

Gestational Trophoblastic Neoplasia

Mahmoud Ibrahim M. Shahin*, Wael Helmy El Sheshtawy, Mohsen Salah El-Din Zikri

Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Al-Azhar University

* **Corresponding author:** Mahmoud Ibrahim M. Shahin, **E-mail:** Mahmoudshahin.s3@gmail.com

ABSTRACT

Background: gestational trophoblastic neoplasia forms a wide variety of rare conditions arising from abnormal proliferation of the trophoblastic cells in the placental microvilli. They consist of vesicular mole “partial and complete”, invasive mole, placental site trophoblastic tumor (PSTT), epithelioid trophoblastic tumor (ETT) and choriocarcinoma. They can be classified into premalignant forms which include vesicular mole and malignant forms which include the rest. **Aim of the Work:** this study aimed to study the epidemiological and clinical data, as well as treatment regimes and their outcome included response and related toxicity among patients with gestational trophoblastic neoplasia treated in this study. **Patients and Methods:** in this retrospective study, medical records of all patients with GTN presented to Oncology Department, Al-Hussein University Hospital in the period from January 2007 to June 2017 was retrieved from the archives and medical data was reviewed and analyzed. **Results:** median age of patient was 37.5 (Range 20-55), molar pregnancy was the most common pathological type (40%), followed by invasive mole (31.4%), while choriocarcinoma was diagnosed in 25.7% and only 2.9% of patients had placental site trophoblastic disease. According to FIGO score; 26 patients (74.3%) showed low risk and 9 patients (25.7%) showed high risk. In low risk patients, 30.8% of patients were kept under follow up while, (69.2%) received chemotherapy, 61.1% of them achieved complete remission on methotrexate as first line chemotherapy, while the rest 38.9% achieved complete response on EMA-CO or dactinomycin as 2nd line chemotherapy. Methotrexate wasn't effective in high risk patients, while EMA-CO had much better response achieving (66.7%) complete response rate, with 2 cases of early death in those patients. **Conclusion:** this retrospective study represented a single center experience and had relatively small number of cases. A large multicenter prospective trial is recommended.

Keywords: trophoblastic, neoplasia, microvilli, epithelioid trophoblastic.

INTRODUCTION

Gestational trophoblastic neoplasia forms a wide variety of rare conditions that arising due to abnormal proliferation of the trophoblastic cells in placental microvilli. They consist of vesicular mole “partial and complete”, invasive mole, placental site trophoblastic tumor (PSTT), epithelioid trophoblastic tumor (ETT) and choriocarcinoma⁽¹⁾. They can be classified into premalignant forms which include vesicular mole and malignant forms which include the rest⁽²⁾. During the 2000 Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) Oncology Committee meeting held in Washington, it was recommended that gestational trophoblastic neoplasia (GTN) should replace terms like gestational trophoblastic tumor, persistent gestational trophoblastic disease (GTD), residual GTD and malignant GTD. Internationally incidence varies from country to another. In a recent cross-sectional study conducted during 2014 at Al-Azhar University hospital the overall incidence was 6.6 per 1,000 deliveries (150/22727) which were relatively higher than reports from different countries⁽³⁾. In USA they

account for only less than 1% of all gynecological tumors accounting for about 1 pregnancy out of 1,000 in which vesicular mole was the most common while, choriocarcinoma were far less common affecting around 2 to 7 of every 100,000 pregnancies⁽⁴⁾. While, the Far East accounts for the highest incidence up to 40.2 per 1000 births for vesicular mole and 5 per 1,000 for choriocarcinoma. However more recent studies reported that incidence has fallen to 2 per 1000 and 0.5 per 1,000⁽⁵⁾. After molar pregnancy evacuation there's no need for prophylactic chemotherapy just a regular follow up with B-hCG every 2 weeks can provide an accurate observational tool⁽⁶⁾. Where a plateaued or rising hCG, was an indication for starting chemotherapy. Also, a tissue diagnosis of choriocarcinoma or spread to other organs was indications for chemotherapy⁽⁷⁾. A sustained elevated HCG after 6 months even if decreasing is a controversial indication for chemotherapy⁽⁸⁾. Despite the rarity of these diseases they're highly curable due to high sensitivity to chemotherapy with cure rates reaching up to 100% even with historical

treatments for GTN (Hertz R et al. 1956). The continuous attempts now are to keep these high cure rates while minimizing unnecessary excess chemotherapy that may decrease future fertility⁽⁹⁾. For this purpose GTN can be practically subdivided into low risk group and high risk group according to the FIGO prognostic scoring system. Where patients were assessed based on age, result of previous conception, interval between its termination and onset of disease and pre-treatment assessment including B-hCG level, largest tumor size, site and number of metastasis and prior chemotherapy. Then they're grouped according to their score to either low risk (Score 0 to 6) or high risk (score >6)⁽¹⁰⁾. Low risk GTN can be treated only by a single agent chemotherapy "methotrexate and folinic acid or actinomycin-D" while high risk GTN requires combination chemotherapy EMA-CO "etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine"⁽¹¹⁾.

AIM of the WORK

This study aimed to evaluate epidemiological and clinical data, as well as treatment regimes and their outcome including response and related toxicity among patients with gestational trophoblastic neoplasia treated in this study.

PATIENTS and METHODS

In this retrospective study, all patients diagnosed with GTN presented to Oncology Department, Al-Hussein University Hospital in the period from January 2007 to June 2017 were included in this study. **The study was approved by the Ethics Board of Al-Azhar University.**

Patients, who missed before active treatment, received unknown chemotherapy outside our department or had double malignancy other than basal cell carcinoma, were excluded from the study. The medical files of included patients were reviewed and all data related to either patient, disease, treatment or response were retrieved and analyzed. Patients were classified according to pathological type into vesicular mole (partial, and complete), invasive mole, choriocarcinoma, or placental site trophoblastic disease; and into two risk groups based on FIGO prognostic scoring system in to low risk group (6 or less), or high risk group (7 or higher). Treatment response was assessed by using B-hCG level, where normalization of its level was considered complete remission, continues decrease in level was a sign of response, while a plateau for 3 consecutive readings

or increasing in level of B-hCG considered disease resistance to treatment. Univariant analysis was done to determine risk factors related to resistance to first line chemotherapy. Survival interval was the time between the date of histological diagnosis and the date of the last follow-up (for censored observations) or the date of death (for uncensored observations).

RESULTS

Out of 10,119 cancer patients presented at Al Husien University Hospital during the period from 2007 to 2017, Gestational trophoblastic disease constituted only 0.35% of the total number (35 patients).

The mean age was 32.1 years (range 20-55 years) (SD ±9.9). Among the 35 cases, 28 patients (80%) were below the age of 40 and 7 females (20%) were above age of 40 year.

Seven patients (20%) had history of multiple previous abortions. One patient (2.9%) has positive family history of V.M. "her mother".

Table 1: demographic features at initial presentation

		Count	%
Age Group	≤40	27	77.1
	>40	8	22.9
Family History	No	34	97.1
	Yes	1	2.9
Abortion	No	28	80.0
	Yes	7	20.0

Thirty three patients (94.3%) were subjected to evacuation primarily except for 2 patients, one biopsy was obtained from lung mets and the other was very risky of severe bleeding. Most of these patients was evacuated by D&C, or suction, but 9 patients (25.7%) was subjected to hysterectomy, 6 patients were old and completed their families, while one had complication during D and C, one had tumor infiltrating whole thickness of uterus and the last had severe uncontrolled bleeding. Antecedent pregnancy was abortion in 9 patients (25.7%), vesicular mole in 19 (54.3%) patients and 7 patients (20%) presented with antecedent full term pregnancy. By reviewing the histopathology, molar pregnancy was present in 14 case "4 partial (11.4%) and 10 complete (28.6%)", 11 histopathology specimens were invasive mole (31.4%), while 9 (25.7%) patients had choriocarcinoma, Only 1 patient (2.9%) had placental site trophoblastic disease. According to FIGO Prognostic Scoring for

Gestational Trophoblastic Neoplasia

Gestational Trophoblastic Disease; 26 patients (74.3%) were classified as low risk {score \leq 6}, and 9 patients (25.7%) were classified as high risk {score \geq 7}. In low risk patients, 30.8% was kept under follow up while, 69.2% received methotrexate as first line chemotherapy, 61.1% of them achieved complete remission, while 38.9% were refractory, all achieved complete response on the 2nd line chemotherapy. The majority of high risk patients received EMACO as first line

chemotherapy with (66.7%) complete response and 2 cases of early death due to bad general condition, and high tumor burden at time of presentation; while Methotrexate wasn't effective. The resistance to first line chemotherapy in this study was correlated to many factors, but only initial high B-hCG level (\geq 10000 mIU/ml) was statistically significant risk factor (p value: 0.05), while early stage disease was a good prognostic factor but p value was (0.08).

Table 2: initial assessment

		Count	%
Content of Last Conception	Abortion	9	25.7
	Mole	19	54.3
	Term	7	20.0
Biopsy	Biopsy from lung	1	2.9
	D&C	22	62.9
	Not done	1	2.9
	S&E	4	11.4
	TAH +BSO	5	14.3
Histology	Choriocarcinoma	9	25.7
	Invasive Mole	11	31.4
	PSTT	1	2.9
	Vascular Mole Partial	4	11.4
	Vesicular Mole Complete	10	28.6
PS at presentation	0 WHO	9	25.7
	I WHO	23	65.7
	II WHO	2	5.7
	III WHO	1	2.9

Table 3: causes and types of intervention

		Count	%
Cause of intervention			
Mets	No	27	77.1
	Yes	8	22.9
Choriocarcinoma	No	29	82.9
	Yes	6	17.1
Increased BhCG	No	18	51.4
	Yes	17	48.6
Residual	No	28	80.0
	Yes	7	20.0
Bleeding	No	28	80.0
	Yes	7	20.0
Type of intervention			
Type of intervention	2 D&C --> chemotherapy	10	28.6
	Chemotherapy	16	45.7
	FOLLOW UP	5	14.3
	Hysterectomy	3	8.6
Chemotherapy arm			
Chemotherapy arm	No	9	25.7
	Yes	26	74.3

Table 4: univariant analysis of risk factors and its relation to resistance to 1st line chemotherapy

		Response				P value
		No		Yes		
		Count	%	Count	%	
Age Group	<40	7	31.80%	15	68.20%	1.000
	>40	2	40.00%	3	60.00%	
Abortion	No	8	40.00%	12	60.00%	0.214
	Yes	1	14.30%	6	85.70%	
Content Of Last Conception	Abortion	2	22.20%	7	77.80%	NA
	Mole	6	46.20%	7	53.80%	
	Term	1	20.00%	4	80.00%	
Histology	Choriocarcinoma	4	44.40%	5	55.60%	NA
	Invasive Mole	3	42.90%	4	57.10%	
	PSTT	0	0.00%	1	100.00%	
	Vascular Mole Partial	0	0.00%	3	100.00%	
	Vesicular Mole Complete	2	28.60%	5	71.40%	
PS at presentation	0 WHO	1	16.70%	5	83.30%	NA
	I WHO	6	31.60%	13	68.40%	
	II WHO	1	100.00%	0	0.00%	
	III WHO	1	100.00%	0	0.00%	
BhCG categories	<1000mIU/ml	1	50.00%	1	50.00%	NA
	1000-10,000mIU/ml	5	41.70%	7	58.30%	
	10,000-100,000mIU/ml	1	14.30%	6	85.70%	
	>100,000mIU/ml	2	33.30%	4	66.70%	
Mets	No	5	26.30%	14	73.70%	0.233
	Yes	4	50.00%	4	50.00%	
Choriocarcinoma	No	7	33.30%	14	66.70%	1.000
	Yes	2	33.30%	4	66.70%	
Increased B HCG	No	6	54.50%	5	45.50%	0.053
	Yes	3	18.80%	13	81.30%	
Residual	No	6	27.30%	16	72.70%	0.295
	Yes	3	60.00%	2	40.00%	
Bleeding	No	7	33.30%	14	66.70%	1.000
	Yes	2	33.30%	4	66.70%	
Stage	I	4	23.50%	13	76.50%	NA
	II	0	0.00%	1	100.00%	
	III	5	62.5%	3	37.5%	
4=IV, V, VI	IV	0	0.00%	1	100.00%	0.083
	I- II	4	44.4	14	77.8	
	III- IV	5	55.6	4	22.2	

Table 5: univariant analysis of FIGO score components and its relation to resistance to 1st line chemotherapy

Gestational Trophoblastic Neoplasia

FIGO Score.		Response				P-value
		No		Yes		
		Count	%	Count	%	
(Age)	0	7	33.3	14	66.7	1.000
	1	2	33.3	4	66.7	
Previous Conception	0	4	26.7	11	73.3	NA
	1	2	40.0	3	60.0	
	2	2	33.3	4	66.7	
Interval From previous conception	0	5	27.8	13	72.2	NA
	1	0	0.0	4	100.0	
	2	1	50.0	1	50.0	
	4	2	100.0	0	0.0	
Pretreatment HCG	0	0	0.0	3	100.0	NA
	1	2	20.0	8	80.0	
	2	4	50.0	4	50.0	
	4	3	50.0	3	50.0	
Largest Tumor Size	0	3	33.3	6	66.7	NA
	1	1	16.7	5	83.3	
	2	4	80.0	1	20.0	
Site of Mets	0	4	57.1	3	42.9	NA
	4	1	50.0	1	50.0	
Number of Mets	1	1	33.3	2	66.7	
	4	3	60.0	2	40.0	
Previous Chemotherapy	1	2	100.0	0	0.0	
	2	1	100.0	0	0.0	

DISCUSSION

The reported incidence of GTD varies widely worldwide, from a 23 per 100,000 pregnancies (Paraguay) to 1,299 per 100,000 pregnancies in Indonesia. In USA they account for only less than 1% of all gynecological tumors accounting for about 1 pregnancy out of 1,000⁽⁴⁾. This divergence in prevalence may be due to the discrepancies between race, local medical conditions, and educational level. Moreover, incidence rate of GTN was less well known because most of the studies were hospital based rather than population based⁽¹²⁾. In this study, GTD represented 0.4 % of the total number of cancer cases presented to Al Husien University Hospital during the period from 2007 to 2017. The mean age of our patients was 32.1 years which is slightly higher than results published by **Abd El Raouf**⁽³⁾, slightly lower than the findings reported by **Sita-Lumsden et al.**⁽⁹⁾ in which the mean age was 35 years, but not very similar to data published by **Kaye et al.**⁽¹³⁾ from Uganda who reported that most of his cases occurred below 20 years or above 35 years and this may reflect a real difference or it shows the heterogeneity among different countries. Twenty eight (80%) patients in our study were below the age of 40 and 7 patients (20%) were above 40 years, these findings are close to a previous report that

80% of GTD cases were at age group between 20-39 years, 16% were below 20 years and only 4% of patients were above 40 years⁽¹⁾, and also close to results of **Abd El Raouf**⁽³⁾ where 18% of patients were over the age of 40⁽³⁾. Most of our antecedent pregnancies were molar pregnancies (54.3%), followed by abortion (25.7%), which is close to results of **Kuyumcuoglu et al.**⁽¹⁴⁾.

By reviewing the histopathology, molar pregnancy was 40%, invasive mole was 31.4%, while choriocarcinoma was 25.7%, Only 2.9% was placental site trophoblastic disease. This finding does not agree with a previous report from Mansoura University Hospital in 2011, in which choriocarcinoma was about (55.5%)⁽¹⁵⁾ and **Sebire et al.**⁽¹⁶⁾ who also reported that choriocarcinoma was the commonest histopathology. However; **Essel et al.**⁽¹⁷⁾ reported that persistent GTN was the commonest histopathology (54%), but they also reported that invasive mole was very uncommon (4%). Lung was the commonest site (73%) of metastatic sites. A close finding was reported by **Kumar et al.**⁽¹⁸⁾ who found that lung was the commonest site of metastases and represented 65% of metastatic sites and **Essel et al.**⁽¹⁷⁾ where lung metastasis was (65%). In our study, 26 patients

(74.3%) were low risk {score \leq 6}, and 9 patients (25.7%) were high risk {score \geq 7}. Gestational trophoblastic neoplasia was highly responsive to chemotherapy and prognosis was excellent following treatment, especially in low-risk patients (19). However, resistance to first line chemotherapy was reported by **Newlands *et al.*** (20) to occur in 33% of low risk cases and about 10% of high risk cases, also **Macdonald *et al.*** (21) reported 44% chemotherapy resistance in low risk group. In the current study, 38.9% of low risk cases were resistant to first line chemotherapy and about 28.6% was of high risk cases which slightly higher than data published by **Newlands *et al.*** (20), but less than **Macdonald** results (21). Sixty six percent of high risk cases (4 out of 6 patients), who received EMACO combination chemotherapy, achieved complete response. This figure coincides with the study reported by **Shen *et al.*** (22) who reported complete remission rate of 67% and 33% were resistant. The highest complete response rate was reported by **Liu *et al.*** (23) reported 67.9% complete response to EMA-CO alone added to 14.8% achieved by EMA-CO with surgery **Liu *et al.*** (23). The remaining 2 patients died early after initiating chemotherapy. This early death was studied by **Alifrangis *et al.*** (24) who noticed that it's more common in patients with high risk, high burden disease, comorbidities and misdiagnosis as GTN and they concluded that the use of genetic analysis to confirm diagnosis in patients with abnormal presentation, and the use of induction low dose etoposide-cisplatin for those patients is linked to decreased rate of early deaths and improved overall survival. The resistance to first line chemotherapy in this study can be correlated to many factors, but only initial high B-hCG level (\geq 10000 mIU/ml) was statistically significant risk factor (p value: 0.05), while early stage disease was a good prognostic factor but p value was (0.08). These findings were supported by data published by **Bagshawe** (25) who showed that there was a significant correlation of chemotherapy response to initial B-hCG (p = 0.001). Choriocarcinoma pathology and HCG clearance \leq 0.37 I.U/day were major independent predictive factors for methotrexate resistance risk as reported by **You *et al.*** (26). The commonest chemotherapy toxicity was hematological toxicity (neutropenia) occurred in (32.1%) of patients, reported mainly, & was more severe (G III: IV) with EMACO. The 2nd most common toxicity was mucositis reported in 27.6% of patients, which was more common and more severe with EMA-CO. With EMA-CO, liver toxicity was reported in (30%) of patients, while G III anemia in (20%). These findings are consistent

with **Maestá *et al.*** (27). While **Lybol *et al.*** (28) reported anemia in 28.2% of patient treated with EMA-CO, neutropenia in 48.5%, hepatotoxicity in 16.5%, and mucositis 9.7%. This little rise of toxicity rates in our results can be attributed to low socio-economics and bad general condition of our patients, while this noted decrease in our rate of reported anemia is because we don't record anemia except if G III or IV.

Surgical procedures may be good adjuncts to chemotherapy in properly selected cases as the majority of women with GTN are young and wish to preserve their fertility. 9 patients (25.7%) was subjected to hysterectomy, 6 patients were old, & completed their families, while one had complication during D&C, one had tumor infiltrating whole thickness of uterus, & the last has severe uncontrolled bleeding. Keeping with **Eysbouts *et al.*** (29), and **Bolz *et al.*** (30) recommendations as they suggested that Primary hysterectomy should mainly be considered in older patients with localized disease and no desire to preserve fertility, whereas patients with chemotherapy-resistant disease may benefit from additional hysterectomy, especially when disease is localized.

The overall survival rates for patients with high-risk GTN are now running as high as 95%, while in low risk GTN The overall complete remission rate is close to 100%, which is close to our result in low risk group, while in high risk group our overall survival was significantly lower, reaching down to 55.6%, this may be due to the low number of our high risk patients, large proportion of bad general condition patients, and the use of methotrexate single agent in one third of them which was proved ineffective.

CONCLUSION

GTN is a very rare and heterogeneous group of disease, though cure rate even in advanced staging and high risk patients is considerably high with appropriate treatment. FIGO scoring system is a good predictive tool in Stratifying patients to risk groups, thus guiding us for more appropriate choice of single versus multi-agent chemotherapy, although it's complicated and need some simplification.

Hysterectomy can be radical treatment in patients with localized disease who don't want to preserve fertility. Methotrexate is a very chemotherapy to start with in low risk GTN, while it has very low effect in high risk patients, in those

patients with high risk disease EMA-CO is the best option, except in patient with bad general, and high disease burden where there's considerable cases of early deaths.

We have to report that this retrospective study represented a single center experience and had relatively small number of cases.

REFERENCES

- 1. Strohl AE and Lurain JR (2014):** Clinical Epidemiology of Gestational Trophoblastic Disease. *Current Obstetrics and Gynecology Reports*, 3(1):40-3.
- 2. Tasha I, Kroil E, Karameta A, Shahinaj R and Manoku N (2010):** Prevalence of gestational trophoblastic disease in ectopic pregnancy. *J Prenat Med.*, 4(2): 26–29.
- 3. Abd El Raouf O. (2014):** Clinical analysis of molar pregnancy in egyptian population, *AAMJ*. 12: 4.
- 4. Altieri A, Franceschi S, Ferlay J, Smith J, La Vecchia C (2003):** Epidemiology and aetiology of gestational trophoblastic diseases. *Lancet Oncol.*, 4(11):670-8.
- 5. Kim SJ1, Lee C, Kwon SY, Na YJ, Oh YK, Kim CJ (2004):** Studying changes in the incidence, diagnosis and management of GTD. <https://www.ncbi.nlm.nih.gov/pubmed/15457855>
- 6. Lurain J (2010):** Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *Am. J. Obstet. Gynecol.*, 203:531–539.
- 7. Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C (2013):** ESMO guidelines working group. Gestational trophoblastic disease: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.*, 24:vi39–vi50.
- 8. Braga A, Torres B, Burlá M, Maestá I, Yazaki SS, Lin L, Madi JM, Maurício EU, Kevin V, Elias M, Berkowitz RS (2016):** Is chemotherapy necessary for patients with molar pregnancy and human chorionic gonadotropin serum levels raised but falling at 6 months after uterine evacuation? *Gynecol. Oncol.* , 143(3):558-564.
- 9. Sita-Lumsden A, Short D, Lindsay I et al. (2012):** Treatment outcomes for 618 women with gestational trophoblastic tumours following a molar pregnancy at the Charing Cross Hospital. *Br J Cancer*,107:1810Y1814.
- 10. FIGO Oncology Committee (2002):** FIGO staging for gestational trophoblastic neoplasia 2000. <https://www.ncbi.nlm.nih.gov/pubmed/12065144>
- 11. Ngan HY, Bender H, Benedet JL, Jones H, Montrucoli GC, Pecorelli S. (2003):** Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. *Int J Gynaecol Obstet.* ,83(1):175-7.
- 12. Sun R, Zhang Y, Zheng W, Tian Q, An R and Xue Y (2016):** Clinical Characteristics of Gestational Trophoblastic Neoplasia: A 15-Year Hospital-Based Study. *Int J Gynecol Cancer*, 26(1): 216-221.
- 13. Kaye DK (2002):** Gestational trophoblastic disease following complete hydatidiformmole in Mulago Hospital, Kampala, Uganda. *African Health Science*, 2: 47- 51.
- 14. Kuyumcuoglu U, Guzel A, Celik Y et al. (2011):** Risk factors for persistent gestational trophoblastic neoplasia. *Journal of Experimental Therapeutics and Oncology*,9:81-84.
- 15. Reda Abd El hady H, Eman T, Hend S et al. (2011):** Chemo-resistant gestational trophoblastic neoplasia, 5-years experience of Mansoura University Hospital, Egypt *Journal of Obstetrics and Gynecology*, 1: 153-157.
- 16. Sebire NJ and Lindsay I (2010):** Current Issues in thepathology of gestational trophoblastic tumors. *Fetal and Pediatric Pathology*, 29: 30-44.
- 17. Essel KG, Shafer A, Bruegl A, Gershenson DM, Drury LK, BA, Ramondetta LM, Wendel RN and Jubilee B (2018):** Complete Resection Is Essential in the Surgical Treatment of Gestational Trophoblastic Neoplasia. <https://www.ncbi.nlm.nih.gov/pubmed/30157165>

- 18. Kumar J, Ilancheran A and Ratnam S (1988):** Pulmonary metastases in gestational trophoblastic disease: A review of 97 cases. *British Journal of Obstetrics and Gynecology*, 70:74.
- 19. Brown J, Wendel RN, Michael JS, Julian S (2016):** 15 years of progress in gestational trophoblastic disease: Scoring, standardization, and salvage. DOI: 10.1016/j.ygyno.2016.08.330
- 20. Newlands ES, Mulholland PJ *et al.* (2000):** Etoposide and cisplatin/etoposide, methotrexate, and actinomycin D (EMA) chemotherapy for patients with high-risk gestational trophoblastic tumors refractory to EMA/cyclophosphamide and vincristine chemotherapy. *Journal of Clinical Oncology*, 18:854-859.
- 21. Macdonald MC, Hancock BW, Winter MC, Coleman RE, Tidy JA (2016):** Management and Outcomes of Patients with Stage I and III Low- Risk Gestational Trophoblastic Neoplasia Treated in Sheffield, UK, from 1997-2006. *J Reprod Med.*, 61(7-8):341-346.
- 22. Shen T, Chen LL, Qin JL, Wang XY, Cheng XD, Xie X, Lyu WG (2018):** [EMA/CO regimen for chemotherapy 24 patients with ultra high-risk gestational trophoblastic neoplasia]. *Zhonghua Fu Chan Ke Za Zhi.*, 53(6):371-376.
- 23. Liu W1, Zhao W, Zhang YQ, Huang XF (2018):** Curative effects and influenced factors of EMA-CO as an initial regimen for the treatment of high-risk gestational trophoblastic neoplasia. *Zhonghua Yi Xue Za Zhi.* ,98(47):3896-3899.
- 24. Alifrangis C, Agarwal R, Short D, Fisher R A, Sebire N, Savage PM, Seckl MJ (2013):** EMA/CO for high-risk gestational trophoblastic neoplasia: good outcomes with induction low-dose etoposide-cisplatin and genetic analysis. *J Clin Oncol.*, 31(2):280-6.
- 25. Bagshawe KD (1976):** Risk and prognostic factors in trophoblastic neoplasia *Cancer*, 38: 1373-1385.
- 26. You B, You B, Pollet-Villard M *et al.* (2010):** Predictive values of hCG clearance for risk of methotrexate resistance in low-risk gestational trophoblastic neoplasias. <https://academic.oup.com/annonc/article/21/8/1643/153884>
- 27. Maestá L *et al.* (2018):** Effectiveness and toxicity of first-line methotrexate chemotherapy in low-risk postmolar gestational trophoblastic neoplasia. <https://www.ncbi.nlm.nih.gov/pubmed/29092742>
- 28. Lybol C, Thomas CM, Blanken EA, Sweep FC, Verheijen RH, Westermann AM, Boere IA, Reyners AK, Massuger LF, van Hoesel RQ, Ottevanger PB (2013)** Comparing cisplatin-based combination chemotherapy with EMA/CO chemotherapy for the treatment of high risk gestational trophoblastic neoplasia. *Eur J Cancer.*, 49(4):860-7.
- 29. Eysbouts YK *et al.* (2017):** The added value of hysterectomy in the management of gestational trophoblastic neoplasia. <https://www.ncbi.nlm.nih.gov/pubmed/28390821>
- 30. Bolze P A, Mélodie Mathe, Touria Hajri, Benoit You, JohannDabi, Anne-Marie Schott, Sophie Patrier, Jérôme Massardier, François Golfier (2018):** First-line hysterectomy for women with low-risk non-metastatic gestational trophoblastic neoplasia no longer wishing to conceive. *Gynecologic Oncology*, 150 : 282–287.