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RESEARCH ARTICLE

LOW-RISK GESTATIONAL TROPHOBLASTIC NEOPLASIA: INSIGHTS FROM A TERTIARY CARE INSTITUTE IN INDIA

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Abstract

Objective: To report clinical characteristics, treatment outcomes and chemotherapy-related toxicities in patients with low-risk GTN at tertiary care centre in India.

Material and Methods: This retrospective observational study was conducted at the Department of Medical Oncology of Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi over 2 years. The clinical and treatment information of every patient diagnosed with GTN between December 2021 and December 2023 were examined retrospectively in their medical records. Methotrexate (MTX) was administered with folinic acid (FA) rescue to low-risk GTN patients. EMA-CO, multiagent chemotherapy, was administered every two weeks to patients with low-risk GTN who were resistant to first-line chemotherapy.

Results: Only 35 of the 40 patients with low-risk GTN were able to be evaluated since five of them were lost to follow-up throughout the course of treatment.The study found that the majority of patients (71.4%) experienced a molar pregnancy before developing gestational trophoblastic neoplasia (GTN), with 91.4% developing GTN within the first 4 months. Of these, 32 patients achieved complete responses (91.4%)with MTX therapy, while 3 experienced treatment failure (8.5%). Following multiagent chemotherapy, all three ofthe patients who had not responded to initial MTX therapy experienced complete remission (CR). All patients with GTN who were at low risk had 100% overall survival (OS) and cure rates.

Conclusion: With a complete response (CR) rate of 91.4% and no serious side effects, the MTX regimen proved to be highly effective in treating women with low-risk GTN.

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Introduction:-

Gestational trophoblastic neoplasia (GTN) includes various conditions originating from placental tissue [1]. Chemotherapy is necessary for persistent or metastatic disease known as gestational trophoblastic neoplasms (GTN). Fortunately, most GTN-affected women respond well to treatment while maintaining their fertility. This group comprises epithelioid trophoblastic tumour (ETT), placental site trophoblastic tumour (PSTT), choriocarcinoma (CCA), and invasive mole (IM) [2]. Notably, high human chorionic gonadotropin (hCG) levels are produced by IM and CCA, which account for the vast majority of cases; this facilitates diagnosis and therapy monitoring.The exceptional susceptibility of these neoplasms to chemotherapy and the usefulness of hCG as a diagnostic and monitoring tool account for successful outcomes, especially in advanced-stage disease [3]. Treatment decisions for GTN are guided by its classification into low- and high-risk groups based on WHO (World Health Organisation) prognostic risk score and FIGO (International Federation of Gynaecology and Obstetrics) anatomic staging [4]. Actinomycin D (Act D) and methotrexate (MTX) are two single-agent chemotherapeutic agents that are commonly effective in treating low-risk GTN, with approximately 100% survival rates [5]. Patients who have a histological diagnosis of choriocarcinoma or a prognosis score of 5–6 have a much higher likelihood of failure to first-line single-agent chemotherapy, and their regimen for combination chemotherapy is chosen based on their high prognostic score [6].

In general, multiagent chemotherapy or hysterectomy are not necessary for the cure of 85–90% of low-risk patients [7]. Approximately 9–30% of patients may acquire resistance to first-line chemotherapy, despite the fact that the disease is exceedingly sensitive to treatment [8,9]. A high FIGO score of 5–6 indicates a fourteen-fold increased chance of resistance compared to a low FIGO score of 0–4 [10].
Uncertainties remain about risk variables that predict molar gestation, malignancy progression, and responsiveness to single-agent chemotherapy, even with advances in diagnosis. There is a dearth of information from developing nations about the results of GTN. Therefore, we provide the clinical characteristics and outcomes of a series of GTN patients who were treated at our centre for 2 years.

Material and Methods:-

Over a period of two years, the Department of Medical Oncology at Vardhman Mahavir Medical College and Safdarjung Hospital in New Delhi carried out this retrospective observational study. Following institutional review board ethical clearance, clinical and treatment details from all patients diagnosed with GTN between December 2021 and December 2023 were retrospectively evaluated from their medical records. The diagnosis of low-risk GTN was established by clinical and histological criteria.
After a molar or non-molar pregnancy, GTN was clinically diagnosed when there was either (i) a plateau (< 15% drop) in the level of human chorionic gonadotropin (hCG) in four readings over the course of three weeks, (ii) a 10% increase in hCG levels for three readings over the course of two weeks, or (iii) choriocarcinoma that was confirmed histologically [11]. (Decrease space on the highlighted line)

All patients who met clinical and/or histological criteria for low-risk GTN diagnosis are included in the inclusion criteria. Among the exclusion criteria are patients who did not finish treatment and were not followed up and high-risk GTN with a FIGO score more than 6.
Following the diagnosis of GTN, an oncology staging workup was carried out as per the hospital protocol. It comprises collecting medical history, doing physical examinations, running lab tests, and imaging. Regarding imaging, typical procedures included chest X-rays and ultrasounds of the whole abdomen and pelvis. Cross-sectional computed tomography (CT) or magnetic resonance imaging (MRI) was carried out if they reveal signs of metastatic disease. (Decrease space on the highlighted line)

After the initial evaluation, patients were classified into groups according to low-risk diseases. The WHO prognostic risk score (**Appendix 2**) and FIGO anatomic staging (**Appendix 1**) were the basis for this classification. Risk assessment is aided by the WHO risk score, which takes into account factors such as age, previous pregnancy, time elapsed before chemotherapy began, serum Beta-hCG level prior to treatment, tumour size, metastasis site and quantity, and previous chemotherapy response. FIGO stage I GTN or stage II/III GTN with a WHO risk score < 7 was used to identify the low-risk disease [4]. Methotrexate (MTX) was administered with folinic acid (FA) rescue to low-risk GTN patients. Leucovorin (15 mg PO) is alternated with methotrexate (1.0–1.5 mg/kg IM every other day for four days) every two weeks. The Chemotherapy regimen for Low-risk GTN resistant to first-line chemotherapy was multiagent chemotherapy EMA-CO every 2 weeks (**Figure 1**).

The treatment must be continued for six to eight weeks after the beta-hCG levels return to normal. Following the end of chemotherapy, each patient underwent a monthly evaluation for a year. During the follow-up phase, all women of reproductive age received contraception advice. The patient was recommended to undergo a blood count, a kidney function test, and a liver function test prior to each treatment cycle. In patients with a WBC count < 3000/mm3 and a platelet count < 1 lakh/mm3, therapy was delayed. Along with treatment, a blood transfusion was performedfor Hb< 10g/dl.
Following a statistical analysis of the data, the percentage, mean, and standard deviation were used to determine the demographic statistics. The statistical package for the social sciences (SPSS) software, version 29, was used for all statistical analyses. (Decrease space on the highlighted line)

Results:-

Of the 40 patients with low-risk GTN, only 35 women were available for evaluation as 5 were lost to follow-up during the treatment period (**Figure 2**).
Table 1:-Shows the patient's clinical characteristics (n=35). The median age was 28 years (range, 18-44 years) (**Figure 3**). The study found that the majority of patients (71.4%) experienced a molar pregnancy (**Figure 4**) before developing gestational trophoblastic neoplasia (GTN), with 91.4% developing GTN within the first 4 months (**Figure 5**). Most patients (80%) had human chorionic gonadotropin (hCG) levels between 1,000 and 10,000 mIU/dL(**Figure 6**), while 94.3% were at FIGO stage I (**Figure 7**)and 48.6% had WHO prognostic scores ranging from 0 to 2 (**Figure 8**). Only 35 patients opted for chemotherapy, with methotrexate (MTX) being the primary single-agent treatment. Patients who did not respond to methotrexate were subsequently administered multiagent EMA-CO chemotherapy. Only 5.7% of patients had extra pelvic spread to the lungs. No patient had spleen, kidney, liver, GIT and brain metastasis.

Table 2 displays treatment outcomes for patients who underwent primary single-agent chemotherapy with MTX (n = 35). Of these, 32 patients achieved complete responses (91.4%), while 3 experienced treatment failure (8.6%) (**Figure 9**). Analysis showed no statistically significant difference in median age between patients with complete and failed responses (P > 0.05, two-tailed Mann-Whitney U test). Patients who failed MTX treatment had a median WHO prognostic score of 5 (range, 5-6), compared to a score of 3 (range, 0–6) for those with complete responses. All three patients who failed primary MTX therapy were subsequently treated with multiagent chemotherapy and achieved complete remission (CR). Overall survival (OS) and cure rates for all patients with low-risk GTN were 100%. Regarding chemotherapy toxicity, no patients experienced MTX-related hepatic toxicity. Among the 35 patients who underwent primary MTX therapy, three developed grade-I oral mucositis, and four experienced grade-II bone marrow suppression. Conversely, among the subset of patients receiving primary methotrexate (n = 3) followed by sequential multiagent EMA-CO chemotherapy (n = 3), one patient encountered grade-II oral mucositis and another experienced grade-III bone marrow suppression.

Discussion:-

Patients with low-risk GTN have an extremely good prognosis; overall survival can reach 90–100% [8,11,12]. Similarly in our investigation, an OS rate of 100% was linked to both first chemotherapy and subsequent multi-agent chemotherapy in cases of failed response. Few patients had a significant risk of treatment failure with single-agent chemotherapy and needed an EMA-CO regimen, although low-risk GTN is quite sensitive to chemotherapy. To more accurately identify which subgroup experiences treatment failure, more research is needed [13]. The 8-day IM MTX-FA regimen used at our institution yielded a very high complete response (CR) rate of 91.4% (n = 32/35) with minimal toxicity.

The therapeutic efficacy, well-tolerated nature, and affordability of MTX have made it a popular choice in clinical settings. To lessen the toxicity caused by MTX, it can be given with or without folinic acid (FA). Worldwide, a number of MTX regimens are in use, such as high-dose intermittent infusion IV MTX-FA, weekly intramuscular (IM) MTX, 5-day IM MTX, 5-day IV MTX, and 8-day IM MTX-FA [12]. The ideal MTX regimen, however, is a topic of debate. The 8-day IM MTX-FA regimen, which we used in our study, showed great efficacy in treating women with low-risk GTN, reaching a CR rate of 91.4% without experiencing appreciable side effects. Another treatment for people with low-risk GTN is actinomycin D (Act D). When using MTX is contraindicated or there is MTX resistance, it is usually used as a second-line single-agent therapy. Sequential Act D therapy shows exceptionally high CR rates, almost reaching 100%, for patients resistant to MTX. But Act D's accompanying toxicity-related side effects, such as hair loss, appetite loss, diarrhoea, and especially blister formation if

extravasation occurs, frequently restrict its clinical usefulness [5,11].
According to Winter et al., a considerable number of patients, especially those with FIGO/WHO prognosis scores of 5-7, show resistance to first-line chemotherapeutic drugs [14]. According to the Sheffield Trophoblastic Disease Centre in the UK, patients with a FIGO/WHO score of 6 had an 81% resistance rate, whereas individuals with a lower score had a 34% resistance rate [15]. Chemotherapy failure rates for patients with FIGO/WHO scores of 0–4 were reported to be 32% in a Canadian trial on low-risk GTN, and increased to 59% for scores of 5-7 [16]. According to Braga et al., almost all patients who remain after single-agent therapy attain complete remission with following multiagent chemotherapy [17]. Approximately 60% of women with gestational trophoblastic neoplasia and a FIGO risk score of 5–6 achieve remission with single-agent therapy.

Patients with choriocarcinoma and metastatic disease, or those identified by predictors such as pre-treatment concentration of more than 4,11,000 mIU/ml, choriocarcinoma, and metastatic disease, are advised to have primary multiagent chemotherapy [17]. In our analysis, three patients (8.6%) showed resistance to first-line chemotherapy and two of them (5.7%) also had lung metastases. All of the patients had prognosis scores of 5–6. In our investigation, the complete response (CR) rates (n = 3) following sequential multiagent EMA-CO treatment were 100%.

For large or chemoresistant uterine tumours and continuous bleeding, a hysterectomy can be required since it can lessen the tumour burden and the number of chemotherapy cycles required. For low-risk GTN, none of the patients in our study needed hysterectomy [18, 19].
Given that the majority of the patients in our research are young, the toxicity profile was favourable and similar with prior studies.
Our study's limitations include its retrospective design, single-center experience, and limited sample size. In the literature, there is a dearth of data on GTN, and our work adds to what little has been reported.

Conclusion:-

Our study contained a retrospective analysis of low-risk GTN patients treated with the 8-day IM MTX-FA protocol at a tertiary care institution. Our results showed that this MTX regimen was very successful in treating women with low-risk GTN, with 91.4% of patients experiencing a complete response (CR) without experiencing serious side effects. Additionally, our data indicates that primary and sequential multiagent therapy is highly effective in treating low-risk GTN, especially when lung metastases and a prognosis score of 5–6 are present.

Conflict of interest:
Nil.

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Nil.

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Nil.

References:-

1. Sekharan PK. Gestational trophoblastic disease. ObstetGynecol India 2008;58(8):299e307.
2. Biscaro A, Braga A, Berkowitz RS (2015). Diagnosis, classification and treatment of gestational trophoblastic neoplasia. Rev Bras GinecolObstet, 37, 42-51.
3. Ravi Byahut, Mithilesh Kumar. Evaluation of the results of chemotherapy in high-risk gestational trophoblastic tumors with multidrug EMA-CO regimen + granulocyte- colony-stimulating factor (G-CSF) support. International Journal of Contemporary Medical Research 2018; 5(1): 1-4.
4. Berkowitz RS, Goldstein DP. Current management of gestational trophoblastic diseases. Gynecol Oncol 2009;112:654-62.
5. Li J, Li S, Yu H, Wang J, Xu C, Lu X. The efficacy and safety of first-line single-agent chemotherapy regimens in low-risk gestational trophoblastic neoplasia: A network meta-analysis. Gynecol Oncol 2018;148:247-53.
6. Chinese Anti-Cancer Association Gynecological Oncology Committee. Guidelines for the diagnosis and treatment of gestational trophoblastic disease (2021 edition). China Oncol (2021) 31(6):520–32.

7. Maestá I , Nitecki R, Horowitz NS, Goldstein DP, Moreira M, Elias KM, et al. Effectiveness and toxicity of first-line methotrexate chemotherapy in low-risk postmolar gestational trophoblastic neoplasia: the new England trophoblastic disease center experience. Gynecol Oncol (2018) 148:161–7.
8. McNeish IA, Strickland S, Holden L, Rustin GJ, Foskett M, Seckl MJ, et al. Low-risk persistent gestational trophoblastic disease: outcome after initial treatment with low-dose methotrexate and folinicacid from 1992 to 2000. J Clin Oncol (2002) 20(7):1838–44.
9. Matsui H, Suzuka K, Yamazawa K, Tanaka N, Mitsuhashi A, Seki K, et al. Relapse rate of patients with low-risk gestational trophoblastic tumor initially treated with single-agent chemotherapy. Gynecol Oncol (2005) 96(3):616–20. doi: 10.1016/j.ygyno.2004.11.011
10. Mousavi AS, Zamani A, Khorasanizadeh F, Gilani MM, Zendehde K. Resistance to single-agent chemotherapy and its risk factors in low-risk gestational trophoblastic neoplasms. J ObstetGynaecol Res (2015) 41(5):776–83. doi: 10.1111/jog.12613
11. Al-Husaini H, Soudy H, Darwish A, Ahmed M, Eltigani A, Edesa W, et al. Gestational trophoblastic neoplasia: Treatment outcomes from a single institutional experience. ClinTransl Oncol 2015;17:409-15.
12. Lawrie TA, Alazzam M, Tidy J, Hancock BW, Osborne R. First-line chemotherapy in low-risk gestational trophoblastic neoplasia. Cochrane Database Syst Rev 2016;6:CD007102.
13. Sita-Lumsden A, Short D, Lindsay I, Sebire NJ, Adjogatse D, Seckl MJ, et al. Treatment outcomes for 618 women with gestational trophoblastic tumours following a molar pregnancy at the Charing Cross Hospital, 2000–2009. Br J Cancer 2012;107:1810-4.
14. Winter MC. Treatment of low-risk gestational trophoblastic neoplasia. Best Pract Res ClinObstetGynaecol. 74:67–80.
15. Macdonald MC, Hancock BW, Winter MC, Coleman CW, Tidy JA. Management and outcomes of patients with stage I and IIIl low-risk gestational trophoblastic neoplasia treated in Sheffield, UK, from 1997-2006. J Reprod Med (2016) 61(7-8):341–6.
16. Hoskins PJ, Le N, Kumar A, Pina A, Sabourin JN, Kim H, et al. Single or two drug combination therapy as initial treatment for low-risk, gestational trophoblastic neoplasia. a Canadian analysis. Gynecol Oncol (2020) 157(2):367–71.
17. Braga A, Paiva G, Ghorani E, Freitas F, Velarde LGC, Kaur B, et al. Predictors for single-agent resistance in FIGO score 5 or 6 gestational trophoblastic neoplasia: a multicentre, retrospective, cohort study. Lancet Oncol (2021) 22(8):1188–98.
18. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. Lancet. 2010; 376: 717–729.
19. Hammond CB, Weed JC, Currie JL. The role of operation in the current therapy of gestational trophoblastic disease. American Journal of Obstetrics and Gynecology. 1980; 136: 844–858.
20. Ghosh J, Dey S, Mandal D, et al. Clinicopathological features and outcomes of choriocarcinoma: a retrospective analysis from an Indian tertiary cancer center. Cancer Res Stat Treat 2021;4:486–491.

Appendix 1:-FIGO staging system.

Stage	Criteria
I	Tumor confined to uterus
II	Tumor extend to other genital structures (Ovary, tube, vagina, broad ligament) by metastasis or direct extension
III	Lung metastasis
IV	All other distant metastases

Appendix 2:- WHO prognostic risk score.

Prognostic factor	**0**	**1**	**2**	**4**
Age (years)	<40	≥ 40	-	-
Antecedent pregnancy	Hydatiform mole	Abortion	Term pregnancy	-
Interval from antecedent pregnancy (months)	< 4	4-6	7-12	>12
PretreatmenthCG (IU/L)	$< 10^3$	10^3 to $< 10^4$	10^4 to 10^5	$\geq 10^5$
Largest tumor size,	<3	3-5	>5	-

including uterus (cm)				
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases	0	1-4	5-8	>8
Previous failed chemotherapy	-	-	Single drug	Two or more drugs

Table 1:- Characteristics of Gestational Trophoblastic Disease.

Characteristics	**Low-Risk GTN (WHO prognostic score≤ 6) (n= 35)**
Age at diagnosis (years)	
Median age	28
<40 year, n (%)	32 (91.4%)
>40 year, n (%)	3 (8.6%)
Antecedent pregnancy	
Mole, n (%)	25 (71.4%)
Abortion, n (%)	10(28.6%)
Term, n (%)	0
Interval from antecedent pregnancy (in months)	
<4, n (%)	
4-6, n (%)	32 (91.4%)
>6, n (%)	2 (5.7%)
	1 (2.9%)
Tumor size (in cm)	
< 3, n (%)	20 (57.15%)
3-5, n (%)	13 (37.15%)
≥ 5, n (%)	2 (5.7%)
Pre-treatment Beta hCG (mIU/dl)	
< 1000, n (%)	2 (5.7%)
10^3- < 10^4, n (%)	28 (80%)
10^4- < 10^5, n (%)	5 (14.3%)
>10^5, n (%)	0
FIGO Stage	
Stage I, n (%)	33 (94.3%)
Stage II, n (%)	0
Stage III, n (%)	2 (5.7%)
WHO prognostic score	
0-2, n (%)	17 (48.6%)
3-4, n (%)	15 (42.8%)
5-6, n (%)	3 (8.6%)
Site of metastasis	
Lung	2 (5.7%)
Spleen, Kidney	0
GIT	0
Liver, brain	0

Table 2:- Treatment outcome of patients receiving methotrexate as primary single-agent chemotherapy.

Variables	Complete response	Failed response
Patients	32 (91.4%)	3 (8.6%)

Median WHO prognostic score	3	5
Median duration of disease (months)	2	4

Figure 1:- Multiagent EMA-CO Regimen.

EMA/CO:

Etoposide, Methotrexate, Dactinomycin/ Cyclophosphamide, Vincristine

Repeat every 2 weeks until hCGnormalisation, then continue for an additional 6-8 weeks.

- Etoposide 100 mg/m^2/ day IV on Day 1 and 2
- Dactinomycin 0.5 mg IV push on Day 1 and 2
- Methotrexate 300 mg/ m^2 IV infusion over 12 hours on Day 1
- Leucovorin 15 mg PO (Preferred) or IM every 12 hours for 4 doses starting 24 hours after the start of methotrexate infusion
- Cyclophosphamide 600mg/m^2 IV on Day 8
- Vincristine 0.8 mg/m^2 (maximum of 2 mg) IV over 5 -10 minutes on Day 8

Figure 2:- Scheme of inclusion of patients with low-risk GTN in the study.

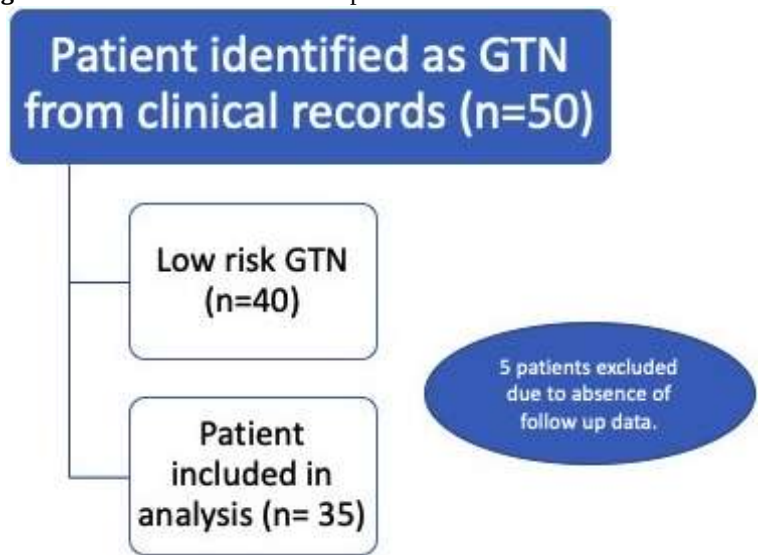

Figure 3:-Pie chart showing Age distribution in low-risk GTN.

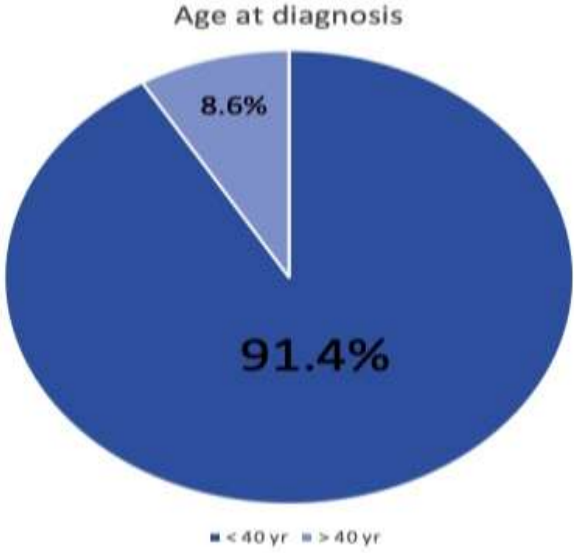

Figure 4:- Antecedent pregnancy at the time of diagnosis of low-risk GTN.

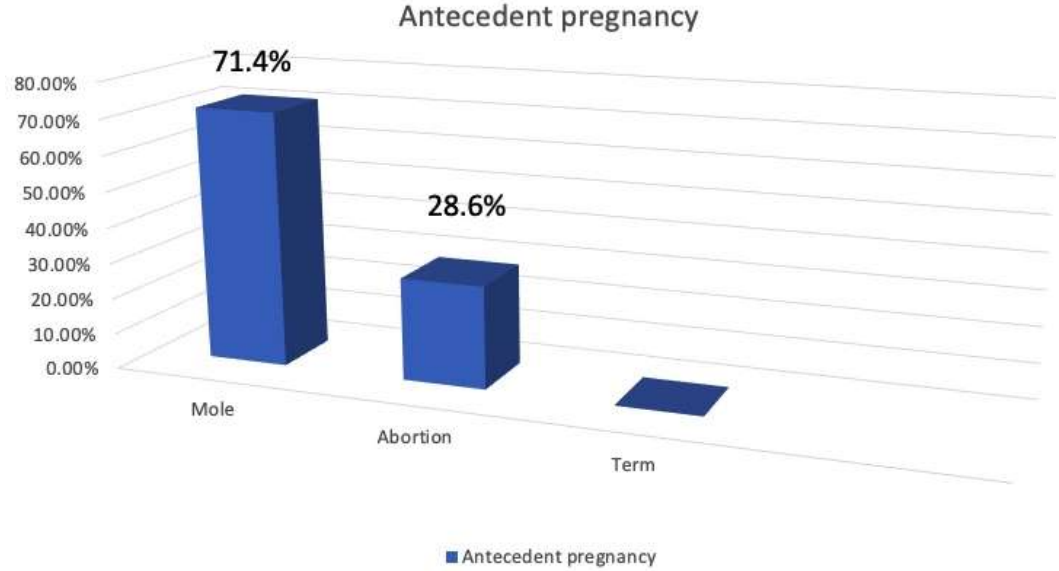

Figure 5:- Interval from antecedent pregnancy.

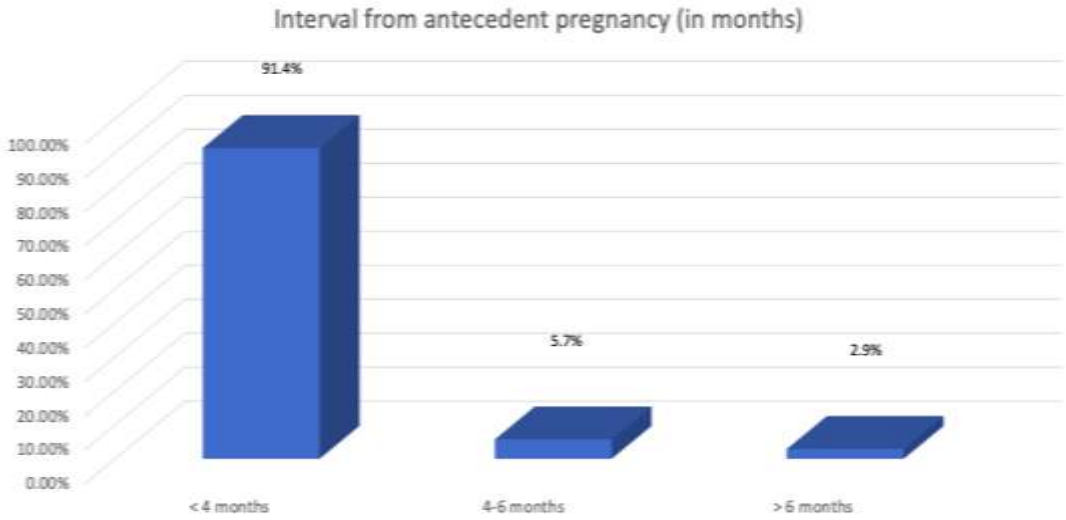

Figure 6:-Pre-treatment beta hCG.

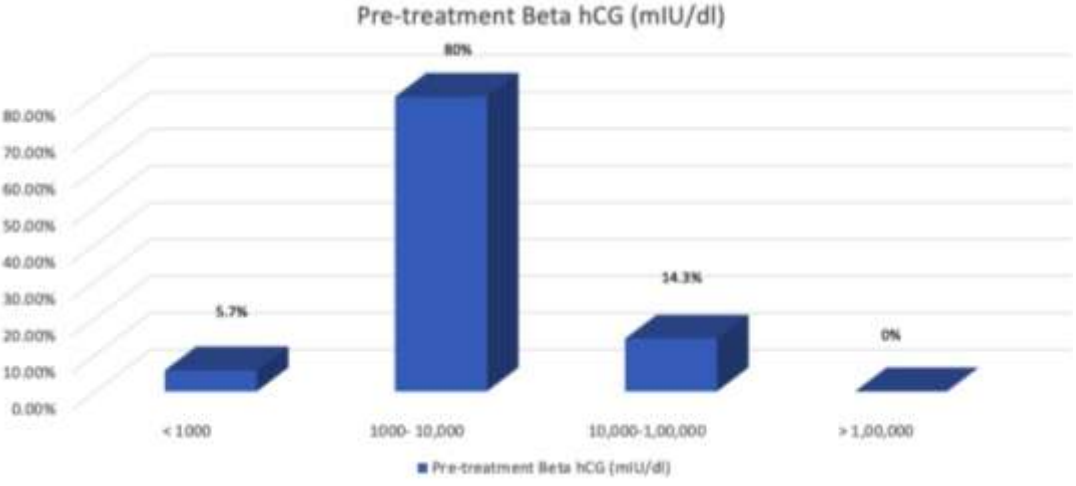

Figure 7:- Stage-wise distribution of low-risk GTN.

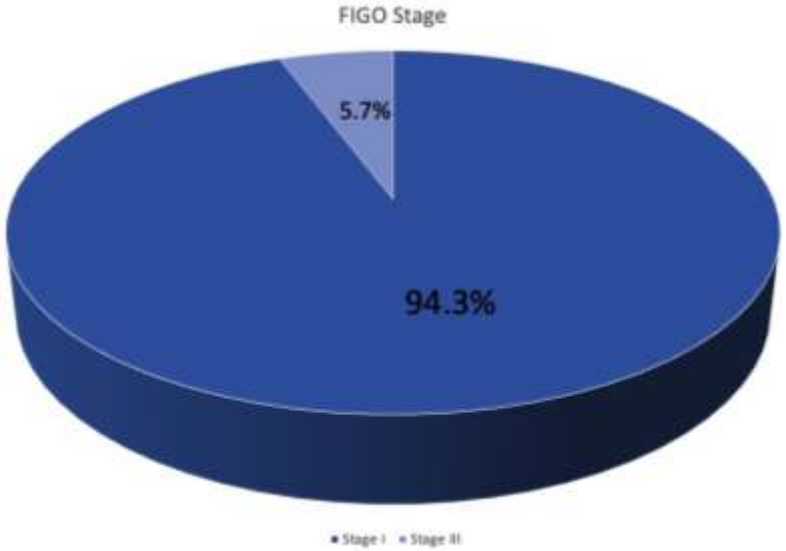

Figure 8:- WHO prognostic score among low-risk GTN.

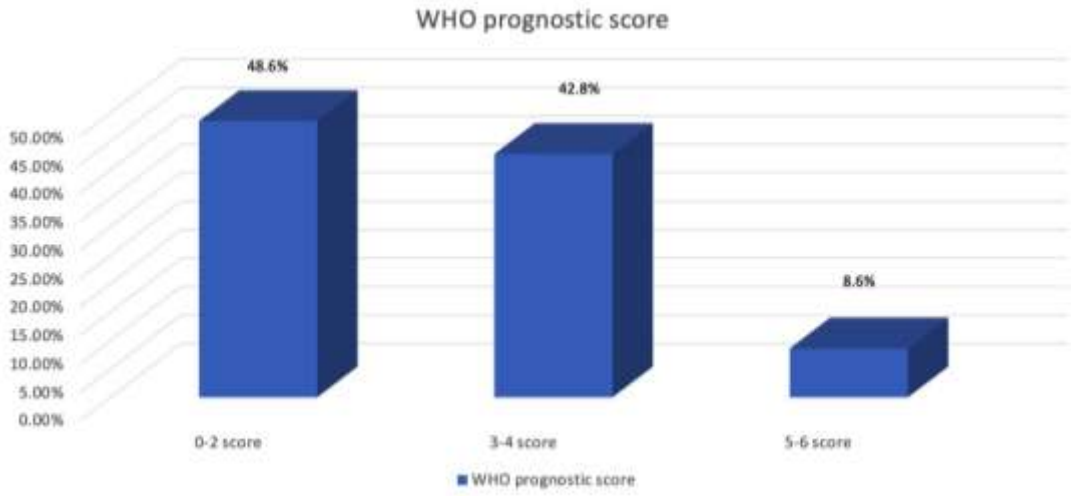

Figure 9:- Response to primary therapy (Methotrexate).