A REVIEW OF OVARIAN TERATOMA IN HOSPITAL UNIVERSITI SAINS MALAYSIA TEN YEARS EXPERIENCE: 2003 to 2012

by

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ABBREVIATIONS AND GLOSSARY

AFP	Alpha Feto Protein
ASR	Age Standardized Incidence rate
BEP	Bleomycine,Etoposide and Platinum Regimen.
BHCG	Beta Human Chorionic Gonadotrophins
CA125	Carcinima Antigen 125-tumor marker
CA19-9	Carcinoma Antigen 19-9-tumor marker
CEA	Carcinoma Embryonic Antigen-tumor marker
CT SCAN	Computed Tomography Scan
DF	Degree of Freedom
FIGO	International Federation of Gynecological Oncology
GCT	Germ cell Tumor
HUSM	Hospital Universiti Sains Malaysia
HPE	Histopatholgical Examination
IOTA	International Ovarian Tumor Analysis Group
IT	Immature Teratoma
LDH	Lactate Dehydrogenase
MCT	Mature Cystic Teratoma
MDT	Monodermal teratoma
MGT	Mixed Germ Cell Tumor
MRI	Magnetic Resonance Imaging
OCP	Oral Contraceptive Pills
PID	Pelvic Inflammatory Diseases
RMI	Risk of Malignant Index
SCC	Squamous Cell Cacinoma Antigen
TAHBSO	Total abdominal hysterectomy & Salphingoopherectomy
UKM	Universiti Kebangsaan Malaysia
USM	Universiti Sains Malaysia
USO	Unilateral Salphingoopherectomy
W.H.O	World Health Organization

TINJAUAN TERATOMA OVARI DALAM SEPULUH TAHUN PENGALAMAN HOSPITAL UNIVERSITI MALAYSIA 2003 HINGGA 2012

Abstrak

Pengenalan

Kanser ovari adalah kanser keempat paling biasa berlaku dalam kalangan wanita di Britain (United Kingdom) dan di Malaysia. Ia meliputi 6.5% jumlah pesakit wanita dengan kadar insiden sebanyak 8.6/ 100,000 dan merupakan unsur kematian dalam kalangan wanita di Malaysia selepas penyakit kanser paru-paru, payudara dan kolon. Teratoma ovari matan selalunya tidak merbahaya.Walaubagaimanapun ianya dikaitkan dengan transformasi sehingga 15% dan tidak bergantung kepada prosedur pre operatif diagnostik untuk mengesan transformasi ini.Teratoma tidak matang mewakili 3% daripada jumlah keseluruhan teratoma ovari tetapi mewakili 20% sel kuman malignan, dan ianya biasa berlaku dalam kalangan wanita berusia di bawah 20 tahun dan mempunyai kemungkinan untuk mengalaminya semula.Pendekatan penjagaan kesuburan amat penting tetapi pada peringkat serius mungkin sukar dan akan membawah komplikasi kematian yang berkaitan dengan kemoterapi.

Objectif

Kajian ini bertujuan untuk meninjau corak klinikal–patologi dan hasil pengurusan pesakit teratoma ovari di Hospital Universiti Sains Malaysia.

Kaedah

Sebanyak 160 kes dikesan dengan teratoma dan diuruskan di Hospital Universiti Sains Malaysia dari tahun 2003 sehingga 2012 ditinjau secara retrospektif.Senarai pesakit yang disahkan dengan diagnosis histologi didapati daripada rekod jabatan patologi dan fail mereka dikesan,data dikumpul dan dianalisa menggunakan SPSS 21.

Keputusan

Teratoma ovari dilihata dalam kalangan wanita berusia 4 ke 75 tahun dan paling biasa dalam kalangan wanita 21-40 tahun (59.4%), 74.4% sudah berkahwin dan kebanyakannya tidak pernah menggunakan pil kontraseptif oral kebanyakannya mempunyai 1- 4 orang anak (64%) dan menyusu sekurang- kurangnya selama satu tahun. Sebanyak 53 (33.1 %) hamil ketika dikesan. Massa abdomen atau distensi dan kesakitan abdomen merupakan simpton utama 32 kes setiap gejala, tetapi 26.8 % dikesan secara kebetulan manakala 18 (11.3%) pesakit mengalami abdomen akut.

Lebih daripada separuh kes merupakan obes (57.5 %). Teratoma sistik merupakan jenis histologi paling biasa iaitu 91.9 %, monodermal 3.1% , tidak matang 2.5% dan transformasi malignan sebanyak 1.25 %. Ciri- ciri ultrasound adalah unilateral (67.5%), bilateral (8.8 %). Terdapat tumor sistik pejal dalam kebanyakan kes (54 %), 18.8% sistik asl, manakala 3.1merupakan tumor pejal asal. Hanya dalam 38 kes (31.1 %) bahan ekogenik tidak menonjol diterangkan.Laparotomi merupakan pendekatan pembedahan paling biasa dalam 114 kes, penbuangan tumor di tempat yang sama dalam pembedahan Caesarean(LSCS) 34, kes pendekatan laparoskopik adalah 12 kes dengan kadar penumpahan 21.1%, 20.6% and 58.3% untuk laparotomi,LSCS dan pendekatan laparoscopik.Dua kes kemoterapi bantuan dan tempoh susulal adalah dalam 3 - 60 bulan dengann dua kes kedatangan semula teratoma ovari matang dikesan tetapi tiada berlakunya peritonise kimia.

Kesimpulan

Teratoma merupakan tumor ovari paling biasa dalam kalangan wanita dalam usia reproduksi,walaubagaimanapun,ditak ditemui perkaitan signifikan dengan faktor seperti status perkahwinan, pariti, penyusuan, penggunaan kontraseptif oral gabungan dan indeks jisim tubuh sekalipun dengan kehadiran faktor- faktor ini dalam majoriti kes,dan ini mungkin disebabkan oleh kekurangan kuasa bagi kajian ini bagi mengesan pakaitan tersebut.

Penjagaan kesuburan adalah perkaran penting,ultrasonografi adalah kaedah yang boleh dipercayai untuk mengesan dan memilih pesakit yang akan bersalin atau intervensi pembedihan,kajian ini juga mendedahkan,majoriti (112/160) kes.Terdapat keperluan untuk memperbaiki laporan sonografi dalam kes yang dikhuatiri teratoma ovari.12 kes teratoma ovari telah menjalani pembuangan laparoskopi tumor dengan kadar tumpahan 58.1%,namun tiada diantara kes-kes ini mengalam semula kanser atau peritonitis kimia oleh itu pendekatan laparoskopi boleh dijadikan alternatif pendekatan tradisional laparotomi.

A REVIEW OF OVARIAN TERATOMA IN HUSM TEN YEARS EXPERIENCE: 2003 to 2012

ABSTRACTS

Introduction

Ovarian cancer is the fourth most common cancer among women in United Kingdom (UK) and in Malaysia. It constituted 6.5% of total female cancer with age standardized incidence rate (ASR) of 8.6 per 100,000, and is a major source of morbidity and mortality among women coming only after cancers of lungs, breast and colon in Malaysia. Mature ovarian teratoma is commonly benign; however it is associated with malignant transformation in up to 15% and no reliable preoperative diagnostic procedures to detect this transformation. Immature teratoma represents 3% of total ovarian teratoma but constitutes 20% of germ cell malignancies, it occurs commonly among women below 20 years old and has tendency of recurrence. Fertility preservation approach of management is highly crucial but in advance stage may be difficult and occasionally the fatal complication associated with chemotherapy is a concern.

Objective

We aim to review the clinico-pathological pattern and outcome of management of ovarian teratoma patients in Hospital Universiti Malaysia (HUSM).

Methodology

A total of 160 women diagnosed with ovarian teratoma and managed in HUSM from 2003 to 2012 were reviewed retrospectively. List of patients with confirmed histological diagnosis was obtained from pathology department record and their folders were traced, data collected and analyzed using SPSS 21 software (Inc., Chicago, USA).

Results

Ovarian teratoma is seen from 4 years to 75 years old women and commonest among 21-40 years age group (59.4%). Majority were married (74.4%) and most of them never use oral contraceptive pills (OCP), 64% have 1- 4 children and breast fed for at least one year and 53(33.1%) were pregnant during diagnosis. Abdominal mass or distension and abdominal pain were the commonest presenting symptoms in 32 in cases, 45 cases were

incidental diagnosis while 18 presented with acute abdomen. 43.1% of the cases were obese. Mature cystic teratoma is the commonest histological type (91.9%), monodermal 3.1%, immature 2.5% while, malignant transformation and mixed germ teratoma have 1.25% each. Ultrasound features were unilateral 108 (67.5%), bilateral 14 (8.8%). There were mixed solid cystic tumors in majority of cases 89(55.6%), 29(18.1%) were pure cystic while 4(2.5%) were pure solid tumors. Only in 38(31.1%) cases had discrete echogenic mass reported. Laparotomy was the commonest surgical approach 114 cases (71.3%), removal of tumor in the same setting during lower segment Caesarean section (LSCS) were 34 cases (21.3%) and laparoscopic approach was 12 cases (7.5%). The rate of spillage was found to be 21.1%, 20.6% and 58.3% for laparotomy, LSCS and laparoscopic approach respectively. Two cases had adjuvant chemotherapy with Bleomycine, Etoposide and Platinum regimen (BEP) involving one case of immature teratoma and the other of mature teratoma with malignant transformation. Follow up period was 3 -60 months and two cases of recurrent mature ovarian teratoma occurred but no chemical peritonitis reported.

Conclusion

Teratoma is the commonest ovarian tumor in the reproductive age women, however, we found no significant association with factors such as marital status, parity, breast feeding, use of combine oral contraceptive and body mass index despite the presence of

these factors in majority of our cases, this might be as a result of low power of the study to detect such an association.

Fertility conservation is a great concern; ultrasonography is a reliable means for diagnosing and careful selection of patients for expectant management or surgical intervention. This study reveals that majority (122/160) of ovarian teratoma cases had ultrasound done pre operatively and diagnosis of teratoma was suspected or made but only one out of many presumed pathognomic features of teratoma was reported in 38/112 cases. As such there is need to improve in sonographic reporting of suspected cases of ovarian teratoma. Twelve cases of ovarian teratoma had laparoscopic removal of the tumor with 58.3% spillage rate, however none of the cases had a recurrence or chemical peritonitis therefore laparoscopic approach can be consider as an alternative to traditional laparotomy approach.

CHAPTER 1

INTRODUCTION

1.1 Overview of Ovarian cancer

Ovarian cancer is the fourth most common cancer among women in UK and is a major source of morbidity and mortality. Each year in UK there are over 6,820 new cases (Coleman et al., 2011). Higher case fatality reflects a delay in diagnosis, since patients often present with non-specific symptoms, diagnosis is generally made when disease has spread to the peritoneal cavity. About 65% of patients are diagnosed with advanced cancer, when 5 years survival is only 28%(Studd, 2005). It presents an increasing challenge to the gynecological oncologist due to the paucity of knowledge of etiological factors and by the failure to achieve dramatic reduction in mortality due to these neoplasm during the past 6 decades (Studd, 2005). According to Malaysia national cancer registry report 2005, ovarian cancer constituted 6.5% of total female cancer with age standardized incidence rate of 8.6 per 100,000.It is also a common cause of women death in Malaysia coming only after cancers of lungs, breast and Colon (Malaysia Ministry of Health 2007).

About 90% of ovarian cancers are epithelial in origin, however in adolescents and children germ cell tumors formed up to 60% of ovarian malignancies.In contrast with epithelial ovarian cancers that arise from the surface coelomic epithelium, ovarian germ

cell malignancies are believed to originate from primordial germ cells that migrate into the gonadal ridge at 6 weeks of embryonic life. Consequently, ovarian germ cell tumors might exhibit a spectrum of histological differentiation that mimics a primitive developing embryo. For example, dysgerminoma appears to be descended from relatively undifferentiated cells, whereas yolk sac tumors show malignant change in a cell line committed to extraembryonic differentiation while immature teratoma are derived from cells predisposed to somatic (embryonic) differentiation and recapitulate tissue from all three primitive germ cell layers, ectoderm, endoderm, and mesoderm (Deligdisch, 2013). When considered together, the dysgerminoma, yolk sac tumor, immature teratoma, and their hybrid (mixed germ cell tumour) comprise more than 90% of malignant germ cell tumors. Non gestational choriocarcinoma, embryonal carcinoma, and polyembryoma manifest rarely as pure entities and comprise the remaining 5–10% (Smith et al., 2006). Although these tumors account for less than 5% of all ovarian cancers, their importance is greater than their numerical incidence implies because they occur in children and young women during the prime of life. The median age at presentation is 18 years, contrasting dramatically with perimenopausal or postmenopausal age associated with epithelial ovarian cancer. Symptoms usually indicate rapidly enlarging abdominopelvic masses. Approximately one-third of patients have ascites, and 10% present with peritonitis secondary to torsion, infection, or rupture of the ovarian tumor. Prepubertal patients might manifest signs of precocious puberty, such as breast development or vaginal bleeding, as a result of hormone production by the tumor (Tewari et al., 2000).

1.2 Ovarian teratoma

Ovarian teratomas are germ cell tumors that are formed by cells derived from more than one of the three primitive embryonic layers, i.e. ectoderm, mesoderm and endoderm. Clinically, ovarian teratoma can occur at any age and cases were reported between 2 and 80 years of age, but frequently detected during child bearing years with median age of 30 years (Bloomfield, 1987). Ovarian teratoma can be mature, immature, monodermal or specialized type of teratoma.

1.2.1 Mature ovarian teratoma

They affect a younger age group (mean age of 30 years) than epithelial ovarian neoplasm. It constitutes 80% of total germ cell tumors and accounting for about 15% of total ovarian neoplasm, it is biologically benign in all ages and is commonest ovarian neoplasm removed at surgery Mature teratoma are commonly unilateral but can be bilateral in 10% of cases and are mostly cystic although solid form can be found rarely (Kim et al., 2011). They composed of well differentiated derivatives from at least two of the three germ cell layers with predominance of ectodermal elements. Characteristically they are unilocular cysts containing hair and cheesy sebaceous material. On section, they reveal a thin wall lined by an opaque, gray-white, wrinkled epidermis. From this epidermis, hair shafts frequently protrude. Within the wall, it is common to find tooth structures and areas of calcification.(Koonings et al., 1989; Outwater et al., 2001).

1.2.2 Mature teratoma with malignant transformation

Although mature teratoma is commonly benign it is associated with malignant transformation commonly reported as 1 -3% of cases although some isolated series reported up to 15% (Wei et al., 2001). Malignant transformation is seen commonly in more advanced age (post-menopausal) and is typically associated with poorer prognosis. It has also been noted that all applied preoperative diagnostic procedures are themselves too unreliable to exclude early stages of ovarian cancer arising from within a mature cystic teratoma (Christopherson and Councell, 1989; Papa et al., 2005).

1.2.3 Immature teratoma

Immature teratoma differs from benign teratoma in that the component tissues resemble embryonic and immature fetal tissue, they may also contain mature tissues. They are defined by the World Health Organization (WHO) as a teratoma containing variable amount of immature embryonal type (generally) neuroectodermal tissues. It represents 3% of total ovarian teratoma but constitutes 20% of germ cell malignancies and only 1% of total ovarian malignancy. These tumors usually grow rapidly, frequently penetrate the capsule and spread either locally or distantly. It is the third most common ovarian germ cell tumor(Saba et al., 2009). These tumors are bulky with smooth external surface. On section they have a predominantly solid structure but mixed solid cystic also occur. Hair, sebaceous material, cartilage, bone and calcification may be present.

It is graded histologically according to the amount of primitive neuroectodermal tissue contents. Tumors with large areas of neuroblast are the highest grade and have worst prognosis. Although it has better prognosis than epithelial cancers especially in early stage with grade 1 disease, it also has tendency of recurrence especially within first 2 year. Furthermore, it seen mainly among women below 20years of age where fertility preservation approaches of management is highly crucial. Late presentation with advance stage may occasionally make such conservation difficult (Outwater et al., 2001; Parkinson and Beilby, 1977).

Table 1.1 Grading Of Immature Teratoma

Thurlbeck and Scully grading system	
Grade 1	Cell well differentiated, rare small foci of embryonic tissues
Grade 2	Moderate quantities of embryonic tissue, atypia and mitosis
Grade 3	Large quantities of embryonal tissues, atypia and mitosis
Norris grading system	**Based on neuro epithelium**
Grade 1	Some immaturity, neuroepithelium in low magnification 40x
Grade 2	Immaturity, neuroepithelium occupy<3 low power field
Grade 3	Immaturity, neuroepithelium occupy >4 low magnification on single slide

1.2.4 The specialized teratoma

Monodermal or specialized type of teratoma is a rare sub type of ovarian teratoma where there is monodermal differentiation of tissue element. Therefore, they usually contain only endodermal, ectodermal or mesodermal elements. The most common of which are struma ovarii and cacinoid. Up to 20% of teratomas contain thyroid tissue. Struma ovarii, defined as containing 50% or more thyroid tissue, is less common, accounting for approximately 5% of all ovarian teratomas Most patients with struma ovarii present with a pelvic mass, and pelvic ultrasonography characteristically shows a heterogeneous, solid mass, occasionally with ascites. They are always unilateral, although a contra lateral teratoma may be present (Yassa et al., 2008). Interestingly, these thyroidal neoplasms may hyper function, causing hyperthyroidism. The ovarian cacinoid, which presumably arises from intestinal epithelium in a teratoma, may also be functional, particularly if large (>7 cm) tumors, producing 5-hydroxytryptamine and the carcinoid syndrome. Even rarer is the strumal carcinoid, a combination of struma ovarii and carcinoid in the same ovary. About 2% of carcinoids metastasize. Other less common groups of monodermal tumors include central nervous system tumor, Cacinoma , Melanocytic, Sarcoma, Sebaceous tumor, Pituitary tumor and Retinal anlage groups.

1.3 Clinical features, complication and treatment

1.3.1 Clinical features

Mature cystic teratomas of the ovary are often discovered as incidental findings on physical examination, during radiographic studies, or during abdominal surgery performed for other indications. Asymptomatic mature cystic teratomas of the ovaries have been reported at rates of 6-65% in various series. When symptoms are present, they may include abdominal pain, mass or swelling, and abnormal uterine bleeding. Bladder symptoms, gastrointestinal disturbances, and back pain are less frequent. When abdominal pain is present, it is usually constant and ranges from slight to moderate in intensity. Torsion and acute rupture commonly are associated with severe pain. Hormonal production is thought to account for cases of abnormal uterine bleeding, but histologic examination has not provided evidence to support this theory. Furthermore, the proportion of asymptomatic patients increase significantly after 20 years of age because the older the age of diagnosis the more likely it is to be a benign tumor, occurrence of torsion has no age specific difference and tumor size tends to be larger in younger patients relative to older patients because of the more tendency to be an immature teratoma which grows more rapidly and tends to present with symptoms than mature teratoma (Kim et al., 2011).

Ovarian teratoma is the commonest pathological tumor encounter in pregnancy and present in 0.3% of pregnancies from weeks 16-20 of gestation(De Santis et al., 2012).

The diagnosis of mature cystic teratomas during pregnancy presents the vexing problem of weighing the risks of surgery under general anesthetic against the risks of an untreated persistent adnexal mass (De Santis et al., 2012; Gasim et al., 2010). Ovarian teratoma can also present with paraneoplstic syndromes, such as paraneoplastic limbic encephalitis even though it is rare, it's recognition is extremely important because the only effective therapy is the surgical removal of the tumor. About 3–4% of this condition concerns ovarian teratoma and 50 -60% of cases involving teratoma are found to have malignant teratoma(Lee, 2012). Autoimmune haemolytic anemia (AIHA) can be induced by a variety of causes including haematological neoplasm such as the lymphoma, however this condition is also reported to be associated with ovarian mature teratoma and the effective treatment was removal of the tumor (Sonn and Merritt, 2010; van Altena et al., 2008).

1.3.2 Complication

Torsion is a dreaded complication of ovarian teratoma. Gangrene or necrosis of the whole ovary frequently results from interference with its vascular supply thus requiring removal of the ovary involved which may be against the wish of any young woman planning many pregnancies in future. It may occur without apparent cause however, the initiating factors include intestinal peristalsis, alternate emptying and filling of the bladder, changes in size and position of uterus and the tumor itself during pregnancy, changes in the intra-abdominal pressure resulting from vomiting or coughing, trauma

and laxity of the abdominal wall. The unusual mobility of the tumours, especially small rather than large tumours with long pedicles will encourage torsion to occur (Lee et al., 1989). Rupture is another complication occurring in 0.3 -2.5 % of ovarian teratoma which potentially cause serious peritonitis. The diagnosis may be difficult without index of suspicion because of bizarre presentation resembling gastro intestinal pathology (Iwata et al., 2009).

1.3.3 Treatment

Traditional therapy for mature teratoma has been cystectomy or oophorectomy via laparotomy. However operative laparoscopy has now become the popular approach because of the advantage of being minimally invasive with minimal compromise to the fertility. Surgical treatment of immature teratoma of the ovary depends on the extent of the disease, although bilateral involvement is rare but it is similar to epithelial cancer in terms of surgical staging and abdominal exploration. However since most of these patients are in their reproductive age and the tumor is excellently chemo sensitive, unilateral salphingoopherectomy with preservation of uterus and contra lateral ovary and tube is recommended practice whenever possible. Adjuvant chemotherapy is recommended except in stage 1, grade 1 tumor and where complete excision is expected with low risk of recurrence (Rushdan M Noor, 2011).

1.4 Screening for ovarian cancer

As compared to cervical cancer, ovarian cancer has no satisfactory screening method (Jacobs and Menon, 2004). Ovaries by the virtue of their location are inaccessible to early diagnosis of pathology. In addition there is no well recognized premalignant stage of ovarian cancer. Even where a premalignant stage is known as in borderline disease, the natural progression to malignancy is unknown and diagnosis is histological following operation. The screening methods are themselves insensitive, poorly predictive and in most cases inapplicable to general population. At present time there is no role for general population ovarian cancer screening in asymptomatic women(Menon and Jacobs, 2000). The result of United Kingdom collaborative trial on ovarian cancer screening (UKCTOCS) is awaited to throw more light on the screening. Therefore careful and effective management of diagnosed benign lesions that have tendency to transform into malignant ovarian cancers like mature ovarian teratoma is a wise decision. Pre operative diagnostic procedures and intraoperative findings are inadequate and unreliable in diagnosis of mature teratoma with malignant transformation especially in early stage, therefore clinic pathological pattern of pure mature teratoma and mature teratoma with malignant transformation is important in predicting those tumors with malignant transformation.

1.5 Rationale of Study

It is important that hospital database regarding ovarian teratoma should be created and periodically updated as ovarian teratomas even though mostly are benign tumors, malignant transformation occurs in good proportion and current series indicate increasing trends of this transformation with potential to significantly add to the current burden of ovarian cancers . As earlier mentioned, all preoperative procedures are unreliable to diagnose this transformation. Moreover, immature teratoma is highly malignant cancer, it constitutes 20% of germ cell tumor and commonly diagnosed among women of less than 20 years of age where fertility conservation modality of treatment is crucial but occasionally this does not guaranteed absence of relapse requiring more radical approach which may compromise fertility. Chemotherapy has its own inherent complications especially in younger age women therefore careful selection of patients for adjuvant chemotherapy is also important, hence the need for a hospital data base for proper counseling of patients and to guide clinician decision.

Identifying factors associated with malignant teratoma as well as the outcome of management of these patients in our setting from this study, could translate into more accurate and early diagnosis of malignant teratoma by having higher index of suspicion from the clinical picture of our patients.

Appropriate and proper counseling of patients and their family members is crucial in management of patient with malignant ovarian teratoma which occurs commonly in reproductive age group and especially if in advance stage or in rare condition of bilateral tumour where decision of a treatment with fertility retaining capacity requires reasonable evaluation, this study may help us with local statistics for proper counseling.

The hospital data base is necessary for a dynamic country equipped with facilities for this purpose like Malaysia, and HUSM is an integral part of this venture. The impact of this kind of study and others of the same nature will be at hospital level and assist in very important future planning at local and national levels. The easy availability of this data to health providers will have an overall effect of standardizing and improving the quality of care to the patients. Such a data base could also assist in directing further research into the issues surrounding ovarian teratoma. Many studies have been carried out regarding ovarian teratoma, however, studies to identify demographic and reproductive factors associated with ovarian teratoma as well as correlating the ultrasound features with histological types of teratoma were few and mostly carried out in other places, conclusion drawn from them may not be applicable to our patients, therefore highlighting the need for a local study.

1.6 Objectives of the study

General objectives

To determine clinico pathological pattern and outcome of management of ovarian teratoma

Specific objectives

1. To determine factors associated with ovarian teratoma.
2. To describe clinical features of ovarian teratoma.
3. To describe ultrasound findings of ovarian teratoma.
4. To describe the outcome of treatment of benign and malignant teratoma.

CHAPTER 2

LITERATURE REVIEW

2.1 An over view of germ cell tumours

Ovarian germ cell neoplasms are thought to be derived from primitive germ cells of the embryonic gonad. They constitute the second largest group accounting for 15 to 20 percent of all ovarian neoplasms. Malignant germ cell tumours comprise less than five percent of all ovarian neoplasms in adult, however forms more than 60% of ovarian malignancies in children and adolescents (Gershenson et al., 1984). In 1973, the World Health Organization classified germ cell tumours as Dysgerminoma, Endodermal sinus tumour, Embryonal carcinoma, Polyembryoma, Choriocarcinoma, Teratomas including Immature, Mature and Monodermal, Mixed and Gonadoblastoma (Gershenson, 1993). This initiative represented a major advance in terms of standardization of nomenclature and histological criteria.

2.2 Incidence of ovarian teratoma

Mature cystic teratoma (MCT) is the commonest ovarian germ cell neoplasm (Rushdan M Noor, 2011). They mainly present in young women and by definition they are characterized by benign histological features.

Teratoma with malignant transformation (TMT) predominantly(88%) to squamous cell carcinomas, may be observed in 1 -3 % (Petousis et al., 2013) although in some reports up to 15% of mature teratomas and less commonly a number of other malignant tumors arising from MCT have been reported, including adenocacinoma, thyroid carcinoma, sebaceous carcinoma, malignant melanoma and sarcoma(Wei et al., 2001). The incidence of ovarian teratoma is not uniform and generally, it depends on the regions, for instance in 1968 to 1975 incidence of 46.4% of total benign ovarian tumors was reported in Kuala Lumpur in contrast, 29% was reported in New York in the same year, which indicates varied incidence(Gosling, 1968).The racial distribution among the Malaysian ladies of benign ovarian teratoma was 77.1% for Malay ladies and 11.4% for each of Chinese and Indians women respectively (Ong and Chan, 1977). In an effort to study the pattern of ovarian tumor among Malaysian women, a 2 year retrospective study 1986 to 1987, total of 280 cases were reviewed, 193 were benign, 81 were malignant and 6 cases were border line malignancy. The ovarian teratomas were the commonest benign tumors among Malays and Chinese while Serous cyst adenoma were the commonest among Indians (Ho, 1992). Bloomfied in 1987 reported mature ovarian teratoma as the commonest germ cell tumor and 1.38% had malignant transformation (Bloomfield, 1987). Kim and his colleagues in 2011 found that mature teratoma formed 93.9% while immature and malignant transformation accounted for 6.1% of all ovarian teratoma with monodermal teratoma forming 2.8% (Kim et al., 2011). Shukiman's series 1999 in HUSM reported teratoma to account for 71% of germ cell tumor, immature and mature teratoma with malignant transformation formed 4.5% each (Shukiman, 1999).

2.3 Histological Type of Ovarian Teratoma

WHO classified ovarian teratoma generally into two categories, the first is biphasic or triphasic group which include immature and mature teratoma, the later which consists of solid, cystic and fetoform types. The second category is the monodermal and somatic type tumor associated with biphasic or triphasic teratoma (WHO 2003).Mixed germ cell tumor forms 10% of primitive germ cell tumors. The single most common combination is dysgerminoma and yolk sac tumor and bilaterality of the tumor occurs in up to 10% in this combination. Prognosis depends on the most malignant components (Rushdan M Noor, 2011).Ovarian teratoma as part of mixed germ cell tumor occurs in significant number of cases. Kurman 1976 found dysgerminoma in 80%,endodermal sinus 70%,teratoma 53%,chorio carcinoma 20% and embryonal cancer 16% (Kurman and Norris, 1976).

2.4 Etiology and Associated Factors

The word teratoma comes from the Greek word “teras” meaning monster, and “oma” meaning swelling. The origin of these cysts was considered to be evil, and early speculations include the invasion of a parasitic demon or the outcome of various forms of sexual misbehavior (Wheeler, 1983). Clinical and histological evidence is consistent with human ovarian teratomas having a germ cell origin. The most compelling reason

for believing this is the fact that teratomas are often phenotypically different from their host, a situation most readily explained by postulating that one or more of the stages of meiosis has occurred during tumor development (Carritt et al., 1982). Parrington in 1984 studied chromosomal and enzymes markers in 21 benign ovarian teratoma and reported markers heterozygous in the patient found to be completely homozygous in 52% of teratoma and completely heterozygous in 19%.The remainder shows mixture of the two, 10% having homozygous centromeres and some heterozygous enzyme markers and 19% having heterozygous centromeres and some homozygous enzyme markers. These findings suggest that ovarian teratoma arise from germ cell in a number of different ways. Those with heterozygous centromeres thought to might have arisen from failure of meiosis I, some with homozygous centromeres must arise by failure of meiosis II, but because of the low level of heterozygous enzymes markers in this group substantial number are thought to arise by duplication of mature ovum to give entirely homozygous genotype, genetically the female equivalent of the complete hydatidiform mole (Parrington et al., 1984). Ohama and colleaques study of immature teratoma for chromosomal heteromorphism, enzymes polymorphism and HLA specificity, confirmed Parrington earlier report (Ohama et al., 1985). Surti in 1990 came up with the report consistent with earlier findings, following study of one hundred and two benign ovarian teratomas and two cases of immature teratoma. They karyotyped and scored teratoma cells for centromeric heteromorphism. They conclusively postulated five mechanisms of origin including meiosis I error, meiosis II error, endoreplication of haploid ovum, mitotic division of premeiotic germ cell, and fusion of two ova (Surti et al., 1990).

Lee and his co workers proposed the process of imperfect pathogenesis as one the mechanism of development of ovarian teratoma. In this theory, it is believed that teratoma arise from undifferentiated germ cells present in the developing gonad anlage. During normal development these cells originate from endoderm of yolk sac and migrate into the gonad at some later times. There because of an unknown inciting factors, they take part in a process of pathogenesis leading to formation of teratoma (Lee et al., 1997).

Many series suggest possibility of familial predisposition and association of ovarian teratoma with various demographic, obstetrics and gynecological factors as well as their similarities to testicular cancers especially with regards to age distribution and in utero hormonal exposure. A good number of report series of ovarian teratoma among the siblings of the patients, twins and triplets sisters together with theory of imperfect pathogenesis of ovarian teratoma suggest familial risk in ovarian teratoma (Baldwin, 1994; Plattner and Oxorn, 1973).

Westhoff in 1988 in one case control study identified higher socio economic status, single marital status or late marriage, low parity and excessive alcohol consumption to be associated with ovarian teratoma. Walker at the same time reported in utero exposure to hormones such as the diethylstielbesterol (DES) or other pregnancy support hormones or inadvertent exposure to OCP during pregnancy as well as the maternal obesity to be associated with subsequent development of ovarian teratoma among the offspring from index pregnancy (Walker et al., 1988).

Margaret Booth report 1992 was consistent with Westerhoff's in terms of association with infertility, however their series and Parrazini data in 1995 found no clear relationship with parity, marital status, OCP use, age at menarche, menstrual pattern or menopausal status (Booth et al., 1992; Parazzini et al., 1995).

2.5 Clinical features

Teratoma is a congenital tumor and thought to be present even before birth, however because of its slow growth nature it is not diagnosed until much later in childhood or in adulthood. It is often discovered incidentally during physical examination, radiographic studies, or abdominal surgery performed for other indications. The patients are usually of reproductive age group with mean age of 30 years, however postmenopausal women are also affected in significant proportion and present with symptoms suggestive of malignant tumor (Hunter et al., 1988; Wei et al., 2001). When symptoms are present, the commonest may include abdominal pain or abdominal mass or swelling. Abnormal uterine bleeding, bladder symptoms, gastrointestinal disturbances and back pain are less frequent. Torsion and acute rupture commonly are associated with severe pain (Ho, 1992; Shukiman, 1999). In contrast to the mature teratoma immature teratoma presents among younger than 20 years old women and because of its rapid growth, it has more symptoms and diagnose much earlier than the mature teratoma.

2.6 Ultrasound features

Owing to their heterogeneous histological structures, cystic ovarian teratomas have variable appearance on sonography. Because of wide range of combinations of different tissues in teratoma their pattern mimics number of pathological pelvic masses. Therefore interpretation of sonographic features in terms of tissue characterization and ascertainment of a particular pattern as an ovarian teratoma can sometimes be confusing. However, with the refinement in the ultrasound technology and increasing experience, sonographic signs suggestive of cystic teratoma has been recognized and knowledge about pathognomic pattern has accumulated (Caspi et al., 1996).

The pathognomic features of ovarian teratoma from sonography has been known for quite some time, with earlier series reporting up to 85% rate of correct diagnosis (Guttman, 1977).These features include dermoid plug or Rokitansky plug which is seen as one or more highly echogenic nodules. The plug is produced by congimelurates within the lesion of fat and sebaceous material, hair, soft tissue, calcification and teeth. The size of the plug varies widely, in some tumors occupies only small portion while in others occupy almost entire volume of the lesion. This plug usually is the compelling observation leading to diagnosis of ovarian teratoma. Unfortunately features in other pelvic lesions can resamble this plug and can give diagnostic differentials such as haemorrhage in pelvic mass, exophytic lipomatous uterine mass, perforated appendicitis with appendiculith and adeno fibroma.

A less common perhaps more specific feature of cystic teratoma is discrete highly echogenic focus with posterior shadowing produced by ectopic teeth or bone fragment. Other features include fine echogenic bands within the cystic area (representing hair) and presence of fat- fluid level (Hertzberg and Kliewer, 1996). In 1996 also Caspi and his co workers studied prospectively 118 cases of echogenic adnexal masses which were confirmed post operatively by histology. Using the pathognomic echo pattern they were able to make correct diagnosis of cystic ovarian tertoma in 115 cases (97.45%) (Caspi et al., 1996). One of the recent series is that of Patel 1998 who demonstrated the positive predictive value for individual features was 80% for shadowing echodensity, 75% regionally bright echoes, 50% for echogenic bands and dots and 20% for fat fluid level. They concluded that any adnexal mass with 2 or more of the pathognomic features is diagnostic of cystic teratoma (Patel et al., 1998).

2.7 Management

Matured ovarian teratoma is a slow growing tumor with an annual growth rate in premenopausal women of 1.77 cm and 1.59 cm in postmenopausal therefore, Caspi and colleagues concluded that expectant management can be adopted in a small asymptomatic tumor of less than 6cm in diameter with annual growth rate of < 2cm by regular follow up ultrasound. This will enable women planning pregnancy to do so and avoid surgery which may impair fertility (Caspi et al., 1997; Caspi et al., 2000). Most affected women are of reproductive age, therefore conservative surgical excision or

cystectomy is warranted. Excision is indicated to determine the nature of suspected teratoma seen on ultrasound as persistent, heterogeneous, sometimes bilateral masses or because of pelvic pain with or without signs of rupture or torsion. Operative laparoscopy has now become a valid alternative to traditional laparotomy over last 15 years because of its recognized advantages, such as reduced adhesion formation (hence, reduced fertility compromise), less post-operative pain, shorter hospital stay and quick recovery. However, laparoscopic approach raises concerns. Firstly, intraoperative rupture, allowing contents to spills over the peritoneal surface and bowel which potentially lead to complications such as peritonitis, adhesions formation or spread of malignancy. Intra operative rupture during laparoscopic management of dermoid cyst appears to occur quite often (up to 80%) (Shawki et al., 2004).However, very few complications occur because of this. Extensive peritoneal washing during surgery to remove spillage contents may be responsible for this low complication rate. The second concern is that of possibility of recurrence after cystectomy by laparoscopic approach (Shawki et al., 2004; Yuen et al., 1997).

Laparoscopic approach to remove dermoid cyst since its description in 1989 by Nezhat and colleagues is continuously proving to be safe and effective in this matter. It is proved to be safe even in pregnancy following patient selection and careful surgical technique (Parker et al., 1996). Many studies have shown that laparoscopic treatment of adnexal masses is safe even in postmenopausal women who are at greater risk of developing a malignant ovarian neoplasm (Ozturk and Sok, 2004).

Similar efficacy of laparascopic approach to laparatomy with no recurrence of tumor or more complications seen in cases operated via laparoscopy as compared with laparotomy over five years of follow up has also been reported by Mais and colleagues (Briones-Landa et al., 2010; Mais et al., 2003). A recent prospective study in Taiwan also confirmed favorable outcome and safety of laparoscopic approach in pregnancy (Koo et al., 2013). Safety has also been demonstrated in a patient with large tumor 15-40 cm following careful selection of cases (Hong et al., 2012; Ye et al., 2012). The role of a frozen section and full staging operation in selected cases is recommended. This can be the case in younger patients of less 20 years with large tumor size. The frozen section shows mature cystic teratoma with preponderance of mature neural elements because foci of immature neural element can be readily be missed by frozen section (Einarsson et al., 2004). Mature ovarian teratoma in postmenopausal women is not uncommon, some series reporting up to 7.6% of cases with malignant transformation occurring commonly in this group, therefore the surgical staging and extensive excision especially in suspected malignant cases is recommended with or without adjuvant chemotherapy decision depends on the stage, grade and histological diagnosis (Wei et al., 2001). Mori and coworkers conclude that laparoscopic approach can also be use safely in patients of age less than 40 years with level of squamous cell cancer antigen of less than 2.5 ng/ml as it significantly differentiate between pure mature teratoma from those with malignant transformation(Mori et al., 2003).

Ovarian immature teratoma usually present with disease confined to the ovary and is typically radio resistant but highly chemo sensitive (Sen et al., 1988). Cure rates are high and therefore fertility sparing surgery is also recommended even when advanced disease is identified. Some patients however do recur and although generally salvage rate are high, there is a subgroup of chemo resistant patients who progress under treatment and succumb to their disease. Use of adjuvant chemotherapy especially in early stage of disease is controversial because even though the chemotherapeutic regimen primarily BEP spares fertility, significant side effects do occur(Weinberg et al., 2011). For example fatal Bleomycine pulmonary toxicity and secondary leukemia has been reported.Treatment recommendation include primary surgical staging procedure for all patients with immature teratoma, however most patients are diagnosed on final histopathology report, therefore treatment decisions are based commonly on pathology, imaging and tumour markers (Kollmannsberger et al., 1999; Simpson et al., 1998; Weinberg et al., 2011). Successful pregnancies have been reported following fertility preservation followed by combine chemotherapy even in advanced stage with high grade disease (Chen et al., 2007).

Cushing suggest reserving adjuvant chemotherapy for only recurrent cases independent of the grade of tumor following complete resection especially in the children and adolescents (Cushing et al., 1999). However the current recommendation is that even after complete resection, recurrence of this tumor is not uncommon, therefore, all except stage 1 with grade 1 tumor should be given adjuvant chemotherapy. The combination of Bleomycine, Etoposides and Cisplatinum (BEP regimen) is now accepted by many.