and the Chi-square test have been used for quantitative and dichotomous variables, respectively. The level of significance was considered 0.05.

The results of this study showed that treatment failure had happened in only one patient (6.2%) in the chemotherapy group. In contrast, this rate was 4(25%) in the second curettage group. The median and range of interval between the two curettages were 35 (24-58) days. The Sign test's p-value is 0.087 for this comparison tends to show a significant difference between these two methods.

There were no significant differences in other characteristics, including age, admission time βhCG, WHO score, and gestational age at the time of diagnosis between the two methods of treatment (Table 1). However, a statistically significant difference was observed in the waiting time for the βhCG being undetectable with the median (interquartile range) of 3 (1) and 5 (2) for the re-curettage and chemotherapy group, respectively ($P = 0.1$).

To find the predisposing factor for surgical treatment of GTN, the four failed cases were reviewed and compared with other patients with successful cases with the same treatment. It was shown that the only variable which might affect the failure chance is the serum's βhCG level before the treatment. The diagnosis of GTN in 75% of patients was based on plateau serum level of βhCG without any difference between thriving or failed cases (βhCG). Table 2 illustrates the variables which were as-

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Table 1. Characteristics of GTN patients treated by re-curettage and chemotherapy and comparison between these two groups

	Curettage (16)	Chemotherapy (16)	*P*-value
Age *	31 (23)	29.15 (19)	0.378
Admission time βhCG*	85500 (61102)	88505 (62417)	0.724
Gestational Age (weeks)*	8.43±2.39	9.27±1.94	0.568
Undetectable βhCG *(weeks)*	3 (1)	5 (2)	0.01
WHO score*	3 (2)	3 (2)	0.755
βhCG before*	4175 (20102)	3588 (9454)	0.926
Success rate **	12 (75%)	15 (93.8%)	0.333

* Calculated using Man-Whitney-Test
** Calculated by Chi-square test

Table 2. Assessment of plausible risk factors for re-curettage failure

		Curettage success (12)	Curettage failure (4)	*P*-value
Age *		31.5(14)	27.5(14)	0.771
βhCG at admission time *		85500(53650)	96135(227318)	0.684
Gestational Age(week)*		7.25(4.63)	9.5(4.88)	0.521
βhCG before treatment*		1700(6402)	24500(33554)	0.069
Who Score		2.5(2)	3.5(2)	0.446
Platue βhCG**		9(75%)	3(75%)	1
Delivery **	NVD	5(41.7%)	2(50%)	0.218
	C/S	5(41.7%)	2(50%)	

* Calculated using Man-Whitney-Test
** Calculated by Chi-square test

sessed for failure risk factors for repeated uterine evacuation. The histopathologic assessment confirmed the persistence of molar pregnancy in all four cases of failure, while this finding was reported only in three cases of successful curettage. Additionally, the presence of molar tissue in histopathology seems correlated with the plateau βhCG trend in patients with successful treatment (Rho = 0.556). For their fertility outcomes, patients were followed in phone-based interviews for 2.5-5 years (Median 3 years). Regular menstrual cycles were observed in all patients with the second curettage, and 9 cases (56.25%) experienced successful pregnancy after the intervention. There were no major or minor complications such as uterine perforation, adhesion (Asherman's syndrome), infection, or bleeding.

The report has briefly explained the result of second uterine evacuation for patients with GTN in comparison with single-agent chemotherapy. The success rate of 75 % without any significant endometrial damage introduces this method as a considerable alternative to the standard single-agent chemotherapy, which is performed faster and more tolerable.

Although the second curettage has been suggested frequently for the treatment of low-grade GTN (4-6), few studies reported this modality alone for GTN, and some chemotherapy courses have been added to curettage mostly. The success rate varied in different studies.

Schlaerth et al. reported a 17.4% of success rate for repeat curettage in a retrospective study with 20 GTN patients, which was completely disappointing since three patients (8.1%) encountered uterine perforation and subsequent hysterectomy (7). In a multi-center prospective study, 64 women with GTN underwent re-curettage, which resulted in a complete cure of 47% of patients without the need for chemotherapy and only one uterine perforation. The methods of uterine evacuation were heterogeneous and contained ultrasound-guided, direct hysteroscopic, or blind. Moreover, they suggested that second curettage is unlikely to benefit patients with a WHO risk score of 5 or 6 (8). In our study, 15 of 16 patients in the second curettage group had a WHO score of 0-4 which may affect the success rate of 75%. Pezeshki et al., in a large observational study, found that 60% of GTN patients with repeat curettage did not require additional chemotherapy. They reported that the chance of successful curative re-curettage in GTN is correlated reversely with the level of βHCG (9) .Van Trommel et al. opposed this result in a letter and claimed that only 9.4% of their 85 patients with GTN positively responded to this intervention (10).

On the other hand, some other observational and interventional studies tried to evaluate the effect of second curettage before chemotherapy to reduce the number of chemotherapy courses .In a randomized clinical trial Hemida et al. showed the pre-treatment second curettage does not significantly reduce the number of chemotherapy courses. However , concurrent with our result and also the Pezeshki study, re-curettage was more beneficial in patients with lower βhCG levels. The failure rate of single-agent chemotherapy after the second curettage intervention was reported as 6.9% (3). This rate was similarly low (3.85) in another observational study with a pregnancy rate of 83% after re-curettage/chemotherapy combined treatment (11).

According to the results of this study, the second curettage can be used as an alternative to chemotherapy in the treatment of patients with low-risk non-metastatic GTN, especially in cases with lower βhCG serum titers. GTN surgical treatment leads to a faster βhCG drop and a shorter duration of medical interventions. On the other hand, the success rate of this treatment is relatively comparable to chemotherapy. A higher success rate of this study rather than other repeat curettage cases may be achieved by direct vision operation under the guidance of hysteroscopy and the skill of a gynecologist-oncologist. Nevertheless, the study's results should be interpreted conservatively due to the study's low sample size, which seems inevitable since the disease is infrequent. Additionally, more follow-up visits were inconvenient due to the long distance. Mul-

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ti-center prospective trials will produce more precise and more valid information to evaluate the outcomes of second curettage and comparison with routine treatment.

Conflict of Interests

The authors declare that they have no competing interests.

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