COMPLETE HYDATIDIFORM MOLE

IN

HOSPITAL UNIVERSITI SAINS MALAYSIA

KUBANG KERIAN

KELANTAN

A REVIEW OF 120 CASES

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Kelantan is one of the states in the Federation of Malaysia. It has borders with Thailand in the north, the states of Trengganu and Pahang in the south, and the state of Perak in the west. It is said that the soul of Malaysia is in the East Coast, which includes the states of Kelantan, Trengganu and Pahang.

The state of Kelantan has an area of 14,943 square kilometres. The state is divided administratively into nine districts. These are; districts of Kota Baru, Bachok, Machang, Pasir Puteh, Gua Musang, Kuala Krai, Tanah Merah, Pasir Mas and Tumpat. An additional sub district of Jeli was recently formed to facilitate proper administration of the development programme.

The state administrative capital is situated in Kota Baru. It is located on the bank of Kelantan river. This is so for the reasons of transportation during olden times, where the main mode of travel was by river.

The state of Kelantan is populated by 1,215,950 people, and the majority of the population is residing in the northern area of the state. It is estimated that about ninety per cent of the population is concentrated in this area. The majority of the population are from the Malay descent, forming about ninety-three per cent of the state population, with the Chinese descent

contributing 5.4 per cent, the Indians about 0.7 per cent and the rest were of the other races. As the majority of the population are Malays, and the Malays are Muslims, the society here are rather conservative.

The main occupation of the people are farming and fishing. They are involved in padi-growing, rubber, oil palm and tobacco farming. For those involved in fishing, they are mainly traditional fishermen, fishing along the legendary beautiful stretches of golden and silver coastline of Kelantan. Apart from being involved in in agriculture, the people of Kelantan are known for being very industrious and for that reason a lot of traditional handicraft factories are found in the state, especially along the road towards the beach.

Kelantan has recorded a birth rate of 42.5 births per 1000 population in 1992 and the population growth rate was 2.6 per cent . Kelantan has undergone a lot of improvement in the last ten years with a number of new district hospitals and primary health centres were put into commission. The state also saw significant development in social, educational and economic achievement.

The medical care of the state is provided by the district hospitals found in each district. In cases that need further investigations and complicated management, the referral centres are the Hospital Kota Baru and the Universiti Sains Hospital, Kubang Kerian. Apart from the medical care, the ministry of health had built and put into commission a number of primary health centres.

These primary health centres contributed to the maternal and child health care, actively conducting immunisation programme, running school health programme and giving advice on sanitation.

In 1992 report of health care programme for the state of Kelantan, there is one primary health centre for 23,384 people. In the district of Kota Baru, each primary health centre serves a population of 37,749 people. Currently, each midwifery clinic serves a population of 6,172 people.

The Hospital Kota Baru was the only referral centre for the state of Kelantan and the northern part of Trengganu. The hospital was built in 1930 and had been operational since then. In 1984 the Hospital Universiti Sains Malaysia was built and started to treat patients since then. With the commissioning of the universiti hospital, it becomes the alternative referral centre for the state of Kelantan and the northern part of Trengganu.

THE UNIVERSITI SAINS MALAYSIA AND THE SCHOOL OF MEDICAL SCIENCES

The Universiti Sains Malaysia was set up in the year 1969 and the main campus is located in Penang. It has branch campuses away from the island of Penag and the school of medical sciences is located in Kubang kerian, Kelantan. This medical school is the only medical institution to be sited in a rural area of the east coast of the peninsula Malaysia. The school of medical sciences had been established in the middle of 1979 and a few batches of

doctors had graduated from the school and a number of them had gone further and obtained postgraduate degrees overseas. Its performance thus far had been comparable to the two medical institutions which are located in the most developed part of the nation, in Kuala Lumpur i.e. the University of Malaya and the National University of Malaysia.

The objective of the medical school is to train doctors who are familiar with the community and would be able to contribute and be part of the health care system of the country.

THE HOSPITAL UNIVERSITI SAINS MALAYSIA

The school of medical sciences of the Universiti Sains Malaysia, conducts its programme in the Hospital Universiti Sains Malaysia, Kubang Kerian. It is situated in a small town of Kubang Kerian, about seven kilometres away from the state capital of Kota Baru. This hospital was constructed in the year 1979 and was completed in 1984. The hospital started its services in January 1984 and its oficial opening by the Royal Highness the Sultan Of Kelantan was held on 26th of August 1984.

The undergraduate teaching programme is conducted in this hospital. The hosptal also offers ts services and facilities to the people of Kelantan. These services include modern laboratories, Computerised Axial Scanning facilties, operation theatres and intensive care management units. The blood bank facility is readily available in this hospital.

The school of medical sciences made further progress when it started postgraduate trainning for local doctors. In 1988 the school started postgraduate programme in Internal Medicine and in 1991 four more postgraduate courses were started i.e. Paediatrics, Obstetrics and Gynaecology, Orthopaedics and General Surgery.

THE DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY
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The medical school functions according to medical and surgical divisions. The department of Obstetrics and Gynaecology has its wards in the firt and the second floors of the hosptal. A total 128 beds were allocated to the department of obstetrics and gynaecology; 78 beds for obstetrics aptients and 56 beds for gynaecological cases. The labour suite is situated in the east wing of the hospital block. It has eight low-risk beds, five high-risk beds and two beds for acute and intensve care management. The labour suite is equiped with central oxygen supply delivered through wall plug and the monitoring of patients is using up to-date gadgetery. The intrapartum patients had access to intermittent or continous cardiotocographic monitoring. For resuscitation of newborns, an adjacent room is equipped with warmer and transport incubator. The labour suite has its opera tion theatre where emergency obstetrical procedures such as caesarean sections are done. The antenatal and post natal patients are warded in the first floor.

The gynaecological wards are housed in the north and south wings of the second floor of the main hospital block. The gynaecological operation theatres are situated on the east wing of the third floor.

The department is presently run by five consultants, five trainee lecturers, five registrars, fifteen medical officers and twelve house officers.

The department of obstetrics and gynaecology conducts the following clinics:

Saturday and Tuesday mornings	Antenatal clinics Combined Clinic for Medical llness
Saturday and Tuesday afternoons	Gynaecological clinics
Sunday morning	New cases for bookng
Monday morning	Ultrasound procedures
Monday afternoon	Oncology clinic
Monday afternoon	Infertility clinic
Wednesday afternoon	Postnatal and Family Planning clinic

Elective operations such as hysterectomies are performed either on Mondays or Wednesdays depending on respective surgeons.

The department of obstetrics and gynaecology of the medical school and the department of obstetrics and gynaecology of Hospital Kota Baru merged and functioned as one unit in July 1985. At that time all obstetrical and gynaecological cases were admitted to the hospital universiti sains. However due administrative differences the merger was broken in 1989 and the two units function independently in respective hospitals.

INTRODUCTION

Hydatidiform mole, invasive mole, and choriocarcinoma are neoplasms that originate in the fetal chorion. According to Hertz (1), the benign hydatidiform mole represents the beginning of a disease continuum, whereas the highly malignant choriocarcinoma represents the end of the spectrum. It has been known for many years that most hydatidiform moles are female. In a collected series of hydatiform mole sex chromatin studies, Lawler (2) reported a 90% overall frequency of chromatin-positive cases. The remaining 10% of the cases were assumed to be male.

In 1978 Szulman and Surti (3) reported that hydatidiform moles could be divided into two distinct syndromes. They described the complete or classic mole without discernable embryo or fetus and with diploid karyotype, and the partial mole in which there was an ascertainable fetus and a triploid karyotype. Complete moles appeared clinically as missed abortions usually during the second trimester, whereas partial moles presented in the first trimester or rarely as spontaneous abortions.

The incidence of gestational trophoblastic disease appears to vary widely in different parts of the world. In the United Kingdom hydatidiform moles occur as a complication of approximately 1 in 1500 pregnancies while in in Indonesia estimates are of the order of 1 in 200 pregnancies (4).

Accurate comparisons between the figures in different parts of the world are difficult because of differing pathological definitions and the inability to get accurate figures of the total number of pregnancies and abortions performed in some countries.

Before it was recognised that molar pregnancies could be divided into two separate entities, it was known that their incidence showed wide regional variation ranging from a maximum of about 1 in 250 pregnancies in areas of high incidence such as Taiwan and the Philippines, to 1 in 2000 pregnancies in areas of low incidence such as Europe and the continental USA (5). No reason for these differences have been established.

The epidemiological study of gestational trophoblastic diseases is fraught with many difficulties (6). There are many reasons for this, not least of which is the lack of uniformity in the nomenclature. While histological diagnosis may be the only objective, the nature of the disease is such that in many cases no histological evidence of the disease is available, the management is carried out on the basis of high levels of human chorionic gonadotrophin, shadows in the chest x-ray or positive pelvic angiogram.

Despite these drawbacks, it is generally accepted that the incidence varies greatly between countries, and this difference does not necessarily related to the factors mentioned above. Hydatidiform mole is more common in Asia and Africa than in the

Western countries (7). It is a point of some interest to determine whether the high incidence in Asiatic women is due to geographic or racial factors. Jacobs et al.(8) reported an increased incidence of complete moles amongst the most recent immigrants,the Filipinos, but only an average incidence among the Asiatic peoples who had lived in Hawaii for some time. These data suggest that Asian racial groups can lose their high risk of having hydatidiform mole once they adjust to an alternative way of life and would support the view that the differences in incidence are geographical or enviromental rather than racial.

In the late 1970s many investigators developed new, highly sensitive urinary radioimmunoassays for human chorionic gonadotrophin that could detect human chorionic gonadotrophin when serum or plasma radioimmunoassays were negative. When controlled for low values of human chorionic gonadotrophin detectable in the urine of normal subjects, such assays clearly enabled the identification of persistent tumour activity and thus the need for therapy (9,10,11,12,13). During this period also, several investigators observed that the presence of of free alpha and free beta subunits in serum, urine, or tumour extracts were an expression of more severe malignancy. In 1980 physicians at the Southeastern Trophoblastic Disease Centre recommended the routine measurement of the alpha subunit in patients successfully treated to identify patients who require additional chemotherapy or more intensive follow up (14).

As a result of rapidly expanding monoclonal antibody technology, radioimmunoassays have become readily available that distinguish free beta subunit human chorionic gonadotrophin in the presence of intact human chorionic gonadotrophin. With these assays it has been possible to demonstrate that the ratio of free beta human chorionic gonadotrophin to total beta human chorionic gonadotrophin beta is markedly higher in patients who develop high risk metastatic gestational trophoblastic disease than in patients with hydatidiform moles or persistent trophoblastic disease in low risk category. Such findings suggest that excessive production of the free beta subunit of human chorionic gonadotrophin may be useful in identifying patients who should be assigned to the high risk category.

Urine from pregnant women contains several peptides related to human chorionic gonadotrophin; the principle moieties include human chorionic gonadotrophin, its free subunits and a population of fragments of the human chorionic gonadotrophin beta subunit called beta core molecules. These fragments are also present in the urine of patients with gestational trophoblastic disease.

Potential applications of the beta core radioimmunoassay in patients with gestational trophoblastic disease include monitoring response to therapy. In fact, the presence of these molecules in some patients who have undetectable serum and urine human

chorionic gonadotrophin may be the sole marker indicating persistent disease.

The majority of complete moles are paternally derived parthenogenones.

The incidence of hydatidiform moles also increases sharply in pregnancies occuring in women over forty years of age. Choriocarcinoma is a rare complication of a full-term normal pregnancy and the incidence in the United Kingdom is approximately 1 in 50000 pregnancies (5).

Many other confounding factors affect the population at risk, which is exclusively women in the reproductive age group. The age at first marriage or the first intercourse may affect the number of years of exposure to risk of conception. Moreover, effective contraception and sterilisation would have a great impact on risk. For every conception that is prevented, a possible mole is averted. Again, the incidence would be greatly affected by abortion rate-both induced and spontaneous. Contraception, sterilisation and abortion all constitute indirect prophylaxis against trophoblastic disease and may be the reasons why in countries like Singapore fewer cases are seen now compared to 20 years ago. The difficulty in knowing the number of conceptions is reflected in the numerous ways that the incidence rates are reported, for instance in terms of number of pregnancies, number of live

births,number of deliveries, and so on.

It has been shown that molar pregnancies are much more frequent among older women, but this alone does not account for regional differences. Age is a factor in the aetiology where an increased incidence occurs in the extremes of maternal ages. It is clear from the number of reported series that the incidence of mole is relative to the number of pregnancies increases steeply over the age of 45 years (5). The suggestion of an increased incidence in pregnancies under 20 years (5) has now been confirmed by Jacobs et al.(8). Socioeconomic conditions may play an important role in the genesis of hydatidiform moles

The failure of the nucleus of the egg that is involved in the genesis of complete mole seems more likely to occur at the beginning and the end of reproductive life. It has been suggested that certain ethnic groups, notably Orientals, are particularly susceptile to gestational trophoblastic disease, and that it is particularly prevalent among the lower socioeconomic classes, but little in the way of definitive data is available to substantiate these suggestions (6). These geographical differences in incidence could be due to genetic or enviromental factors or an interaction of both. When the incidence of a cancer changes in a migrant population it suggests that environmental and cultural factors are playing a major role in its aetiology. That the high incidence of a mole may not continue in Oriental women if they live in western countries is suggested by findings of Dr Jacobs

and her colleagues in Hawaii. They compared racial incidence in different population living under defined socioeconomic conditions. They contrast the continued high incidence in Filipino women, most of whom were recent immigrants born in the Philippines, with the Japanese, who were mostly born in Hawaii and who show a lower incidence than that quoted for the Japanese born in Japan.

Data relating to ABO blood groups have been collected in various series but many reported series were inadequate for valid conclusions. The heterogeneity of the clinical material and of blood groups demands careful analysis of large series. The ABO blood groups of patients and consorts also appears to have a link in both the development of trophoblastic tumours and the clinical outcome. Bagshawe 1976 (14) in his analysis of 328 patient-consort pairs show that there is an excess of patients who are blood group A. He also found that patients who are either blood group B or AB also tend to have poorer prognosis.

Generally, it is believed that about 15 per cent of hydatidiform moles will become malignant (15). There is a 500 to 1000-fold increased risk of choriocacinoma after a molar pregnancy, compared with normal term delivery. The various types of gestation that preceded choriocarcinoma in Singapore are: molar pregnancy, 82.5 percent: normal term pregnancy, 4.2 per cent; abortion, 9.6 per cent and ectopic pregnancy, 2.1 per cent (7).

Hydatidiform mole is a form of pregnancy related trophoblastic proliferative abnormality in which conceptus is a paternally derived parthegenome that is a total allograft in its mother. The success of tissue grafting in humans is known to be strongly influenced by the human leukocyte antigen system. Therefore this powerful antigenic system may play a role in the incidence and progress of the allogenic neoplasms which arise from the tropoho-blast. Hydatidiform mole may be more immunogenic than normal fetuses because 36 per cent of them induced antibody formation, whereas the frequency of antibody formation found in women with one or more normal pregnancies was 21 per cent (2).

COMPLETE HYDATIDIFORM MOLES IN HOSPITAL UNIVERSITI SAINS MALAYSIA

A REVIEW OF 120 CASES

THE OBJECTIVES OF THE STUDY

TO STUDY THE EPIDEMIOLOGY OF COMPLETE HYDATIDIFORM MOLES IN HOSPITAL UNIVERSITI SAINS MALAYSIA

TO DETERMINE THE REGRESSION OF URINARY HUMAN CHORIONIC GONADOTROPHIN IN RELATION TO AGE, PARITY, BLOOD GROUP

TO PROVIDE A MEAN OF PREDICTING THE PROGNOSIS OF THE DISEASE

TO PROVIDE EVIDENCE SUPPORTING EXISTING GUIDELINES IN THE MANAGEMENT OF COMPLETE HYDATIDIFORM MOLES

M E T H O D

This is a retrospective study for a period of six years extending from January 1986 to December 1992. All patients that were admitted to the Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan and were diagnosed as molar pregnancy were included in the study. One-hundred and twenty patients were included into the study after excluding thirty three patients who had failed to attend further followup. All the information in this study was obtained from patients' records, and compared with theatre records and later on cross-checked with histopathological records. They were diagnosed as molar pregnancy based on clinical suspicion. Since ultrasound facility is available, beta human chorionic gonadotrophin was not done to indirectly confirm pregnancy. Immediate confirmation of pregnancy using immunological test would be requested. This immunological test has sensitivity of detecting urinary human chorionic gonadotrophin of 250 international units per litre.

The clinical features that were assessed prior to evacuation of the uterus were; maternal age at diagnosis, history of previous molar pregnancy, main presenting symptoms, maternal blood group, presence of theca lutein cysts and maximum pre-evacuation beta human chorionic gonadotrophin level.

Symptoms of hyperemesis, hyperthyroidism, respiratory distress, or toxaemia were also noted.

Results of preoperative investigations such as haemoglobin values, blood urea, serum electrolytes and creatinine estimation, liver function tests and chest x-ray were noted. Blood grouping and cross-matching was urgently requested at the time of admission. Unfortunately, blood groups of husbands of these patients were not available for analysis due to various reasons.

All patients undergone evacuation of the uterus by means of suction dilatation and curettage, under general anaesthesia and the procedure was performed by senior medical officers. The evacuation of uterus was done almost immediately on confirmation of the clinical suspicion. The procedure was carried out under syntocinon cover. To further confirm the diagnosis of hydatidiform mole, all the available specimens of curettings and material removed by suction was sent to histopathological laboratory for confrmation of molar pregnancy. If the uterus is big, a repeat dilatation and curettage is planned a week after the first evacuation. The curettings specimen obtained at the second procedure was also sent the histopathological laboratory.

After the evacuation of molar pregnancy, all patients were followed up according to the hospital protocol in the management of trophoblastic disease. At every visit, urine was collected for

estimation of urinary human chorionic gonadotrophin level, clinical examination including pelvic examination was performed and if necessary, utrasonographic examination of the abdomen and pelvis would be requested. Chest x-ray would be repeated depending on on clinical findings. If urinary human chorionic gonadotrophin had been undetected, serum beta human chorionic gonadotrophin would be assayed. Patients were advised against embarking on a new pregnancy within a year following the evacuation of the mole. The were acquainted to the various contraceptive methodology available. Patients were monitored regularly till the serum beta human chorionic gonadotrophin was within normal limit. Thereafter, the followup schedule would be more infrequent. Usually they were monitored regularly for two years and if there is no evidence of of any sequelae of hydatidiform mole taking place, the patient is considered to be in complete remission. This would be evidenced by the level of serum beta human chorionic gonadotrophin remaining less than or equal to 4 international units on multiple assays taken during followup visits. At this juncture, the patients would be free to plan another pregnancy if they wish to.

R E S U L T S

COMPLETE HYDATDIFORM MOLE IN HOSPITAL UNIVERSITI SAINS MALAYSIA

INCIDENCE

Table 1 shows the number of complete hydatidiform moles seen and the number of deliveries in Hospital Universiti Sains Malaysia.

	1986	1987	1988	1989	1990	1991	1992
Hydatiform mole	22	36	39	12	14	20	16
No.of deliveries	6450	7282	8474	4587	5996	6927	7730
Incidence	1:294	1:202	1:217	1:382	1:428	1:346	1:483

Total number of deliveries in Hospital Universiti Sains Malaysia for that period was 47 602 deliveries. The average incidence of complete hydatidiform moles in this hospital was 1 in 298 deliveries. In 1989 there were 12 cases seen and this slight drop in the number of complete hydatidiform moles detected in this hospital was due to the demerger of the two obstetrical units.