TROPHOBLASTIC DISEASE IN SINGAPORE

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The aetiology and pathogenesis of hydatidiform mole remains unknown and considerable disagreement still exists over the definition and classification of malignant growths of the chorion. (Acosta-Sison, 1959; Tow, 1966; Chun and Braga, 1967; Parks, 1967). Normal trophoblast presents some of the characteristics of malignancy such as rapid growth, invasiveness and embolisation and hence the distinction between normal and malignant trophoblast becomes somewhat arbitrary and histological predictions from curettings have been of very little value.

At the University Department in Singapore, the histological demonstration of myometrial invasion, the clinical and radiographic evidence of metastases at distant sites and the persistence of trophoblastic activity as demonstrated by chorionic gonadotrophic estimations are the accepted criteria for diagnosing malignancy of hydatidiform mole.

Trophoblastic disease has been a subject of interest in the University Department of Obstetrics and Gynaecology at the Kandang Kerbau Hospital for Women, Singapore for many years. The results that are presented in this paper began as a prospective study of all cases of hydatidiform mole admitted to the hospital but since 1966, the two other units at the hospital and another two units in the country have managed their own patients. This report refers only to cases seen at the University Department.

The present paper will present an overall picture of the disease, followed by observations of the maligant sequelae. Many aspects have already been described in previous publications and references will be made to them.

Incidence

The incidence of hydatidiform mole has been worked out at around 1 in 823 pregnancies in Singapore (Teoh *et al;* 1971) with relatively higher incidences in teenagers and patients above 40 years. This is confirmed in our present review (Table 1). In this table, we have compared our molar pregnancies with the mean age specific fertility rates of the country for the period in question, and there is a definite excess of cases in the early age group. The age-specific fertility rate for women over 45 years (by convention the reproductive period is taken as 15-44 years) is unfortunately not available for comparison.

Annual Variation

Previous reference has been made to a "seasonal variation" (Teoh *et al;* 1971) and indeed we have again confirmed that

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TABLE 1

Age Distribution of Trophoblastic Disease

Age	Moles (1) No.	(2) %	(3) Age-specific* Fertility Rate	Column 2 Column 3
Under 15	1	0.2	Not Available	-
15-	60	10.3	24.5	0.41
20-	164	28.0	159.7	0.17
25-	130	22.2	226.7	0.09
30-	110	18.8	149.7	0.12
35-	50	8.5	80.7	0.10
40-	33	5.6	30.8	0.18
Over 45	38	6.4	Not Available	-

* Figures from F.P.P.B.

there is an increased incidence in May and September. The increase is however not statistically significant and previous attempts to correlate it with temperature or rainfall were abortive. (Table II).

TABLE II

Seasonal Variation

Month	No.	%
January	55	7.9
February	58	8.4
March	53	7.6
April	47	6.8
May	70	10.1
June	54	7.8
July	56	8.1
August	56	8.1
September	64	9.2
October	69	9.9
November	49	7.1
December	61	8.0

Racial Influence

Previous publications have shown a slightly increased incidence of molar pregnancy in Indians as opposed to Chinese and Malays in Singapore. However, this expanded series has shown no difference. (Table III).

TABLE III

Moles & Ethnic Group

Race	No.	%	Population%* in Singapore
Chinese	446	76.1	76.2
Malay	94	16.0	15.0
Indian	40	6.8	6.7
Eurasian	3	0.5	2.1
Others	3	0.5	

* Census 1970

Socio Economic Status

Other studies in Singapore have proven that questions related to income and social status are 'sensitive issues' and data from questionnaires is grossly misleading. We were unable to get a satisfactory response on this. However our previous study on topographic distribution of cases as well as other international studies have shown that poor communities are affected more than affluent ones. (Acosta-Sison 1959; Chun *et al*, 1964; Teoh *et al*, 1971).

Mode Of Presentation

Table IV shows the main mode of presentation of all our cases. In 15 patients, no record was available. Clinical

TABLE IV

Initial Presentation

Symptoms	No.	%
Threatened abortion	536	77.5
Hyperemesis	24	3.5
Intrauterine death	16	2.3
Rapidly enlarging uterus	5	0.7
Pre-eclampsia	18	2.6
Asymptomatic	8	1.1
Abdominal pain	7	1.0
Aborted mole	52	7.6
Unknown	15	2.7

examination on these patients revealed that in 60.3% the uterus was larger than expected for the period of amenorrhoea, and in 15.8% it corresponded to the period of amenorrhoea. In 23.9% it was smaller than expected.

Unilateral ovarian enlargement was found in 8.5% of cases and bilateral enlargement in 12%.

Management

Increasing awareness of the high incidence of trophoblastic disease in Singapore and the availability of sophisticated methods of diagnosis have led to earlier recognition and prompt management of the condition. Patients presenting with bleeding in early pregnancy, exaggerated symptoms of pregnancy or toxaemia will be suspected of having a hydatidiform mole.

The diagnosis and management have changed over the years. Previously confirmation was achieved by plain abdominal X-Ray, the Probe test, quantitative estimation of urine and serum HCG and amniogram. Since 1973, we have been using the ultrasonic B scan and in over 30 cases, it proved 100% accurate. (Results to be published). It has proved to be valuable especially in the early periods of gestation when X-Rays are not only inaccurate but may prove harmful if it were a normal pregnancy..

In young patients who have not completed their families, the policy is to conserve the uterus. In the early cases, hysterotomy was performed in 8 cases but this has been abandoned in favour of a high dose oxytocin infusion to abort the mole, followed by curettage. The oxytocin infusion would keep the uterus well contracted, thus minimising bleeding and the danger of perforation. We now use vacuum aspiration under oxytocin cover, giving a rapid and complete evacuation.

In patients over 40 years of age, and those who have completed their families, hysterectomy is carried out. The patient's ovaries are conserved unless they are over 45 years of age.

Followup

All patients who have had a molar pregnancy are followed up indefinitely. They are kept in hospital until the urine and serum values of HCG have declined and there is no evidence of distant metatases. They are then followed up at the trophoblastic follow up clinics at weekly intervals for the first 2 months; at monthly intervals the next 10 months and at 3 monthly intervals until the end of 2 years. Thereafter they are followed up at 6 monthly intervals for life.

At each of these visits, a full clinical examination, X-Ray of her chest, and urine and serum are taken for HCG estimations.

At the end of six weeks, persistence of positive HCG in serum or urine or the presence of metastases at distant sites would be considered as malignancy and treated with chemotherapy.

TABLE V
Malignancy in Relation to Treatment

Initial Treatment	Choriocarcinoma	Total	% Malignant
D & C	41	466	8.8
Total Hysterectomy	31	137	22.6
T.H.B.S.O.	27	70	38.6
Hysterotomy	2	8	25.0
Others	1	2	50.0
No Treatment	2	7	28.6

Prophylactic Methotrexate

In an attempt to reduce the incidence of malignant trophoblastic disease, prophylactic chemotherapy was suggested by Hreshchyshyn in 1962 and still has supporters. (Chun *et al*, 1967, 1970; Goldstein, 1971). In our experience, the malignancy rate was reduced from 8.7% to 4.5% but there was considerable toxicity and a significantly increased mortality rate (2.2% compared with 0.5% in controls) (Ratnam *et al*, 1971).

The reduction in malignancy rate for both groups is statistically not significant (see Table VI).

As there was no added advantage to the use of prophylactic methotrexate when the follow up facilities were good, the practice has been abandoned.

Choriocarcinoma

The classification of malignant disease of the chorion remains confusing (Acosta-Sison, 1959; Tow, 1966; Chun and Braga, 1967) and the principle that destructive and metastatic moles should not be considered benign (Parawirohardjo *et al*, 1957; Tow, 1966) is followed in this Unit.

The distribution of choriocarcinoma patients in relation to antecedent pregnancies is shown in Table VII.

TABLE VI
Value of Prophylactic Methotrexate

Regime	Malignancy	Total	% Malignant
Prophylactic MTX	3	121	2.4
D & C Only	10	330	3.0
Hysterectomy only	17	136	12.5
Hysterectomy & prophylactic MTX	2	26	7.6

TABLE VII
Antecedent Pregnancies

Country	No. of Cases	Mole %	Abortion %	Normal Delivery
England and Wales	164	66	15	19
Phillippines	105	60	23	11
Hong Kong	115	57	22	21
Singapore*	106	78.3	7.5	11.3

* 2.9% after Ectopic pregnancy (not included above).

The incidence has been worked out at 1 in 4298 deliveries (Teoh *et al*, 1972). Since the Government Units in the hospital have been managing their own cases after 1966 and two other gynaecological units have been opened after 1969, we will not attempt to calculate the incidence of choriocarcinoma from this study.

The racial distribution is shown in Table VIII. There is a relatively high incidence amongst the Malays. In this series however, it is not statistically significant ($P > 0.05$). Previously, Malays had been found to have significantly higher incidence (Teoh, 1972).

TABLE VIII

Racial Distribution of Choriocarcinoma

Race	No.	%	% in Singapore
Chinese	77	72.6	76.2
Malay	22	20.8	15.0
Indian	6	5.7	6.7
Eurasian	1	0.9	2.1

Presenting Features

As the majority arose from moles, the presentation was that of the molar pregnancy. A small number presented with secondaries.

Metastases

The commonest site of metastases was the lungs followed by the vagina. Table IX shows the distribution of metastases.

All those with cerebral metastases had pulmonary secondaries. As some of these were post mortem diagnosis, the malignancy rate cannot be calculated. It is of interest that choriocarcinoma does involve the lymph nodes, though it is relatively uncommon. In our experience cerebral metastases were always fatal although temporary remissions were obtained.

TABLE IX

Site of Metastases and Mortality

Site	Total	Mortality	% Mortality
Lungs	66	11	16.6
Vagina	14	3	21.4
Serosa of Uterus	7	2	28.5
Brain	5	5	100.0
Tubes and Ovaries	3	1	33.3
Liver	3*	3	100.0
Nodes	2	-	-
Rectum	1	-	-
Kidney	1*	-	-

* Post mortem diagnosis.

In 14 cases, thoracotomy was carried out for a solitary lung metastases. The results of these will be published later. Unlike other malignancies, we have found that pulmonary metastases if solitary and non responsive to chemotherapy can be excised with good results. The removal of the fibrotic pseudocapsule may allow the chemotherapeutic agent to act on the malignant cells.

Treatment

The treatment of choriocarcinoma has changed considerably over the years. Prior to 1962, methotrexate was not available and surgery, where possible, was the only form of treatment. When chemotherapy became available, the patients with proven choriocarcinoma were treated with an oral combination of 2.5 mg of methotrexate and 100 mg of 6 mercaptopurine, 6 hourly for a 5 day course. After a lapse of 2 weeks, the course was repeated. Repeated courses were administered at 2 weekly intervals until all evidence of the disease disappeared. The toxicity associated with oral methotrexate was unpleasant for the patients and the response was not satisfactory. The regime was then changed to parenteral adminis-

tration of methotrexate alone. The patients were given 10 mg per day intramuscularly in four divided doses until toxicity developed. The course was repeated when all toxicity had disappeared and the total white cell count had risen to 5,000 per cubic millimetre. Treatment was resumed until all evidence of the disease had disappeared.

In 1973, the chemotherapy was modified further. Initially the patients were treated with parenteral methotrexate only for 3 courses, and if they failed to respond rapidly, as shown by a rapid decline in the HCG levels, a daily combination of 10 mg intramuscular methotrexate and 0.5 mg actinomycin D given intravenously was administered until they developed toxicity. Each course was repeated after the patient had recovered. Results of the various drug regimes are shown in Table X.

TABLE X

Mortality of Different Drug Regimes

Drug	Total	No. of Deaths	% Mortality
M.T.X. Only	47	2	4.3
M.T.X. & M.P.	30	5	16.7
M.T.X. & Act.-D	4	2	50.0
M.T.X., 6 M.P. & Act.-D	4	3	75.0

Of the 21 patients seen before the chemotherapeutic era, 5 died (23.8%). The overall mortality of the patients treated with drugs was 14.1% but the difference is statistically not significant. Statistical analysis of the results of the various drug regimes shows that there was no significantly superior regime. Statistical comparison between the patients on methotrexate alone and those on all three drugs shows a statistically significant difference in mortality ($P < 0.05$) but this is due to the fact that only resistant cases were put on all 3 drugs in a desperate attempt. Hence the difference is due to patient selection.

Table XI shows the mortality from choriocarcinoma in relation to antecedent pregnancy. It would appear that molar pregnancy has the lowest mortality risk (excluding ectopics because the numbers are too small for a fair comparison). This is probably due to the early detection of abnormality as all molar pregnancies are closely followed up.

TABLE XI

Mortality from Choriocarcinoma in Relation to Antecedent Pregnancy

Antecedent Pregnancy	Death	%
Mole	13	15.6
Abortion	2	25.0
Normal pregnancy	2	16.6
Ectopic	0	0

This is well shown in Table XII. It is seen that if the interval between pregnancy and detection of malignancy is over 6 months, there is a great increase

TABLE XII

Relation between Mortality and Detection of Malignancy

Interval before Detection (Months)	No.	Deaths	% Dead
Within 1 month	50	3	6.0
1-2 months	25	3	12.0
3-5 ,,	11	3	27.3
6-8 ,,	6	2	33.3
9-11 ,,	1	1	100.0
12-17 ,,	4	2	50.0
18-23 ,,	2	2	100.0
24-48 ,,	2	1	50.0
49-70 ,,	1	-	-
71 and over	4	-	-

in the incidence of fatal choriocarcinoma. This difference is statistically significant ($P > 0.05$). However, when the interval is very long (the longest being 12 years) there has so far been no mortality. However, one of these patients is currently under treatment, and the outcome is uncertain.

Discussion

Up to now, the aetiology and pathogenesis of trophoblastic disease has been elusive. Although previous publications have suggested a preponderance of the disease in the lower socio-economic group of a population and seasonal variations of epidemic nature suggestive of infective origin, there has been no significant finding in this study suggestive of any of these.

Better awareness of the condition and careful screening of patients with bleeding and toxaemia in early pregnancy will lead to early diagnosis and management of the condition. Where facilities for vacuum aspiration are available, this will form the choice method of evacuating the uterus. The procedure is simple, rapid, safe, associated with very little blood loss and complete.

Once the uterus has been evacuated, there is general agreement that if chemotherapy is indicated, the sooner it is given the better would be the prognosis. This is demonstrated in Table XII of this paper. There is however a considerable amount of uncertainty and confusion on the routine use of chemotherapy in all patients with molar pregnancy. The question that has to be seriously considered before adopting a policy of prophylaxis, using highly toxic agents, is whether it is justifiable to give these agents to women of reproductive age. Besides the morbidity and mortality to the mother, one has to also take into consideration the possible teratogenic effect resulting from chromosomal damage and recessive mutagenic damages. Methotrexate when used prophylactically in this study did not significantly reduce the incidence of choriocarcinoma but the overall mortality, including deaths from drug toxicity, was higher in the treated group (Table VI). More recently, prophylactic chemotherapy with Actinomycin D has been suggested by Goldstein and his co-workers. He however concluded that though Actinomycin D reduced the incidence of neoplastic disease, it did not avoid the need for systematic follow up with gonadotrophic assay.

The more sensible approach to the problem therefore appears to be to select patients for chemotherapy on the basis of post-evacuative regular gonadotrophic assay, which provides a good indication of residual trophoblastic activity. The policy in the department at present is to follow the patients closely with regular serum and urinary gonadotrophic assays using sensitive haemagglutination inhibition and radioimmunoassay methods. Only if the assay remains positive or becomes positive after being negative, is treatment with chemotherapy instituted.

The regime of treatment and the choice of chemotherapeutic agents varies from one centre to another. The superiority of administering methotrexate parenterally over orally is generally accepted. However the question of whether treatment should be confined to one chemotherapeutic agent or to a combination is unsolved. We have found no statistical difference between the use of a single agent and multiple ones. In fact, there is a danger of cumulative toxicity to the patient. It would seem prudent to begin with a single welll-tried and familiar drug such

as methotrexate, and only to use others if there is poor response. However it is obvious, as we have shown, that if the patient requires many drugs, the outlook is extremely grave and the mortality is uniformly and significantly high.

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