PROPHYLACTIC CHEMOTHERAPY IN GTN.

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SUMMARY

Gestational Trophoblastic Neoplasm (GTN) is a problem because of its morphological & biological relation to pregnancy, genetic heterogenecity, immunological behaviour, ability to produce H.C.G., difficulty in diagnosis and curability because of occult metastasis and tendency towards malignancy.

Object is to observe that prophylactic chemotherapy in GTN is prognostically significant. Retrospective study of 350 cases of H. Mole from 1982 to 1992 at C.S.S. showed an incidence of 1: 312 and prophylactic chemotherapy was instituted in 53 cases.

Risk cases were selected in a self scoring assessment reviewing clinical parameters, U.S.G. report and serum B-HCG titre.

Different protocols with Methotrexate, Adriamycin and Cyclophosphamide either single or, combined were employed. Recovery was to the extent of 95 per cent and sequelae 5 per cent.

Place of Chemotherapy in GTN needs no emphasis. Gynaecological oncologists often hesitate to advocate chemotherapy till the cases are at high risk. Prophylactic chemotheraphy in risk cases based on suitable scoring is essential in risk community as per study.

INTRODUCTION

Gestational trophoblastic disease dates from antiquity with wide range from benign to malignant with an incidence of 1:200 to 300 in South East Asian country to 1:2000 to 3000 in Western countries (Buxton - 1959). It was 1 : 409 in Delhi (Vohra & Madan 1970). Follow up of H. Mole after surgical intervention is of prime importance to isolate high risk cases. Patient left uncared may develop invasive mole,

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or choriocarcinoma with distant metastasis. Serum B. HCG titre, U.S.G. and histopathological report help to diagnose risk cases in early stage and administer chemotherapy with good success rate.

The study was undertaken to institute prophylactic chemotherapy in risk cases.

MATERIALS & METHODS

It is a retrospective analysis of 350 cases of hydatidiform mole out of total 1,09200 obstetric admission at C.R. Seva Sadan, Calcutta from 1st January 1982 to 31st December 1991 with an incidence of 1:312 there were 306 cases of benign mole, 14 cases of invasive mole and 30 cases of chorio-carcinoma.

Amongst 306 benign mole 53 cases were treated with prophylactic chemotherapy, of which 26 had only chemotherapy, 10 had hysterectomy and 17 had chemotherapy followed by hysterectomy though the safety of vaginal evacuation in molar pregnancy had long been well documented (Tow - 1966).

RESULT AND ANALYSIS

From Table-I it is obvious that though over all incidence of molar pregnancy is 1 in 312, the incidence of benign mole is 1:359 and of all molar pregnancy the incidence of invasive mole is 4 per cent, malignant sequale 5.1 per cent and the prevalance of chorio-carcinoma (1:3640). The risk of chorio-carcinoma is estimated to be 3.5% in higher age and parity (Goldstein 1977, Lewis-1980).

The relative risk of malignant sequeale of molar pregnancy has been quoted as 6 % (U.K.) and 15% (Hong Kong) and several workers advocated chemotherapy for all cases of mole as a prophylaxis against chorio-carcinoma though prophylatic chemotherapy is associated with significant morbidity and mortality (Ratnam and Chew 1975).

High risk cases were screened on scoring system (Table-II) Cases with score value 7 or less are less malignant whereas higher score value of 8 to 14 and 15 to 21 had more malignant sequeale in the range of 19.7 per cent (Table-III).

Table - I
Incidence of Trohoblastic Diseases

G.T.N.	NO.	Incidence
Benign Mole	306	1:359
Invasive Mole	14	4% of H. Mole
Chorio-Carcinoma	30	1:3640
Malignant - Scqueale	18	5.1% of H. Mole.
Total No. of GTN	350	Total Obstt. 1,09200 Admission.

Table - II
Assessment of Risk-cases of H.Mole on Scoring System

Score	0	1	2	3
Factors				
Age in years	19	20-29	30-39	40
Parity	0	1-2	3-4	4
Uterine size in weeks	Normal size	20	20-24	24
Ovarian enlargement in cm.	Not Palpable	Slightly 3 to 5cm.	Moderately 5 to 10	Bilateral Enlargement 10
Serum HCG in m. i.u.	200-1000	2000-10,000	10,000-40,000	50,000
Bleeding per Vaginum	Nil	Slight	Moderate	Heavy
Blood Group	AB.	B	O	

TABLE - III
Risk cases according to scoring system

Score	No.of cases	Malignancy	Sequalae
0-7	149	0	
8-14	83	13	15.6% - 19.7%
15-21	21	5	23.8%

Follow up after evacuation of mole is more important and excessive production of free beta-subumit of HCG may identify patients likely to develop metastasis long before the tumor could be detected (Rinker 1989). If the patient is clinically well as well as radiologically and bio-chemically negative at the end of 2 years of follow up it is highly unlikely that she will develop persistent disease (Ratnam

Table - IV
Follow up of G.T.N. Cases

Duration	No.	Malignant Sequalae	Death
Less than 1 year	306	11	4
1 year	150	4	2
3 years	78	2	1
4 years	57	1	0
6 years	15	0	0
		18	7

TABLE - V
Diagnosis of Invasive Mole & Chorio-Carcinoma

Parameter	Invasive Mole No.of cases-14	Chorio-carcinoma No. of cases-30
CLINICAL:		
Uterine Enlargement	14	30
Vaginal Bleeding		
Ovarian Enlargement	8	28
HORMONAL		
Serum HCG	Above 10,000 min. to 50,000 (14 cases)	60,000 min. (30 cases)
HISTOPATHOLOGICAL:		
Diagnostic Curretage	Villi-present in Myometrium (5 cases)	Villi present in Myometrium (20 cases)
U.S.G.		
Uterus	Moderately	Moderately
Ovary	Enlarged 10 cases	Enlarged 25 cases
Adnexa	(71.04%)	(83.3%)
RADIOGRAPHY		
Metastasis		
Lungs	2	4
Bone	1	1
Brain	1	2

chew 1975).

In our study, 18 cases developed malignant trophoblastic diseases (Table-IV) during follow up - 11 cases within 1 year after evacuation and 7 cases within 1 to 6 year. Seven of the 18 cases developed malignancy and died with an incidence of 7/306 i.e. (2.3. per cent).

DIAGNOSIS OF INVASIVE MOLE & CHORIOCARCINOMA

In all these cases uterine enlargement persisted with rising HCG titre, and presence of villous in endometrial curretage was revealed in 5 cases of invasive mole and 20 cases with avillous structure (Table V). Berkowtiz et al (1980) revealed no Trophoblastic tissue in (54%) cases.

TABLE - VI
Diagnosis of Malignant Sequealae

Criteria	Chorio-Carcinoma	Invasive Mole
A. Clinical Symptoms Histopathology Report HCG Titre	3	4
B. Lung Metastasis	2	2
C. Multiple Distant Metastasis	Nil	2
D. Uterine Pathology after Hysterectomy	5	Nil

TABLE - VII
Treatment Schedule for Low-risk group

No.of Day	Drug	Doses
D1	Methotrexate	100 mg.i.v. in 5% Dextrose Drip
D2	Leucovorin Calcium	6 mg. 1 m.
D3	Methotrexate	As before
D4	Leucovorin Calcium	" "
D5	Methotrexate	" "
D6	Leucovorin Calcium	" "
D7	MTX (Methotrexate)	" "
D8	Leucovorin Calcium	" "

Course repeated after 30 days monitoring by serum MCG/Blood count/Platelet count Hb%

USG report revealed uterine and ovarian enlargement in 70 to 80 per cent cases. Metastasis in lung and brain were also revealed by radiography.

DIAGNOSIS OF MALIGNANT SEQUEALE

Rising HCG titre, distant metastasis, and uterine pathology in deep endometrial curettage revealed malignant sequeale in 1/3rd of the cases where as distant metastasis were noted in both the groups (Table VI).

PROPHYLACTIC CHEMOTHERAPY

Agents that have been used include Methotrexate (Ratnam and Chew 1975; Kin et al 1986) and Actinomycin D (Berkowitz et al 1980). Different regimes have been advised by various authors. We follow the regime with Methotrexate and Leucovorin Calcium (Table VII).

In this schedule Inj.Methotrexate 100 mg in I.V. drip in 540 cc. of 5% Dextrose Solution was given on first day followed by Inj. Leucovorin Calcium 6 mg. on 2nd day repeating in the same order on 3rd and 4th day and subsequently upto 8th day. Progress of treatment was assessed by haematological study, platelet count; serum B. HCG tirre and the course repeated after 4 to 6 weeks till the HCG titre was less than 3/1 u/ml.

PROPHYLACTIC TREATMENT AND MALIGNANT SEQUALAE

In this series prophylactic treatment was given in 53 cases and malignant sequeale was only in 5.6 per cent, whereas in control group the malignant sequeale was 14.6 per cent. Again when prophylactic treatment was given by chemotherapy only malignant sequeale was 11.5 per cent (Table VIII). In fact, the incidence of sequeale requiring chemotherapy was found to be increased in patients who had hysteoctomy or hysterectomy (Curry et al 1975, Stone and Bagshave 1979). Similarly, age was reported to be an important factor (Tow 1966, Remy & Meglynn 1989) with elderly women at an increased risk of developing sequelae which required chemotherapy.

TABLE - VIII
Prophylectic Treatment & Malignant Sequeala

Prophylactic Treatment	No.of cases	No.of Malignant Cases	Sequalae
No Prophylactic Treatment	253	37	14.6%
Prophylactic Treatment	53	3	5.6%
Chemotherapy	26	3	11.5%
Hysterectomy	10	0	
Hysterectomy followed by Chemotherapy	17	0	

TABLE - IX
Treatment of Chorio-Carcinoma & Invasive Mole

Drugs	No.of cases of Chorio-Carcinoma	No.of cases of Invasive Mole	Death
1. Large doses of Methotrexate	17	7	3
2. Large doses of Actinomycin D.	3	2	1
3. Methotrexate & Actinomycin D.	3	1	2
4. Heavy curretage	-	2	-
5. Chemotherapy followed by Hysterectomy	7	2	1
	30	14	7

TREATMENT OF CHORIO CARCINOMA & INVASIVE MOLE

Histopathological nature of the trophoblastic tissue, serum B. HCG titre and the desire for future pregnancy is to be considered before administering high dose of Methotrexate, or large doses of Actinomycin D single or combined with cyclophosphamide as per Table IX.

Doses are to be adjusted according to the bodyweight of the patient and to be monitored by platelet count greater than 100,000 c.m., H.C.G. titre greater than 3/1 u.ml. and stomal ulcer, and alopecia. There were 7 deaths following different regimes of treatment. Mortality may be high in this regime because of massive immune suppression. Hysterectomy is the treatment of choice where there is persistent bleeding, adnexal growth and sepsis. But, Bahar et al (1989) were of the opinion that patients treated by primary hysterectomy show significant decrease in H.C.G. regression rate compared to those treated with chemotherapy.

CONCLUSION

The benefit of prophylactic chemotherapy with proper monitoring is encouraging. According to some authors benefits of prophylactic chemotherapy have not been conclusively established with some studies showing lower mortality in those who were not given chemotherapy after evacuation, (Ratnam and Chew 1975, Bagshawe et al 1986).

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REFERENCES

1. *Bahar A.M. Ashnehi M.S., Senthilselvan A. : Int. J. Gynae. & Obst. 29 (3) : 233, 1989.*
2. *Bagshawe KD, Dent J. Webby J. Lancet II: 673, 678, 1986.*
3. *Berkowitz R.S. Desai U. Goldstein D.P., Drisco S.G. Marean A.R. Bemstein M.R.: Gynae. Oncol 10, 39, 1980.*
4. *Buxton CL Am. H.Y. acad SCI, 80, 121, 1959.*
5. *Curry SL. Hammond C.B. Tyreyl etal : Obstet & Gynec. 45, 1, 1975.*
6. *Goldstein D.P. Test Book of Gynaecology by Russel D. Alvare, Lea and Febiser Philli 320, 1977.*
7. *Kin D.S. Moon A, Kim K : Obstet Gynec: 67, 690-694, 1986.*
8. *Lewis J.L.: Am. J Obstet Gynec. 136, 163, 1980.*
9. *Ratnam S.S. Chew SC.: J. Obstet Gynec. India 25, 127, 1975.*
10. *Remy J.C., Mcglynn M. Mcguirence. Int. J. Gynaec Obstet 28(4), 355, 1989.*
11. *Rinker A.D. Tietz NW : Clini. Chem. 35, 1799, 1989.*
12. *Stone M., Bagshawe K.D. : Brit. J. Obstet Gynec. 86, 782, 1979.*
13. *Tow WSH : J. Obstet & Gynaec Brit C'Wealth: 73, 345,1966.*
14. *Vohra S and Madan P : J. Obstet Gynec Ind. : 20, 455, 1970.*