Distinguishing the Benign and Malignant Adnexal Mass: A Prospective External Validation of a Risk of Malignancy Index (RMI) Based on Intraoperative Features*

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The aim of the proper was to perform an external validation of a proposed scoring scheme for the prediction of ovarian malignancy which uses the following intra-operative variables: 1) presence or absence of papillary excrescences, 2) tumor volume, 3) presence or absence of ascites, 4) wall thickness, and 5) presence or absence of extraovarian implants. One hundred forty one (141) patients were studied from February 15 to August 15, 2004. Of these, 73 women had benign cysts and 68 had malignant ovarian tumors. For each patient, the risk of malignancy index (RMI) was computed using the proposed scoring system. A cutoff score of ≥ 6 was chosen to indicate high likelihood of ovarian malignancy. Using this cutoff, the sensitivity, specificity, positive and negative predictive values were computed across each cutoff level. Cross validation of the scoring model on the prospectively assembled data gave a sensitivity of 85.95%, specificity of 96.53%, positive and negative predictive values of 83.00% and 90.81%, respectively. The area under the ROC curve of the proposed model was 0.856 and was deemed to have a relatively good performance. Diagnostic models might be of value in the intraoperative assessment of the adnexal mass.

Key words: adnexal mass, risk of malignancy index, receptor operative curve

One of the most bothersome situations faced by a gynecologist is the performance of an inappropriate or inadequate surgery on a patient with ovarian mass. This is not an uncommon occurrence since an ovarian mass can appear benign although malignant and appear malignant although benign. The prognostic worth of accurate and complete surgical staging and cytoreductive surgery can not be underestimated. Thus, it is of utmost importance to distinguish the malignant and benign ovarian masses. This important step can be done either preoperatively or intraoperatively.

A number of studies have emphasized the significance of preoperative characterization of an ovarian neoplasm. This will allow more precise preoperative counseling as well as surgical treatment planning. Furthermore, it will also result in more patients being appropriately referred to a gynecologic oncologist.

Numerous non-invasive modalities can be used to assess an adnexal mass preoperatively. The most widely

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studied were sonologic features, serum CA-125 levels, and color Doppler findings.

Several authors have formulated models combining these diagnostic tools in order to distinguish benign and malignant pelvic masses, preoperatively. However, many areas in the Philippines, like any other third world country, are weighed down by problems of access to these diagnostic methods.

Gynecologists often perform surgeries on women with ovarian masses without definite preoperative diagnoses. Their assessment whether the ovarian mass is benign or malignant would rely much on the intraoperative morphologic descriptions of the mass.

A previous retrospective study has proposed a weighted scoring scheme to determine the probability of malignancy for any patient with an ovarian mass. This was done by application of multivariate regression analysis to the intraoperative variables recorded at the time of surgery. According to this paper, those significantly contributing to predicting the malignancy were as follows:

A. Papillary projections
B. Tumor volume
C. Presence of ascites
D. Wall thickness, and
E. Presence of extra-ovarian implants

Proposed weighted scoring scheme.

Parameters	Score			
	0	1	2	3
Papillary Projections	(–)			(+)
Tumor Volume		< 250 cm^3	≥ 250 cm^3	
Ascites		(–)	(+)	
Wall Thickness		< 0.3 cm	≥ 0.3 cm	
Extraovarian Implants		(–)	(+)	

A cut-off score of ≥ 6 indicated high likelihood of ovarian malignancy. Cross internal validation of the scoring model on the test data gave a sensitivity of 78.62 percent and specificity of 91.73 percent, positive and negative predictive values of 81.55 and 88.01, respectively.

One of the recommendations of the said study was to do an external validation of the proposed scoring system in a prospective manner.

For the purpose of easy reference, the author of this paper will use the term "O-RMI" to refer to the scoring system.

Objectives

A. General Objective

To perform an external validation of the proposed scoring system for the prediction of ovarian malignancy "O-RMI."

B. Specific Objectives

1. To determine the incidence of malignancy among patients who underwent primary surgery for ovarian masses - primary pathology or incidental finding.
2. To test the performance of the O-RMI in a prospectively assembled population with an adnexal mass.
3. To construct a receptor operator curve (ROC) for the population.

This is a prospective case control study.

Materials and Methods

A. Study Subjects

The study population consisted of female patients admitted to a tertiary hospital who underwent primary abdominopelvic surgery for an adnexal mass from February 15 to August 15, 2004.

All patients who underwent emergency and elective abdominopelvic gynecologic surgery with intra-operative findings of adnexal mass were eligible into the study.

1. Inclusion Criteria: Female patients with intraoperative findings of ovarian neoplasms on exploratory laparotomy.
2. Exclusion Criteria: Patients who underwent surgery for a non-adnexal pathology.

B. Sample Size

The study included all patients admitted and eventually underwent surgical procedures for adnexal pathology from February 15 to August 15, 2004.

C. Methodology/Study Procedure and Data Analysis

Between February 15 to August 15, 2004, one hundred forty one (141) patients were treated for a pelvic mass at this tertiary hospital.

A review of medical records of all patients was conducted. Patient demographics (age, gravidity and parity) were extracted. Intraoperative clinical findings with respect to the following morphologic variables: presence of papillary projections, tumor volume, presence of ascites, wall thickness and presence of extraovarian implants were recorded.

The O-RMI was validated in the data set. The final histopathological diagnosis was considered the gold standard. In the event that an intraoperative diagnosis of malignancy was found, it was staged based on the International Federation of Gynecology and Obstetrics (FIGO) scheme.

D. Outcome Measurements

The outcome of interest was the presence of malignancy as reported in the final histopathologic report.

The following intraoperative variables were studied: 1) size of the ovarian mass/masses (in cm). The length, width and height (thickness) of the ovarian pathology were all measured. The volume of the tumor is defined as the product of the three diameters taken in perpendicular planes using the formula for a prolate ellipsoid (Length x Width x Height x $\pi/6$). 2) presence of ascites; 3) presence of extra-ovarian implants; 4) wall thickness, (in cm) and 5) inner wall structures: presence of papillary excrescencies.

E. Data Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc.), version II. The sensitivity was defined as the percentage of patients with ovarian malignancy having a score of ≥ 6. The specificity was defined as the percentage of patients having a benign adnexal mass with a score of < 6. The positive predictive value was defined as the proportion of patients with a O-RMI of ≥ 6 having a malignant disease and negative predictive value was defined as the proportion of patients with score of < 6 having a benign mass.

For the O-RMI model, a ROC was constructed demonstrating the capacity of the model to diagnose malignancy. The performance of the O-RMI was expressed as an area under the ROC.

Results

One hundred forty one (141) cases were eligible from February 15 to August 15, 2004. Of these, 73 women had benign cysts and 68 had malignant tumors. The mean age of women in the benign group was 39 years, compared to 51 years in the malignant group. ($p = 0.02896$) (Table 1). Fourteen percent of women with benign cysts were postmenopausal, compared with 68 percent of women with malignant tumors. Similarly, a larger proportion of women with ovarian cancer have ascites and papillary excrescences.

Table 1. Characteristics of benign tumors compared with malignant tumors.

Parameter	Benign Tumor N = 73	Malignant Tumor N = 68	p value $p < 0.05$
Age			
Mean	39	51	0.02896
Range	14-68	12-77	
Postmenopausal (%)	14%	68%	0.0001
Intraoperative Findings%			
Tumor Volume (cm^3)*			
Mean	248.4	1109	0.0001
Range	12-1980	6-41813	
Papillary Projections	4	57	0.0001
Unilocular	65	40	NS
Bilateral	31	38	NS
Ascites	4	65	0.0218
Adhesions	50	54	NS
Rupture	28	36	NS
Extraovarian Implants	4	81	0.03961
Wall Thickness (cm)			
Mean	0.3	1.0	0.03258
Range	0.1-0.8	0.5-2.0	
Solid Consistency	35	75	NS

Of the 73 benign cases, majority had cystadenomas, dermoid cysts, endometriomas or functional cysts (Table 2).

Table 2. Histologic classification of benign tumors (n = 73).

Histology	N (%)
Cystadenomas	41 (56%)
Dermoid Cysts	12 (16%)
Functional Cysts	9 (12%)
Endometriomas	5 (7%)
Fibroma/Thecoma	2 (3%)
Pelvic Inflammatory Disease/Abscess	3 (4%)
Brenner Tumor	1 (1%)

Of the 68 women with malignant tumors, 52 had invasive epithelial tumors, 3 had non-epithelial ovarian carcinomas and 13 had tumors of borderline malignancy.

Table 3. Histologic classification of malignant tumors (n = 68).

Histology	N (%)
Borderline Tumors	13 (19%)
Epithelial Tumors	
Serous Cystadenocarcinomas	31 (46%)
Mucinous Cystadenocarcinomas	11 (16%)
Endometrioid Adenocarcinomas	8 (12%)
Clear Cell Adenocarcinomas	2 (3%)
Non-epithelial Tumors	
Yolk Sac Tumors	1 (1%)
Granulosa Cell Tumors	2 (3%)

Each of the 141 women was scored according to the scoring system (Table 4).

Table 4. Proposed ovarian cancer intraoperative predictive scoring scheme.

Parameters	Score			
	0	1	2	3
Papillary Projections	(–)			(+)
Tumor Volume		< 250 cm^3	≥ 250 cm^3	
Ascites		(–)	(+)	
Wall Thickness		< 0.3 cm	≥ 0.3 cm	
Extraovarian Implants		(–)	(+)	

* If the score is ≥ 6, there is high likelihood for malignancy.

The sensitivity and the specificity curves were drawn in order to determine the positive predictive value and negative predictive value of each proposed cut-off. The proposed cut-off for likelihood of malignancy is greater or equal to a score of 6 (Figure 1). At a cut-off of 6, the sensitivity was 85.95 percent, the specificity was 96.53 percent and the positive and negative predictive values were 83.00 percent and 90.81 percent, respectively.

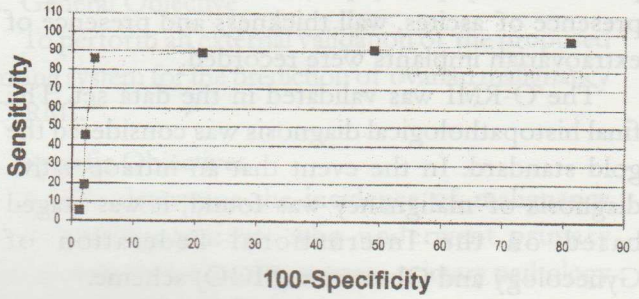

Figure 1. Receiver operator curve.

Table 5 shows the area under the ROC curve analysis. This represents the probability that the proposed model's score for a randomly chosen malignant mass will exceed the result for a randomly chosen benign case. In our case, the area under the ROC curve is 0.856 which is a relatively good performance score. Also, from this table, the asymptomatic significance is less than 0.05 (0.000) which means that using the model is better than guessing.

Table 5. Area under the ROC curve.

Test Result Variables	Area	Std. Error	Asymptomatic	Asymptomatic 95% Confidence Interval	
				Lower Bound	Upper Bound
O-RMI	.856	0.016	.000	.825	.886

Discussion

One of the objectives of this study was to justify a proposed diagnostic model in a tertiary hospital. This model has the potential to be utilized particularly in distinguishing between the benign and the malignant

adnexal mass. According to the results of this paper, the proposed scoring scheme has the ability to correctly identify benign and malignant pelvic masses.

The study confirms the relatively high specificity as well as sensitivity of the proposed scoring system at an optimal cutoff level of 6. The specificity of the scheme was 96.53 percent. This finding is critical for the decision regarding referral of patients with ovarian tumors to specialized centers. A lower specificity would lead to an undue number of referrals of benign cases, which is unacceptable for the referring physician and unmanageable for the specialty surgeons. Likewise, this will aid in selection of cases for a conservative surgical approach, for example, unilateral salpingo-oophorectomy for ovarian cysts without papillary excrescences.

This study exemplifies the value of external validation of a prediction model before they can be used in clinical practice. Furthermore, the applicability of the proposed scoring model is increased at external validation. The more relevant question now is whether this model will actually be good enough to be utilized in clinical practice.

The absolute value of the sensitivity at which the diagnosis of malignancy is made should ideally be almost perfect. The reason behind this is to avoid unnecessary operation at suboptimal conditions. In this paper, such sensitivities can be obtained if specificities can be dropped to around 20 percent. On the other hand, specificity of 97 percent was obtained if the sensitivity is dropped to approximately 15 percent.

The proposed scoring system is a very simple model that can be utilized directly into practice without bringing about lengthy, lavish and complex methods. However, the level of cutoff chosen for referral will depend in the local resources and the availability of specialists. In our country, for example, where trained gynecologic oncologists are insufficient and local resources are scant, this simple model will assist in appropriate referral to a specialist, so that the patient will benefit from primary treatment with optimal debulking and adequate surgical staging.

Summary and Conclusion

The utility of diagnostic models would allow a uniform approach when assessing an adnexal mass during the exploratory laparotomy. The capability to approximate the probability of being malignant or benign is very helpful in both decision making and patient counseling. It would ensure reproducibility of diagnosis and reduce the dependence on operator experience. The utilization of the ovarian cancer intraoperative predictive score scheme allows active involvement of the general obstetrician-gynecologist in the intervention of the disease in a low resource setting.

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Neonatal and Developmental Effects of Antepartum Administration of Antineoplastic Agents*

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Cancer is the second most common cause of death during the reproductive years, complicating approximately 1 in 1000 pregnancies. Most reports of cancer in pregnancy have focused on neonatal morphologic observations at the time of delivery with little data known regarding the children's long-term neurodevelopment following in-utero exposure to malignancy and its treatment. **Objective**: To determine the neonatal and developmental effects of antepartum administration of antineoplastic agents. **Methods**: All pregnant patients with a diagnosis of malignancy at a tertiary hospital from January 2000 to June 2005 were included in the study. Maternal and fetal outcomes of these pregnancies and the subsequent neonatal and neurologic development of the children were compared between the groups with and without in-utero exposure to antineoplastic agents. Descriptive statistics using range, mean, standard deviations and percentages were calculated. **Results**: A total of 84 out of 107 pregnancies complicated by malignancy were included in the analysis as the medical records of the other cases could not be retrieved. Only 11 (13.1%) received chemotherapy during pregnancy and this comprised the exposed group. There was no significant difference in the percentage of preterm deliveries between the two groups but the mean birthweight of babies born to mothers who received chemotherapy was significantly lower ($p = 0.011$). No congenital malformations were observed in babies exposed to antepartum chemotherapy. There was note of developmental delay in 2 children whose mothers received chemotherapy during their pregnancies. **Conclusion:** Antepartum exposure to antineoplastic agents may result in lower birthweights and delayed developmental effects.

Key words: cancer, pregnancy, child development, antineoplastic medications

Cancer is the second leading cause of death in women during their reproductive years.[1] It complicates approximately 0.7 to 1 in 1000 pregnancies. The most common malignancies associated with pregnancy are those that have an ascending incidence curve during the reproductive years, such as breast and cervical cancers, lymphoma and melanoma.[2,3,6] With the exception of a recent protocol for breast cancer[4], guides for management of malignancies during pregnancy do not exist. Significant advances have been made with current chemotherapeutic agents in increasing longevity

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and improving survival. Cures and long-term remissions are obtained in diseases that were previously untreatable.[1] However, the decision to start antineoplastic therapy in a patient who is pregnant poses a dilemma for the physician, the patient and her family. Active treatment of the malignancy and continuation of the pregnancy are often presented as mutually exclusive options, pitting the life of the mother against that of her unborn child.[4]

The common denominator of antineoplastic drugs is the ability to affect cell division adversely. Therefore, the same qualities that make those compounds desirable for cancer therapy, may also render them detrimental to the developing embryo.[5] The dose of medication and time of exposure are critical during embryogenesis or organogenesis when susceptibility to teratogenic agents is high, with the heart, neural tube and limbs being affected earlier than the palate and ear. After the period of organogenesis, the eyes, genitalia, together with the haemopoietic system and central nervous system remain vulnerable to continued exposure.[2,5] Second and third trimester exposure to chemotherapy increases the risk of intrauterine growth restriction and low birthweight. The rate of chemotherapy-associated malformation is 12.7-17 percent and that of low birth weight is 40 percent. In contrast, the usual rate of malformations in the general population is around 1-3 percent.[6] Studies done by Harada[7] in 1978, Gililland and Weinstein[8] in 1983, Doll[9], et al. in 1988 and Cantini and Yanes[10] in 1984 focused on congenital malformations at the time of delivery. They concluded that when chemotherapy is administered to women before conception or after the first trimester, normal births are experienced in majority of cases. These conclusions, however, may not be applicable to the central nervous system which continues to develop throughout gestation and postnatally and is therefore vulnerable to the effects of chemotherapy administered at any time during the entire pregnancy.

Cognitive and behavioral functioning of children of mothers with any form of malignancy whether exposed to chemotherapy or not remains largely unexplored. The cancer patient has an increased tendency to experience febrile illnesses from infection or from the tumor itself and the relationship between hyperthermia, fetal brain development and the incidence of impairment in children has not been fully addressed. Also, malignancy may be associated with maternal malnutrition and adverse neonatal outcome. The neurodevelopmental effects of in-utero exposure to chemotherapy are also largely undefined. Review of literature reveals small series and case reports which suggest that gross and mental development of children exposed in utero to chemotherapy appear to be normal but most authors did not conduct formal motor, cognitive and behavioral tests and may have missed detection of subtle neurodevelopmental abnormalities in these children. Mental health effects, which act as strong predictor of a child's quality of life, merit closer attention, as do the cognitive and behavioral effects of these drugs.[5] This study was undertaken in order to determine the neonatal and developmental effects of antepartum administration of antineoplastic agents.

General Objective

To determine the neonatal and developmental effects of antepartum administration of antineoplastic agents.

Specific Objectives

1. To determine the demographic characteristics and clinical profile of pregnant patients diagnosed with concomitant malignancies.
2. To determine the distribution/frequency of the different types of cancers found during pregnancy.
3. To determine the maternal and fetal outcomes of pregnant patients diagnosed with cancer, whether exposed to chemotherapy or not.
4. To determine the neonatal and developmental effects of the cancer itself, as well as the exposure to chemotherapeutic agent, taking into account the timing of exposure, the type of agent used, and the number of courses that were administered.

Materials and Methods

Patient Population

All pregnant patients diagnosed with cancer at a tertiary hospital from January 2000 to June 2005 were included in the study. Information about the cancer, its evolution and therapeutics particularly the histopathologic diagnosis and stage, date of diagnosis in relation to the pregnancy and period of gestation during which patients received specific medications were obtained by reviewing the outpatient and

admission hospital records. Detailed obstetric history or clinical complications were also obtained. For pregnancies that resulted in liveborn children, data such as APGAR scores, anthropometry, neonatal complications and assessment of congenital malformations were recorded. Birth weight was adjusted for gestational age according to the Colorado chart. Manner of delivery was also recorded and for cases of cesarean section, the reason for the choice of this method was obtained.

The patients were then divided into two groups: Exposed Group included those who were exposed to chemotherapy during pregnancy and Unexposed Group included those who were not exposed to such treatment. In this study, chemotherapy exposure was defined as the use of antineoplastic agents (alkylating agents, antimetabolic agents, tumor antibiotics, alkaloids and miscellaneous agents). Pregnancy outcomes and follow-up results were then compared between the two groups.

Methodology

The clinical notes, hospital records and drug charts of both mothers and babies were examined independently with the developmental pediatrician blinded to chemotherapy exposure. A detailed data set, the Case Registry Form was completed by recording information on maternal demographics, preexisting maternal disease, obstetric history and antenatal, intrapartum, neonatal and maternal complications. Factors of interest were the type of cancer, type and number of chemotherapy courses administered during pregnancy, timing of delivery of chemotherapy in relation to the age of gestation and chemotoxicities. The children underwent physical and neurological examination in a "blinded" manner after obtaining a written consent from their parents or guardians. The Denver Developmental Screening Test was administered to the children according to their ages and the result of the two groups were compared. The principal value of this tool is to provide an organized clinical impression of a child's overall development and to alert the user to potential developmental difficulties. This is used to screen children 0-6 years of age. The Denver II screens the four domains of development namely gross motor, fine motor, language and personal/social domains. Interpretation of each domain of development is either delayed, cautioned, advanced, normal or refused. Outcome of the screening is normal, suspect or untestable.

Participants who entered the study less than 6 months of age also underwent a complete physical and neurological examination but Denver II was administered once they reached 6 months of age.

Operational Definition of Terms

Denver Normal - no delay and a maximum of one caution

Denver Suspect - two or more caution and/or one or more delay

Untestable - refusal scores on one or more items completely to the left of the age line or on more than one item intersected by the age line in the 75-90 percent area.

Chemotherapy exposure - use of cytotoxic agents (alkylants, antimetabolic agents, tumor antibiotics, alkaloids and miscellaneous agents)

Malignancy- histopathologic evidence of cancer.

Sample Size

This is a pilot study on the developmental effects of antenatally administered chemotherapy. It was originally designed to be a cohort study but because of the inherent rarity of the cases and the difficulty in tracking the potential subjects resulted in a small sample size which necessitated analysis of the paper as a case series. Thus, a sample size was not calculated for this study anymore being just a case series in end design.

Statistical Analysis

Collected data were electronically managed using Microsoft Excel. Data encoding, preliminary data management and analysis were done using the Statistical Package for the Social Sciences (SPSS v12). Descriptive statistics using range, mean, standard deviations and percentages and crosstabulations for all data sets were analyzed using SPSS.

Results

From January 2000 to June 2005, there were a total of 107 pregnancies complicated by malignancy admitted in a tertiary hospital, giving an incidence of 0.29 percent or 3 in 1000 pregnancies (Table 1). Of these, only 84 subjects were included in the analysis as the medical records of the other cases could not be retrieved.

Table 1. Incidence of pregnancy complicated by malignancy in tertiary hospital (total incidence and year-specific incidence).

Year	Pregnancies with malignancy	Deliveries per year	Incidence
2000	13	6828	0.19%
2001	25	7186	0.35%
2002	18	6865	0.26%
2003	14	6557	0.21%
2004	16	6926	0.23%
Jan-Jun 2005	18	2575	0.70%
Total	107	36937	0.29%

Out of the 84 patients who had a malignancy complicating their pregnancy, only 11 (13.1%) received chemotherapy during pregnancy and this comprised the exposed group. The unexposed group consisted of the 73 subjects (86.9%) who did not have any exposure to antineoplastic agents during pregnancy.

The mean age of patients diagnosed with malignancy during pregnancy is 30 years (standard deviation of $\pm$ 6 years). The youngest was 18 years old while the oldest was 43 years old. Seventy-eight percent of the patients were multipara and only 22 percent were primigravids. The mean gravidity for the study population was 3 and the mean parity was 2 (Table 2).

Table 2. Characteristics of pregnant patients diagnosed with a malignancy at tertiary hospital from January, 2000 - April, 2005.

Characteristics	Exposed	Unexposed	P value
Mean age, years (SD +/- years)	31.82 (SD +/– 6.983)	30.09 (SD +/–6.122)	>0.05
Gravidity, mean	3 (SD +/– 1)	3 (SD +/–2)	
Parity, mean	2 (SD +/– 1)	2 (SD +/–2)	

The specific type of malignancy found in each group is presented in Figure 1. The most common type of malignancy is ovarian with an incidence of 29.8 percent (25% in the exposed group and 30.3 percent in the unexposed group). Primary malignancy from the ovary was common to both primigravids (42%) and multiparas (57.9%). Breast cancer (19%) and thyroid malignancies (14.3%) follow in decreasing order of frequency. Cervical cancer, hematologic and head and neck malignancies, each having an incidence of 6 percent, came fourth in the series, while lymphomas having an incidence of 4.8 percent came fifth. There were 2 cases for neurologic malignancies and bone and soft tissue sarcomas, accounting for 2.4 percent. Gastrointestinal malignancies occurred in 1.2 percent. A number of patients (8.3%) whose primary malignancies cannot be ascertained were classified under the group "others".

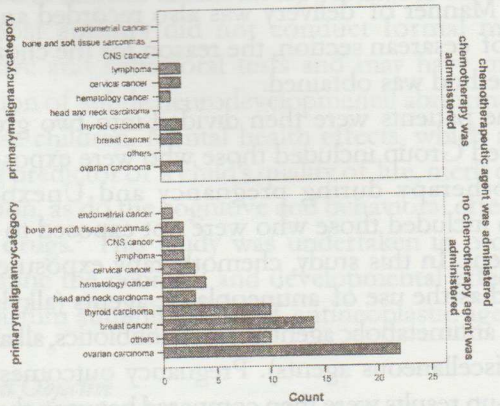

Figure 1. Distribution of cases per type of malignancy.

In majority of the cases (70.8%), the malignancy was diagnosed prior to the pregnancy. Twenty-four percent of the patients were diagnosed with cancer during the second and third trimesters, and the remaining 13.6 percent, during the first trimester. The earliest time of detection of the malignancy in relation to the age of gestation (AOG) was at 2 weeks, while the latest was on admission at 41 weeks. The average AOG when the malignancy was first recognized was at 19 weeks.

Almost half of the mothers with complicating malignancies had their prenatal check-ups at a High Risk Clinic of this tertiary hospital, 17.5 percent of whom underwent antepartum chemotherapy (Table 3). These patients comprise 63.6 percent of the exposed group. The number of prenatal consults ranged from 0 to 13, giving a mean of 6 visits.

Table 3. Antenatal care.

Antenatal Care	Exposed	Unexposed	Total
General clinic		3	3
High-risk clinic	7	33	40
Local health center	1	3	4
Government hospital		2	2
Private physical	3	5	8
No prenatal check-up		2	2
Total	11	73	84

The type of malignancy and the specific antineoplastic agents administered, as well as the timing of chemotherapy induction are presented in Table 4. The mean AOG when the first chemotherapy was given was at 18 weeks and 31 weeks for the last course. The mean number of chemotherapy courses given was 3. The earliest time in which a cytotoxic drug was instituted was at 1 week AOG which was in a patient diagnosed with non-Hodgkins lymphoma. She was not aware that she was pregnant when she was undergoing multiagent chemotherapy. She gave birth to a term baby girl whose birthweight was adequate for gestational age (AGA). The neonate did not have any congenital anomaly. The latest time in which chemotherapy was administered was at 34 weeks AOG, a few days before the patient went into labor. She was diagnosed with breast cancer during pregnancy, received 4 courses of epirubicin and delivered a term, small for gestational age (SGA) baby boy who had no congenital anomalies. One mother experienced myelosuppression while she was on her 14th week of chemotherapy with hydroxyurea for chronic myelogenous leukemia (CML). Immediate discontinuation of the drug was done and the patient was admitted for closer monitoring. During delivery, no maternal adverse outcome was observed. The neonate was term and SGA.

Table 4. Exposed group: Pregnancy outcome, chemotherapy employed and Denver Developmental Screening Test results.

ID No.	Neoplasm	Drug	Time of chemotherapy induction, trimester	# of courses	Pediatric aging, weeks	Birth weight, grams	Congenital malformation	Age at follow-up, years	Denver test result
1	Ovarian	Cyclophosphamide, Cisplatin	2nd - 3rd	4	38-39	2500	(–)	3 1/4	Normal
2	Ovarian	Cyclophosphamide, Cisplatin	3rd	1	38	2300	(–)	1 2/3	Normal
3	Thyroid	Radioactive iodine	2nd	3	38-39	2700	(–)	3 1/3	Normal
4	CML	Hydroxyurea	2nd - 3rd	Daily x 14 wks	38	2100	(–)	1 5/6	Normal
5	Hodgkin's	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	2nd	1	35	1400	(–)	1 1/3	Suspect
6	Breast	Epirubicin	1st	4	37	2200	(–)	7/12	Suspect
7	Thyroid	Radioactive iodine	1st	1	40	2700	(–)	Not screened	
8	NHL	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine w/ Cobalt therapy	1st	1	38	2700	(–)	Not screened	
9	Cervix	Cisplatin	2nd	1			Fetal death in-utero		
10	Breast	Cyclophosphamide, Doxorubicin, 5-fluorouracil	2nd	1	34	2100	(–)	Not screened	
11	Cervix	Cisplatin w/ brachytherapy	1st	5			Fetal death in-utero		

Of all the pregnancies complicated with malignancy, 88 percent resulted in livebirths, 8 percent were fetal death in-utero (FDU) and 4 percent were abortions. Of the livebirths, 80.3 percent were delivered term and 19.7 percent were preterm. Of the mothers who underwent chemotherapy, no pregnancy resulted in abortion (Table 5). Although 18.2 percent were stillbirths, majority were still carried to term. The rest of the 18.2 percent (N = 2) were preterm, one of which was a case of CML. The fetus was exposed to hydroxyurea daily from 16 weeks to 30 weeks age of gestation. The second preterm neonate had a pediatric aging of 35 weeks and was small for gestational age. His mother was diagnosed to have Hodgkin's lymphoma and had one course of chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine 1 week prior to delivery.

Table 5. Comparison of pregnancy outcomes between exposed and unexposed patients.

Fetal Outcome	Exposed N = 11	%	Unexposed N = 64	%
Full term	7	63.6	46	71.9
Weight appropriate for age	4	36.4	42	65.6
Weight large for age			2	3.1
Weight small for age	3	27.3	2	3.1
Preterm	2	18.2	11	17.2
Weight appropriate for age	1	9.1	3	4.7
Weight small for age	1	9.1	8	12.5
Malformations	0		1	
Spontaneous abortions	0		3	4.7
Stillbirths	2	18.2	4	6.2

Of the livebirths in the exposed group, nearly half were SGA with an average birth weight of 2300 g and a range of 1400 g to 2700 g. Six out of the 9 babies were admitted in the neonatal intensive care unit.

In the unexposed group, 71.9 percent of the pregnancies resulted in term livebirths, 17.2 percent were preterm, 6.3 percent were stillbirths and 4.7 percent ended in abortions (Table 5). Seventy-nine percent of the livebirths were AGA and 17.5 percent were SGA. In addition, two babies (3.5%) were large-for-gestational-age. Of the 11 preterm deliveries in this group: 2 were because of bleeding placenta previa; 1 was due to preterm prelabor rupture of membranes; 2 had pregnancies complicated by hypertension, one of the which had uncontrolled hypertension and the other had abruptio placenta; 1 went into uncontrolled preterm labor after undergoing surgery for ovarian cancer; and 5 had unexplained preterm labor, 1 of which eventually underwent cesarean section (CS) for fetal distress, 2 underwent CS with completion surgery for ovarian cancer when the preterm labor progressed and one underwent CS for tumor previa. Two neonates were SGA, that of the mother with uncontrolled hypertension and the patient who underwent emergency CS for fetal distress.

Comparing the outcomes of the two groups, it can be seen that there was no significant difference in the percentage of preterm deliveries between the two groups (18.2% in the exposed group vs. 17.2 percent in the unexposed group) but the mean birth weight of babies born to mothers who received chemotherapy were significantly lower than that compared to the unexposed neonates ($p = 0.011$). The APGAR scores of both groups did not differ significantly. Only one fetus exhibited congenital anomalies (Dandy-Walker syndrome, cleft lip and palate, club foot) -- stillbirth who had no exposure to chemotherapy in-utero. No congenital malformations were observed in any of the babies who had exposure to chemotherapy antenatally. Due to the small number of patients on a particular regimen, no association between a specific chemotherapeutic scheme with a particular adverse outcome could be deduced. Comparing the effect of monotherapy versus polytherapy was also not possible.

Gross and microscopic examinations of the placenta showed no metastasis, both for the exposed and unexposed groups.

The children born of the subject population (i.e. pregnant patients with malignancy) were followed-up for neurodevelopmental assessment. Of the 84 pregnant women included in the study, 68 resulted in livebirths but only 22 children were able to undergo neurodevelopmental testing: 6 children in the exposed group and 16 in the unexposed group. Reasons for the non-screening of the other children are enumerated in Table 6. At the time of neurodevelopmental assessment, the children's ages ranged from 5 months to 5 years and 4 months old, with a mean age of 2 years and 9 months. The test employed was the Denver Developmental Screening Test. Under the exposed group, 2 children were Denver suspects: 1 with cautions in the language domain and in weight for age and another with delay in motor domain (Table 6). The former was 1 year and 4 months old at the time of testing, was incidentally born preterm and SGA. The latter was 7 months and 23 days at the time of evaluation and was born SGA. On the other hand, 1 child under the unexposed group was a Denver suspect with caution in the language domain and in weight for age (Table 7). She was born term and AGA.

Discussion

In this series, the incidence rate of cancer in pregnancy was found to be 0.29% or 3 in 1000 pregnancies -- a higher number than the reported in literature (1 in 1000 pregnancies).[1] A possible explanation is that the institution where the study was

undertaken is a tertiary hospital which serves as a referral center for difficult and complicated cases from different parts of the country, thus, apparently increasing the incidence rate. The most common malignancy complicating pregnancy found in this series was ovarian cancer, followed by breast cancer and thyroid cancer. This is in contrast to that found by Donega in 1983 that breast, cervical, lymphoma and melanoma are the more frequent cancers associated with pregnancy.[11] Surprisingly, ovarian cancer-- the most common type of malignancy found in this population, is a disease more prevalent in nulligravid women, unlike the subject population (mean gravidity = 3) which is comprised of mostly multiparas (78%). It was also seen from the study that primary malignancy from the ovary was common to both primigravids (42%) and multiparas (57.9%).

Table 6. Number of patients lost to long-term follow-up and reasons.

Reason	Number of Patients
No consent for the developmental assessment	6
Did not show-up on appointed time	2
Residency in the province	4
Change of residence	8
Incomplete addresses	7
Baby deceased	2

Table 7. Outcomes of pregnancies in the unexposed group whose babies underwent Denver Developmental Screening Test.

ID No.	Neoplasm	Baby				
		Pediatric aging, in weeks	Birth weight, in grams	Congenital malformation	Age at follow-up, years	Denver test
1	Ovarian	39-40	3300	(–)	1 5/12	Suspect
2	Ovarian	39-40	2800	(–)	1 5/12	Normal
3	Ovarian	38	2300	(–)	4 4/12	Normal
4	Breast	39-40	2750	(–)	1 9/12	Normal
5	Ovarian	38	2500	(–)	3 4/12	Normal
6	Neuro	39	2900	(–)	3 10/12	Normal
7	Hema	38	2400	(–)	9/12	Normal
8	Ovarian	38-39	2700	(–)	3 1/12	Normal
9	Ovarian	35	2000	(–)	4 9/12	Normal
10	Breast	38-39	2750	(–)	1 4/12	Normal
11	Ovarian	37	2550	(–)	2 6/12	Normal
12	Ovarian	39	3150	(–)	5/12	Normal
13	Thyroid	39	2900	(–)	91/2	Normal
14	Osteosarcoma	36	1850	(–)	6/12	Normal
15	Others	41	3500	(–)	2 2/12	Normal
16	Ovarian	38	2900	(–)	1 4/12	Normal

Of all the 107 pregnancies complicated with cancer admitted to the institution from January 2000 to April 2005, only 84 were included in the analysis as the medical records of the other patients could not be retrieved. Of these, 68 were livebirths but only 22 children were able to undergo neurodevelopmental assessment. Seventeen of the babies were less than 6 months of age and are thus not yet candidates for the Denver Developmental Screening Test. A number of problems that contributed to this low turnout were identified. Most of the patients either had incomplete addresses or a change in residence, thus locating them became impossible. There were a number who were not able to come for testing since they lived in far away places-- as this hospital is a referral center which receives cases from all over the country. Some parents did not consent to the neurodevelopmental evaluation of their children. Two did not show up on the appointed time and another two were already deceased at the time the study was being conducted.

Out of the 84 analyzed subjects, only 11 (10.28%) were exposed to chemotherapy antenatally and this comprised the exposed group. The pervading

reluctance of both the physicians and the patients in considering chemotherapy during pregnancy stems from the paucity of well-designed studies documenting its effects on the fetus. When chemotherapy is offered, financial limitations prevent some of the patients from availing of this option. It is precisely because of financial constraints that some of them are being referred to government hospitals.

Most cytotoxic agents exert their effects by interfering with DNA and RNA synthesis, thereby interrupting essential metabolic pathways and eventually destroying actively dividing cells and tissues, not just the tumor tissues but also the normal ones. In the case of pregnancy, both maternal and fetal tissues are exposed to their systemic toxicity and teratogenicity.[3] The teratogenicity of any drug depends on the timing of exposure, the dose and the characteristics affecting placental transfer, including high lipid solubility, low molecular weight and loose binding to plasma proteins which all favor transfer from the mother to the fetus.[2] When progeny is exposed to such substances during organogenesis, major malformations and increased risk of miscarriage are observed. Exposure after organogenesis is associated with increased rate of prematurity, stillbirths and intrauterine growth retardation. Doses in animal studies, however, are higher than those used for human cancers, thus making it difficult to extrapolate animal data to humans.[14]

Comparing the two groups, it has been shown that the mean birth weight of babies born to mothers who received chemotherapy were significantly lower than that compared to the unexposed neonates. This is similar to what Doll and associates observed in 1988, that exposure during the second and third trimesters, well after organogenesis, increases the risk of intrauterine growth restriction (IUGR) and low birth weight.[9] In addition, they also found that stillbirth rates and prematurity rates are also increased in this type of pregnancies.[9] In this study, however, there is no significant difference in the rate of preterm deliveries and there is only a trend to an increased rate of stillbirths. Exposure to cytotoxic drug during the first trimester, on the other hand, is said to increase the risk of spontaneous abortion and major malformations[9] since this is the period in which major organ systems develop. The results of this series show the contrary: in the group of gravid patients who underwent chemotherapy, there were no pregnancies which ended in abortion and no congenital malformations were observed in their babies. One of these patients indeed received therapy during her first trimester of pregnancy. Interestingly, in the unexposed group, there were 2 abortions and 1 fetus was assessed to have multiple malformations. Cardonick and Iacobucci in 2004 stated in their review that the underlying malignant disease itself can cause adverse perinatal outcomes.[2] Direct effects of the tumor sometimes confound the risks of fetal loss.[12] In a similar manner, maternal nutritional deficiencies, also caused by the tumor itself or by chemotherapy-induced anorexia, as well as febrile illness caused by infection secondary to the relative immunodeficient state of cancer patients, or again the tumor per se can also affect growth and birth weight.[2] The relationship between these maternal cancer complications and the incidence of adverse pregnancy outcomes and of impairment in human children has not been fully addressed.[5]

Placental metastasis is a very rare occurrence that has been documented in literature which theoretically can possibly cause uteroplacental insufficiency leading to intrauterine growth restriction and subsequently low birth weight.[13] In this study, there was no placental metastasis observed for both groups.

Aside from the timing of administration, the type of chemotherapeutic agent used, the dose and the number of courses also have significant impact in the outcome of both the mother and the baby. Chemotherapeutic agents are divided by drug class. Table 9 shows the examples of chemotherapeutic agents by drug class. Among the alkylating agents, cyclophosphamide is an integral part of regimens used for the treatment of breast cancer, ovarian cancer and non-Hodgkin's lymphoma. Three of the patients in the exposed group in this series were given cyclophosphamide in combination with cisplatin for 2 cases of ovarian cancer and doxorubicin in a case of breast cancer. None of the babies had congenital malformations nor were they growth retarded. Malformations, including absent toes, eye abnormalities, low-set ears and cleft palate have been reported with the use of cyclophosphamide during the first trimester.[2] Safe use of cyclophosphamide during the second and third trimesters have been reported by

Cantini[3], et al. wherein 92 patients were exposed to the agent and 7 percent having intrauterine growth restriction.

Anthracycline antibiotics such as Doxorubicin are high molecular weight agents that act by interposing between DNA. Turchi and Villasis[15] summarized 28 pregnancies exposed to Doxorubicin and Daunorubicin for the treatment of acute myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin's lymphoma, sarcoma and breast cancer. All patients were treated after the first trimester and all were physically normal.

Berry and colleagues[4] treated 24 breast cancer patients with cyclophosphamide, 5-fluorouracil and doxorubicin after 12 weeks and there were no congenital anomalies nor growth restriction noted. This finding was supported by the results of Cardonick[2], et al. thus it was recommended that this combination of chemotherapy be the preferred chemotherapeutic drug for breast cancer in pregnancy. One breast cancer patient in the exposed group in this series was given this regimen for 2 courses with no untoward effect on the baby, while the others received 4 courses of epirubicin starting during the first trimester. Her baby showed motor delay at the age of seven months. In a study done by Peres and associates in 2001, epirubicin was used in 13 women, 3 fetuses of which were affected: 1 died after second trimester exposure to epirubucin, vincristine and prednisone; another after a combination with cyclophosphamide; and the third neonate died at 8 days after third trimester exposure to epirubucin, cyclophosphamide and 5-fluorouracil.[3,16] Twenty-three percent of cases exposed to epirubucin died either as fetuses or neonates. Because the use of epirubucin has not been extensively investigated as the preferred combination of cyclophosphamide and doxorubicin has, Cardonick and Iacobucci in their review of chemotherapy used during pregnancy did not recommended its use antenatally.[2] They also concluded that if possible, chemotherapy, should be avoided during the first trimester, as should low-molecular-weight and highly diffusible drugs. If multidrug treatment in the first trimester is required, anthracycline antibiotics, vinca alkaloids, or single-agent treatment, followed by multi-agent therapy after 12 weeks should be considered, as the use of chemotherapy during the second and third trimesters seems to be safe.[2]

The ABVD regimen for Hodgkin's lymphoma has been reported to be safe, although dacarbazine is the least investigated.[2] The patient in this series who was diagnosed with Hodgkin's lymphoma was given this regimen but one week after the treatment, the patient went into preterm labor and eventually delivered a 35 week-old infant who was small for gestational age. The maternal illness may have contributed to the low birth weight of the baby.

The two other patients in the exposed group received hydroxyurea for chronic myelogenous leukemia and radioactive iodine for papillary cancer of the thyroid glands. Both pregnancies were carried to term, however, the baby exposed to hydroxyurea had a low birth weight. None of them had congenital anomalies. No studies dealing with these drugs were found in the literature search.

Some case reviews compared the use of polychemotherapy vs. monotherapy. Polychemotherapy was associated with a higher risk of congenital malformation.[3] Due to the limited number of patients included in this study, association between a specific chemotherapeutic scheme and adverse neonatal outcome could not be deduced. Testing the effect of monotherapy versus polytherapy could also not be ascertained from the sample size.

Of the 22 children who were able to undergo Denver Developmental Screening Test, 6 had in-utero exposure to chemotherapy. Two of these were assessed to be Denver suspects: 1 with caution in language domain and inadequate weight gain, the other with delay in motor domain. There have been several studies concerning the late effects of chemotherapy on children's neurodevelopment. Table 8 shows the result of the various studies including the results of this present study. Blatt, et al. assessed retrospectively pregnancy outcome in patients who received chemotherapy for various oncologic diseases. All 4 children underwent Denver Developmental Screening Test and all had normal development and school performance. Aviles, et al. conducted 3 different studies on patients with hematologic malignancies who were exposed to chemotherapy and all 75 children tested using the Wechsler and Bender-Gestalt cognitive test were at par with the children in the control group.[5] Contrary to the findings in the above studies, the results

in this series indicate that administration of chemotherapy during pregnancy may not be completely safe, with 1 of the 6 exposed children manifesting inadequate weight gain and 2 children exhibiting neurodevelopmental delays. This finding, however, cannot be solely attributed to the administration of chemotherapy alone. As previously discussed, the maternal illness in itself may have contributed to the child's developmental status at present. One cannot also discount other factors such as prematurity, nutritional status, economic status, parental education, and the child's environment. Assessment of the relative risk solely attributed to chemotherapy exposures, however, could not be deduced from the limited data that were gathered due to the small sample size.

The results of this study indicate that chemotherapeutic agents have adverse effects to the fetus when administered during pregnancy, causing a significantly increased rate of low birthweights, although the maternal illness itself could have contributed to this occurrence. There was no significant difference between the incidence of preterm deliveries and stillbirth rates in both the exposed and unexposed group. There was 1 case in which congenital malformations were noted but this was in the unexposed group. No congenital malformations were observed in the exposed group. Results of the neurodevelopmental testing done in children exposed to chemotherapy is not very reassuring, unlike the reports in other studies in the literature.

The data presented regarding late effects of chemotherapy on children's neurodevelopment are incomplete and are hampered by a lack of population-based, well designed studies. Majority of available reports have focused on immediate maternal and fetal pregnancy outcomes, not considering later neurodevelopment as a primary endpoint. The present data serve as additional evidence that a rigorous multidisciplinary approach is needed in the management of pregnant women with cancer.

Conclusion

In this series, the incidence rate of cancer in pregnancy was found to be 0.29 percent or 3 in 1000 pregnancies. The most common malignancy complicating pregnancy was ovarian cancer, followed by breast cancer and thyroid cancer.

The mean birth weight of babies born to mothers who received chemotherapy was significantly lower than that compared to the unexposed neonates. However, there is no significant difference in the rate of preterm deliveries and poor APGAR scores. There were no reported congenital anomalies seen in the exposed group.

Due to the limited number of patients included in this study, association between neonatal outcomes versus a specific chemotherapeutic scheme, the timing of exposure or the number of courses that were administered could not be deduced. Testing the effect of monotherapy versus polytherapy could also not be ascertained from the sample size.

The presence of abortions and congenital malformations in the exposed group may signify that the underlying malignant disease itself can cause adverse perinatal outcomes and of impairment in human children has not been fully addressed by the study due to the limitation in number of subjects.

It is, thus, important for clinicians to inform pregnant patients with cancer about their options in antenatal therapy for their cancer and the possible risks and benefits that such therapy may hold to both mother and child.

Limitations and Recommendations

This is an update on the pilot study on the neonatal and developmental effects of antenatally administered chemotherapy for cancers in pregnancy. It was originally designed to be a cohort study but because of the inherent rarity of the cases, limitations in the hospital record keeping and the difficulty in tracking the potential subjects, data collection resulted in a small sample size which necessitated analysis of the paper as a case series. To firmly establish the association of antenatal chemotherapy use to adverse pregnancy outcomes, a multicenter national database is needed to record all pregnant patients with cancer and their offsprings, and to keep track not only of the neonatal outcomes and morphologic observations, but also of the children's long-term neurodevelopment.

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Endometrial Carcinoma in Women 40 Years and Younger: A Tertiary Hospital Experience*

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Objective: To compare the clinical characteristics, histopathologic results, clinical outcomes, risk factors and survival rates of endometrial cancer patients 40 years of age and younger with those of patients older than 40 years of age. **Methods:** A retrospective cohort study involving women diagnosed to have endometrial carcinoma who consulted and were managed at a tertiary hospital from January 1, 1996 to June 30, 2004. **Results:** A total of 633 women with endometrial carcinoma were included in this study. Seventy-eight (12.4%) were 40 years old or younger, while five hundred fifty-five (87.6%) were more than 40 years old. At the time of diagnosis, the mean age for those patients in the younger age group was 34.3 and 54 for the older age group. The younger age group presented with longer duration of symptoms prior to the time of diagnosis (15.9 months vs. 11.9 months, $p = 0.01$) and twice more likely to be nulliparous (71.8% vs 31.2% $p \leq 0.01$). There were no statistical differences between the two groups with regards to their age of menarche, prevalence of smoking history, oral contraceptive use, personal and family history of malignancies. The younger age group had a higher median weight with 75.9 percent noted to be obese compared to 67.9 percent in the older age group. However, this difference was not statistically significant ($p=0.149$). The women in the older age group were more likely to be hypertensive and diabetics. The histology for both age group was predominantly adenocarcinoma, endometrioid type. In the older age group, however, other poor histologic types were also noted. In the younger age group, they were more likely to have disease confined to the corpus, with less than 50 percent myometrial invasion, with well-differentiated tumors and with histology of hyperplasia with atypia in the uninvolved endometrium and cystic follicles in their ovaries. Those with extrauterine spread had more ovarian metastasis compared with the older age group. There was no significant difference between the two groups with regards to their mean length of follow-up and disease status. As to the different risk factors, the only factor that had a statistical significance was the stage of the disease ($P=0.02$). Although the survival rate was higher in the younger age group, this was not statistically significant ($P=0.11$). **Conclusion:** In this study, although the younger age group presented with earlier stage of the disease, less myometrial invasion and well-differentiated tumors compared to the older age group, there was no statistical difference in their overall survival.

Key words: endometrial carcinoma, myometrial invasion

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Endometrial carcinoma can occur during the reproductive and menopausal years. It is statistically a tumor of the postmenopausal period, with most patients in the age between 50 and 65 years, mean age of 63.1 years at diagnosis.[1] While only between 1.5-14.4 percent of the endometrial cancer will be 40 years old or younger..[2-9]

In the recent years, there is an increasing incidence of endometrial carcinoma, but still, this disease remains uncommon in the premenopausal women.

In premenopausal women, the diagnosis is more difficult to establish because symptoms are often confused with dysfunctional uterine bleeding. When discussing endometrial cancer, "young" is defined variously as either premenopausal, or 45 years of age or younger. A review of the literature suggested that endometrial carcinomas in young women are often associated with favorable pathologic features (early-stage disease, high differentiation of the tumor, minimal myometrial invasion) and are believed to be associated with excellent survival rates. Thus, some authors suggested conservation of the ovaries to avoid hormonal deprivation.[1,4-8] However, in three recent studies, it was suggested that the pathologic features and outcome of younger women with endometrial carcinoma may be less favorable than previously thought. In the study by Evans-Metcalf, et al., there was a similar distribution of incidence of poor prognostic factor and outcome in young women compared with older women.[2] Gitsch, et al. reported a 29 percent prevalence of stage III and IV endometrial disease and with frequent lymph node metastases in their younger group of women, indicating a worse prognosis in a subset of these women than reported in the previous studies.[3] In the study by Tran, et al., there was a similar survival and more frequent nodal involvement in the younger age group.[4] Some authors have reported a relatively high incidence of coexisting ovarian neoplasms.[3]

Given the disparity of reported risk, the objective of this retrospective study was to determine whether the younger women were uniformly at low risk or whether there was a subgroup with poor prognostic factors. This determination is particularly important because the potential for advanced stage endometrial disease in these patients has significant impact on preoperative counseling, intra-operative management, and recommendations for adjuvant therapy.

Objective

To compare the clinical characteristics, histopathologic results, clinical outcomes, risks and survival of endometrial cancer patients 40 years of age and younger with those of patients older than 40 years of age.

Materials and Methods

A. Study Subjects

Six hundred fifty-three consecutive patients with documented endometrial carcinoma who were primarily managed in our institution or were primarily operated from another institution and were subsequently referred to our institution from January 1, 1996 to June 30, 2004 were eligible for the study. Data were obtained by review of medical records. Nineteen patients were excluded because of lack of adequate data in their records or had received radiotherapy prior to surgery. These were dichotomized on the basis of age: Group A was composed of women 40 years old and younger, and group B, was composed of women older than 40 years. They all fulfilled the following criteria:

1. Primary endometrial carcinoma
2. Primary treatment included total abdominal hysterectomy and removal of existing adnexal structures

Excluded from this study were the following:

1. Those patients who received radiotherapy or chemotherapy prior to surgery of endometrial carcinoma.
2. Those patients who just underwent total abdominal hysterectomy without removal of the ovaries.

The following clinical characteristics were recorded: age at the time of operation, duration of symptoms, body mass index, menarche, parity, smoking history, oral contraceptive use, history of hypertension and diabetes mellitus. Personal and family history of carcinoma of the breast, colon, endometrium or ovary

were recorded to aid in the identification of familial cancer syndromes such as Lynch syndrome. For this study, an affected first or second degree relative with one or more of these malignancies constituted a positive family history. The body mass index (BMI) was calculated as body weight divided by the square of height (kg/m^2). Values of 23 and above were regarded as obese, and those with values below 23 had normal BMI.

The following histopathologic data were recorded: surgical staging, histological type, histological grading of the tumor, depth of myometrial invasion, status of the uninvolved endometrium (atrophic, proliferative, secretory, hyperplasia without atypia, hyperplasia with atypia, endometrial polyp) and ovaries (cystic follicles, corpora lutea, corpora albicantes, atrophy, inclusion cyst, metastatic tumor and others).

Staging was defined according to the International Federation of Obstetricians and Gynecologists (FIGO) surgical staging system. Histologic classification was performed according to the World Health Organization classification. Architectural grading was based on the degree of glandular differentiation in accordance with the FIGO guidelines.

B. Sample Size

There were 633 women who were included in this study with documented endometrial cancer, seventy eight were 40 years old or younger and five hundred fifty five were older than 40 years. All of them were treated with primary surgery.

Postoperatively, adjuvant radiotherapy, vaginal brachytherapy, chemotherapy or combination of these were given to some of the patients. Postoperative management was according to the Clinical Practice Guidelines for Gynecologic Cancers 2002 by the Society of Gynecologic Oncologists of the Philippines.

C. Study Procedure

A review of individual charts of all eligible patients was done. The surgicopathologic factors such as grade, histologic cell type, depth of myometrial invasion, status of the uninvolved endometrium and ovaries were reviewed by a certified pathologist of the same institution. Follow-up information about the survival and recurrence were collected in the clinical records.

Results

A total of 633 patients were included in this study (Table 1). Seventy eight (12.4%) were 40 years old or younger, and five hundred fifty five (87.6%) were older than 40 years. The mean age was 34.3 for group A and 54 for group B at the time of diagnosis. Although group A had a higher median body mass index than group B (28.3 vs 25.6; $p = 0.149$), this was not statistically significant. Group A presented with a statistically significant longer duration of symptoms prior to the time of diagnosis (15.9 months vs 11.9 months, $p=0.01$). However, there were no statistical difference between the two groups with regards to their age of menarche, smoking history and oral contraceptive use. Group A was more than twice likely to be nulliparous than the women in group B (71.8% vs 31.2%, $p\leq0.01$). Group B has a higher incidence of accompanying hypertension and diabetes mellitus ($p\leq0.01$ and <0.01, respectively). There was no statistically significant difference between the two groups in the prevalence of a personal history of breast, colon, or ovarian malignancies or family history of breast, colon endometrial or ovarian malignancies (Table 2).

Table 1. Comparison of demographic characteristics of women with endometrial carcinoma by age group.

	≤ 40 yrs n = 78		> 40 yrs n = 555		P-value
	Mean	SD	Mean	SD	
Age	34.3	4.7	54.0	7.8	
BMI	28.3	6.1	25.6	12.5	0.11
Duration of symptoms before treatment (in months)	15.9	17.9	11.9	12.8	0.01*
Age of menarche	13.2	1.8	13.7	2.0	0.07
	N	%	N	%	P-value
Nulliparity	56	71.8	173	31.2	<0.01**
Smoker	7	9.0	49	8.8	0.96
OCP Use	11	14.1	84	15.1	0.81
Hypertensive	7	9.0	165	29.7	<0.01**
Diabetic	1	1.3	68	12.3	<0.01**

* Test significant at 0.05
** Chi-square test significant at 0.05 level
– too few observations to compute statistics

Table 2. Personal and family history of other cancers in women with endometrial carcinoma by age group.

	≤ 40 yrs n = 78 N	%	> 40 yrs n = 555 N	%	P-value
Personal history of cancer					
Breast	0	0.0	5	0.9	-
Colon	0	0.0	2	0.4	-
Ovary	0	0.0	0	0.0	-
Family history of cancer					
Breast	2	2.6	26	4.7	0.57
Colon	0	0.0	19	3.4	-
Endometrium	4	5.1	25	4.5	0.96
Ovary	1	1.3	5	0.9	-

- too few observations to compute statistics

After reviewing all the patient data (Table 3), only four hundred fifty six women had available data on both height and weight for calculation of body mass index (kg/m^2). In Group A, fifty four had available data and thirteen (24.1%) were classified as having normal BMI, and forty one (75.9%) were obese. While in Group B, four hundred two women had available data, one hundred twenty nine had a normal BMI and two hundred seventy three (67.9%) were obese. There was no significant difference between the two groups with regards to obesity (p=0.149).

Table 3. Distribution by body mass index of women with endometrial carcinoma by age.

	≤ 40 yrs n = 54 N	%	> 40 yrs n = 402 N	%	P-value
Normal	13	24.1	129	32.1	
Obese	41	75.9	273	67.9	
					.149

Table 4 shows that there was a significant difference in the stages between the two groups. Women in the younger age group were more likely to have an early stage disease while the women in the older age group are in the advanced stage of disease (p=0.003).

Table 4. Distribution of women with endometrial carcinoma according to stage by age groups.

		≤ 40 yrs n = 78 N	%	> 40 yrs n = 555 N	%	P-value
I	IA	5	6.4	31	5.6	
	IB	28	35.9	119	21.4	
	IC	4	5.1	51	9.2	
II	IIA	8	10.3	24	4.3	
	IIB	2	2.6	43	7.7	
III	IIIA	9	11.5	34	6.1	
	IIIB	0	0.0	3	0.5	
	IIIC	4	5.1	83	15.0	
IV	IVA	0	0.0	12	2.2	
	IVB	5	6.4	18	3.2	
Inadequately staged		13	16.7	137	24.7	
						.003*

* chi-square test significant at 0.05 level
- too few observations to compute statistics

Table 5 shows that the histology in both groups was predominantly adenocarcinoma, endometrioid type (group A = 97.4%; group B = 91.5%). In the older age group, however, twelve had uterine papillary serous cell type (2.2%) and seventeen had clear cell type (3.1%), both of which were considered poor histologic types.

Table 5. Distribution by endometrial histology of women with endometrial carcinoma by age group.

	≤ 40 yrs n = 78 N	%	> 40 yrs n = 555 N	%	P-value
Adenocarcinoma	76	97.4	508	91.5	
Adenosquamous	2	2.6	16	2.9	
Papillary serous	0	0.0	12	2.2	
Clear cell	0	0.0	17	3.1	
Mucinous	0	0.0	1	0.2	
Mixed	0	0.0	1	0.2	
					.460

Table 6 shows that there was a significant difference in the histologic grading between the two groups. More women in group A had a well-differentiated tumors, while more women in group B had moderate to poorly differentiated tumors (p=0.001). With regards to myometrial invasion, more women in group A had less than 50 percent myometrial invasion, while more

women in group B had more than 50 percent myometrial invasion and this was statistically significant (p=0.046).

Table 6. Distribution by histologic grading and myometrial invasion of women with endometrial carcinoma by age group.

	≤ 40 yrs n = 78 N	%	> 40 yrs n = 555 N	%	P-value
Histologic grading					
Grade I	50	64.1	230	41.5	
Grade 2	17	21.8	196	35.3	
Grade 3	11	14.1	129	23.2	
					.001*
Myometrial invasion					
None	7	9.0	43	7.8	
< 1/2	52	66.7	296	53.3	
> 1/2	19	24.4	216	38.9	
					.046

In Table 7, with regards to the histology of the uninvolved endometrium, endometrial hyperplasia with atypia was noted to be significantly higher in the younger age group (14.1% versus 4.1%, p <0.01).

Table 7. Distribution by histology of uninvolved endometrium of women with endometrial carcinoma by age group.

	≤ 40 yrs n = 78 N	%	> 40 yrs n = 555 N	%	P-value
Atrophic	0	0.0	32	5.8	-
Proliferative	1	1.3	4	0.7	-
Secretory	2	2.6	7	1.3	0.68
Hyperplasia without atypia	1	1.3	5	0.9	-
Hyperplasia with atypia	11	14.1	23	4.1	<0.01*
Endometrial polyp	3	3.8	19	3.4	0.88
Not specified	60	76.9	465	83.8	0.09

* chi-square test significant at 0.05 level
- too few observations to compute statistics

Table 8 shows that patients in the younger age group had a higher incidence of ovarian metastasis (23.1% versus 12.1%, p<0.01) and cystic follicles (34.6% versus 11.7%, p<01). More than half of the women in the older age group had a normal ovarian histology (58.2% vs 34.6%, p<0.01).

Table 8. Distribution by ovarian histology of women with endometrial carcinoma by age group.

	≤ 40 yrs n = 78 N (Mean)	% (SD)	> 40 yrs n = 555 N (Mean)	% (SD)	P-value
Cystic follicles	27	34.6	65	11.7	<0.01*
Corpora lutea	0	0.0	19	3.4	-
Corpora albicantes	1	1.3	16	2.9	0.65
Atrophic	0	0.0	19	3.4	0.50
Metastasis	18	23.1	67	12.1	<0.01*
Normal	27	34.6	323	58.2	<0.01*
Inclusion cyst	0	0.0	3	0.5	-
Mature cystic teratoma	0	0.0	7	1.3	-
Endometriosis	3	3.8	17	3.1	0.91
Fibroma	0	0.0	1	0.2	-
Mucinous cystadenoma	1	1.3	2	0.4	-
Mucinous, LMP	0	0.0	1	0.2	-
Serous cystadenoma	1	1.3	9	1.6	0.79
Struma ovari	0	0.0	6	1.2	-

* chi-square test significant at 0.05 level
- too few observations to compute statistics

Multivariate analysis using forward conditional Cox Regression Analysis with entry criteria of 0.20 and removal criteria of 0.40 was done to determine the effect of important risk factors. The only factor that was found to have a significant effect on endometrial carcinoma by increasing the risk of dying was the stage of the disease at the time of surgery with a p value of 0.02 (Table 9).

Table 9. Risk of dying based on age and clinical parameter.

	Odds Ratio	95% CI	p value
Age	1.02	0.99 and 1.04	0.09
Smoking	0.86	0.53 and 1.39	0.54
Oral contraceptive use	1.08	0.75 and 1.56	0.66
Cancer type	0.97	0.79 and 1.19	0.80
Stage	1.04	1.01 and 1.08	0.02**
Grade	1.09	0.93 and 1.29	0.27
Invasiveness	0.92	0.74 and 1.14	0.43

The mean length of follow-up was 18.7 months for group A and 15.7 months for group B (Table 10). It provided details regarding the status of patients at the time of their last follow-up period. There was no statistical difference between the two groups with

regards to those patients with no evidence of disease, undergoing adjuvant treatment, with recurrent/ persistent disease and lost to follow-up.

Table 10. Disease status over time in women with endometrial carcinoma by age group.

	≤ 40 yrs n = 78 Mean	SD	> 40 yrs n = 555 Mean	SD	P-value
Duration of follow-up (in months)	18.7	21.8	15.7	20.7	0.24
	N	%	N	%	P-value
No evidence of disease	40	51.3	250	45.0	0.21
On-going treatment	5	6.4	24	4.3	0.64
Alive with disease	7	9.0	62	11.2	0.26
Lost to follow-up	26	33.3	215	38.7	0.14
Died of disease	0	0.0	4	0.7	-

In Figure 1, a Kaplan-Meier curve was constructed to show overall survival and the survival difference between age groups. The log rank test was used to determine the significance of the difference in the curves.

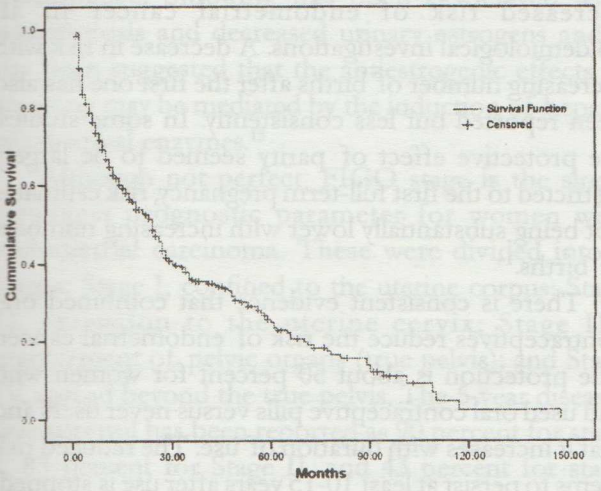

Figure 1. Kaplan-Meier curve showing overall survival of all patients.

The overall mean survival time in all patients was 37.5 months (95% CI 32.8 and 42.2 months). The overall survival rate was 55.7 percent.

Figure 2 shows that the mean survival time among patients who were 40 years and below was 37.9 months (95% CI 24.8 and 50.9) and was relatively similar to the mean survival time of the older age group which was 37.6 months (95% CI 32.8 and 42.4). Although the survival rate was higher in the younger age group with a rate of 70.5 percent compared to the older age group which was only 53.7 percent, this was not statistically significant (Log rank test p=0.11).

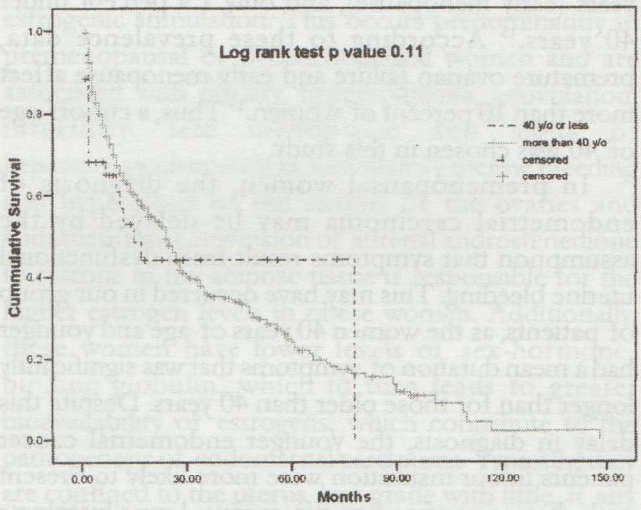

Figure 2. Kaplan-Meier curve showing overall survival of all patients based on age group.

Discussion

According to the 2005 Philippine Cancer Facts and Estimates, cancer of the corpus uteri is the 9th leading site among women, with 3.2 percent incidence rate. In 2005, there will be 1,777 new cases and 546 deaths.[10]

Endometrial cancer is most commonly found between the ages of 50 and 65 years, and is rare before the age of 40. The peak incidence occurs in the post-menopausal age group.[11] Depending on the age cut-off used for the study, proportions between 1.5 to 14.4 percent have been reported.[3]

According to WHO, ideally, premature menopause or premature ovarian failure should be defined as menopause that occurs at an age less than two standard deviations below the mean estimated for the reference

population. In practice, in the absence of reliable estimates of the distribution of age at natural menopause in populations in developing countries, the age of 40 years is frequently used as an arbitrary cut-off point, below which menopause is said to be premature.[12]

In the study by Coulam, et al. about 1 percent of women in the general population experience cessation of ovarian function under the age of 40. Recently, it was reported that 88 percent of women over 45 years of age experience menopause, 9.7 percent before 45 years (early menopause), and only 1.9 percent under 40 years.[13] According to these prevalence data, premature ovarian failure and early menopause affect more than 10 percent of women.[13] Thus, a cut-off age of 40 was chosen in this study.

In premenopausal women, the diagnosis of endometrial carcinoma may be delayed by the assumption that symptoms result from dysfunctional uterine bleeding. This may have occurred in our group of patients, as the women 40 years of age and younger had a mean duration of symptoms that was significantly longer than for those older than 40 years. Despite this delay in diagnosis, the younger endometrial cancer patients in our institution were more likely to present with disease confined to the corpus, lower histologic grading, less myometrial invasion and less likely to have a poor endometrial histology. Those with extensive disease were more likely to have ovarian metastasis at the time of surgery.

The association between weight and endometrial cancer risk has generally been explained in terms of an increased availability and unopposed peripheral estrogen (particularly in the postmenopausal period), when aromatization of androgens to estrogens in the adipose tissue is the major source of estrogens. Likewise, progesterone is completely lacking and there is a lower concentration of sex hormone binding globulin in obese women, leading to an increased availability of peripheral estrogens to hormone-responsive tissues such as the endometrium. The relative risks ranged between 2 and 10.[11]

Although there had been very few research on this, approximately 5 percent of women between the ages of 20 and 54 with endometrial cancer have a family history of such as cancer and 2 percent of colorectal cancer.[13] Two forms of inherited endometrial carcinoma have been described: a predisposition for endometrial cancer and the Lynch II syndrome. In the Lynch II syndromes, families are at risk of developing nonpolyposis colon cancer and other adenocarcinomas. Females are at risk of developing ovarian and/or endometrial carcinoma.[14] It was observed that there was a 50 percent increase in risk associated with a family history of endometrial cancer. In particular, a family history of endometrial cancers appears to be associated with a greater risk of disease in young women (aged <50 years).[13]

In relation to age of menarche, all the studies considered found that the risks decreased with increasing age of menarche, with about a 50 percent reduction in risk in women with a later menarche. The protective effect of late menarche could be more or uniquely important in premenopausal women, in whom the addition of a few years of cyclic hormonal stimulation is probably more relevant. This finding has plausible biological correlates in the likely late-stage (promotional) effect of hormonally-mediated menstrual factors. Furthermore, age at menarche may appear to be more important in younger women because their recall is better. Obesity early in life is associated in turn with overweight in adults, as well as early onset of menstrual cycles.[11,14]

Nulliparous women have been found to be at increased risk of endometrial cancer in all epidemiological investigations. A decrease in risk with increasing number of births after the first one has also been reported but less consistently. In some studies, the protective effect of parity seemed to be largely restricted to the first full-term pregnancy, risk estimates not being substantially lower with increasing numbers of births.[14]

There is consistent evidence that combined oral contraceptives reduce the risk of endometrial cancer. The protection is about 50 percent for women who had used oral contraceptive pills versus never users and that it increases with duration of use. The reduced risk seems to persist at least 10-15 years after use is stopped, but the limited number of women aged 60 years or more who had used oral contraceptive pills does not as yet provide definitive estimates of relative risk for longer periods and according to different times of exposure. In the absence of direct information on the possible persistence of the protection in older age, the

impact of the OC should be considered still relatively limited on a public health scale, in consideration of the age distribution of endometrial cancer patients.[13,14]

A history of diabetes has been repeatedly associated with increased frequency of endometrial cancer. The reported risks range between 1.2 and 2.1. Few studies have taken into account the role of potential confounding factors such as overweight or socioeconomic status, although those that have done so confirmed an increased risk in diabetic women. The biological explanation of this finding is not obvious, although elevated serum levels of estrone have been found in diabetic women.[14]

The association between endometrial cancer and hypertension has been analyzed in several studies. Most, though not all, reported an increased frequency and higher risk of the disease in hypertensive women, and the association seemed to persist after allowance for potential covariates, chiefly overweight.[11,14,15]

Several studies have shown a lower risk of postmenopausal endometrial cancer in smokers. The apparent protection increases with duration and number of cigarettes smoked per day, the relative risks being about halved in long-term and heavy smokers. Smokers have an early menopause, so the observed protective effect in postmenopausal women, could at least partly, be due to the anticipation of age of menopause. Smoking has been associated with osteoporosis and decreased urinary estrogens and it has been suggested that the antiestrogenic effects of smoking may be mediated by the induction of hepatic microsomal enzymes.[13]

Although not perfect, FIGO stage is the single strongest prognostic parameter for women with endometrial carcinoma. These were divided into 4 stages: Stage I, confined to the uterine corpus; Stage II, extension to the uterine cervix; Stage III, involvement of pelvic organs (true pelvis); and Stage IV, spread beyond the true pelvis. The 5-year disease-free survival has been reported as 90 percent for stage I, 83 percent for Stage II, and 43 percent for stage III.[15]

It has been consistently recognized that cell type is an important predictor of the biological behavior of endometrial carcinoma. It has been postulated that endometrial cancer may represent the end process of a spectrum which begins from adenomatous hyperplasia, passes through atypical adenomatous hyperplasia and results in frank cancer. Despite this, only one fourth of patients with the disease have such a history. Therefore, it is likely that although endometrial cancer may follow atypical hyperplasia, it can develop independently of it. Over the last 15 years, based on Bokhman's clinical model for explaining the pathogenesis of endometrial carcinomas, these tumors have been classified into 2 types. Type I tumors (about 80%) are endometrioid carcinoma, which are estrogen-dependent type. These are frequently preceded by complex atypical hyperplasia and associated with estrogenic stimulation. This occurs predominantly in premenopausal or perimenopausal women and are associated with obesity, hyperlipidemia, anovulation, infertility, late menopause and signs of hyperestrogenism such as anovulatory uterine bleeding and hyperplasia of the stroma of the ovaries and endometrium. Conversion of adrenal androstenedione to estrone in the adipose tissue is responsible for the higher estrogen levels in obese women. Additionally, these women have lower levels of sex-hormone-binding globulin, which in turn leads to greater bioavailability of estrogens, which contribute to the pathogenesis of endometrial carcinoma. Typically, they are confined to the uterus, low grade with little, if any myometrial invasion with a favorable prognosis. In contrast, type II tumors (about 20%) are nonendometrioid (predominantly serous and clear cell) carcinomas, occasionally arising in endometrial polyps or from precancerous lesions (endometrial intraepithelial carcinoma) in the vicinity of atrophic endometrium. They are usually not associated with estrogen stimulation or hyperplasia, readily invade the myometrium and vascular spaces, poorly differentiated and carries an unfavorable prognosis.[15]

The grading of endometrioid carcinomas is prognostically important, whereas nonendometrioid carcinomas are considered high-grade tumors by definition and thus need not be graded. The 1988 International Federation of Gynecology and Obstetrics (FIGO) grading system is based primarily on architectural features. Tumors that are $\leq 5\%$ solid are grade I, and those that are 6 to 50 percent solid are grade 2, and those that are > 50 percent solid are grade 3. However, the presence of grade 3 nuclear features (ie, marked nuclear pleomorphism, coarse chromatin,

prominent nucleoli) in architecturally grade 1 or 2 tumors increases their grade by one.

The value of FIGO grading system was demonstrated by Zaino, et al. stating that the 5-year relative survival was 94 percent for the patients with grade 1 tumors, 84 percent for those with grade 2 tumors, and 72 percent for those with grade 3 tumors.[15]

Numerous investigators have noted that young women who seek treatment primarily presented with low grade, minimally invasive, organ-confined disease.[6,8,9,18,19,20] However, in three recent reports, it was suggested that young women may have less favorable pathologic features than previously thought. Evans-Metcalf, et al.[2] noted no difference in the distribution of tumor stage between 40 women aged 45 or younger compared with 249 women aged 45 or older. Stage I, II, III and IV tumors were seen in 69 percent, 5 percent, 18 percent and 8 percent, respectively, of the young group compared with 66 percent, 15 percent, 12 percent and 7 percent, respectively, of the older group (p=0.27). No differences were noted in the frequency of unfavorable histologies, positive cytology and adnexal involvement. Gitsch, et al.[3] compared characteristics of 17 patients age 45 years or younger with endometrial carcinoma with a cohort of 237 women age 45 years or older. Stage III-IV disease was seen in 29.4 percent and 15.2 percent of young and older patients, respectively. In the study by Tran, et al.[4] young women with endometrial carcinoma had similar tumor stages, histologies, incidence of lymphovascular invasion and involved peritoneal cytology.

In other series, they have observed that age is one of the most important independent risk factors for endometrial carcinoma. Majority of the studies that evaluate age as a prognostic factor in endometrial cancer study women 40 years old or younger. These patients are likely to be premenopausal at the age of diagnosis. This is an important subset of patients because of their potential desire for future fertility a the time of diagnosis, which directly conflicts with the sterilizing therapy that treats most endometrial cancers.[5,16] Most of the other studies showed no real difference in survival for endometrial carcinoma when diagnosed between ages 30 and 50. Survival decreases significantly in patients older than 50. This decreased survival associated with age is unrelated to surgical stage or grade of adenocarcinoma. The decreased in survival could involve molecular differences in the developing endometrial cancer or an increased risk of death from other non-cancer-related factors.[3,17] In a recent series of 17 women under age 45 with endometrial carcinoma, two had pulmonary metastases. Both of these women had complete regression of their lesions after progestin therapy and were free of disease 33 and 46 months after treatment.[3] In a randomized study, it was shown that adjuvant progestin therapy has not improved the survival in patients with early endometrial carcinoma who were not selected for age. These data suggest that endometrial cancer is biologically different in young women. This has important implications for clinical management. In women under 40, the histologic differentiation of atypical hyperplasia from well-differentiated carcinoma may not be critical because both lesions are highly responsive to progestin therapy. If the patient desires to preserve her fertility, then progestin treatment may be reasonably considered in either case.[18,19] In women over 55, however, a diagnosis of either atypical hyperplasia or well-differentiated carcinoma on endometrial biopsy confers a substantial risk of residual carcinoma in the uterus that may be deeply invasive and moderately or poorly differentiated. Because fertility is not an issue for women in this age group, hysterectomy is the treatment of choice in either lesion.[17]

It is the continued practice in our institution to perform total abdominal hysterectomy with bilateral salpingo-oophorectomy in all of our endometrial cancer patients, as supported by the high prevalence of advance stage (stages III and IV) endometrial diseases in our report (23%) and in the reports of Gitsch, et al. (29%), Evans-Metcalf, et al. (26%) and Tran, et al. (29%).[2,3,4]

Removal of the ovaries in this age group will cause loss of hormonal function, menopausal symptoms and the long-term morbidity. Thus, question of ovarian conservation may arise. If consideration is given to ovarian conservation, careful preoperative counseling is necessary. Additionally, informed consent of the possibility that metastases may escape detection if the ovaries do not undergo microscopic analysis should be included. Among a series of patients with metastases to the ovary from various primary tumors, it was reported that the affected ovaries often were small, less than 5 cm in size in 75 percent of their cases, and that the malignancy often was occult in 24 percent. Thus,

the risk of occult disease, although difficult to estimate, is not zero. Thus, knowledge of the increased risk of metastasis to other different abdominal organs will require a careful intraoperative assessment of the ovaries, lymph nodes, omentum and peritoneal structures at the time of hysterectomy to afford optimal treatment planning.[1] Unilateral oophorectomy at the time of hysterectomy may be considered if only one ovary is enlarged and if frozen-section examination of the ovary reveals a benign tumor. Bilateral ovarian conservation is best reserved for particularly young patients with apparent stage IA, grade I disease; however, this controversial aspect deserves further study.[2]

Presently, with the quality of life in cancer patients receiving increasing attention, there have been several recent reports of hormone replacement therapy in patients with endometrial cancer. The reports suggest that the use of hormone replacement therapy in patients with endometrial cancer is safe, although randomized trials on this issue are lacking.[3]

The limitations of this study were the following: retrospective nature, lack of data regarding hormonal history, bleeding irregularities, clinical signs of hyperandrogenism and some of the patients were not surgically staged. The retrospective nature does introduce potential selection bias; however, all patients were included, therefore, it should statistically affect all patients equally regardless of age. Data regarding hormonal history, bleeding irregularities and signs of hyperandrogenism, ultrasound findings of the ovaries prior to surgery should be included to be able to determine the incidence of polycystic ovarian syndrome using the revised 2003 Rotterdam Criteria.

Conclusion

In our study, endometrial cancer patients with less than or equal to 40 years old presented with longer duration of symptoms, higher median weight and twice more likely to be nulliparous. While those patients more than 40 years were more likely to have associated medical illnesses like hypertension and diabetes mellitus. There were no significant difference with regards to both their personal and family history of carcinoma.

Patients in the younger age group were more likely to be associated with early stage of disease, well differentiated tumor, superficial myometrial invasion and hyperplasia with atypia in the uninvolved endometrium. Those with extrauterine spread, were found to have higher incidence of ovarian metastasis.

Stage was the only clinical parameter noted that can significantly increase the risk of dying in patients with endometrial carcinoma

The survival rate was higher in the younger age group but it was not statistically significant (70.5% vs 53.7%, p=0.11).

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Human Papilloma Virus and Genital Infections and Neoplasia

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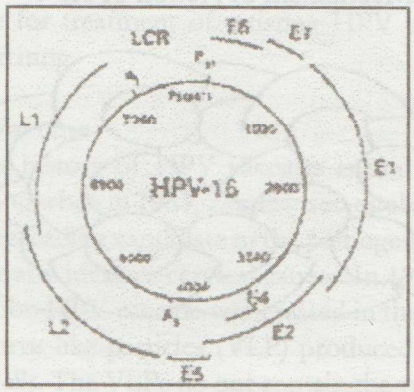
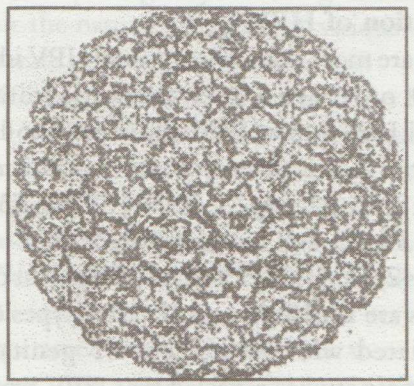
Human papilloma viruses (HPV's) belong to the family Papovaviridae. They consist of a 72-capsomere capsid or an outer shell containing the viral genome.[1] The capsomeres are made up of two structural proteins: the 57 kD late protein Ll and a minor capsid protein L2. HPV's are relatively stable but they can remain infectious for months in a moist environment because they have no envelope.[2] A viremia with viral spread to distant organs does not occur.

The genome which is contained in the capsid is a double standard DNA molecule. It is divided into three regions: the long control region (LCR) which has no coding potential; the region of early proteins (E1–E8) and the region of late protein (L1 & L2).

E6 and E7 are the most significant oncogenic proteins as transcription of E6 and E7 genes was observed always to occur in cervical cancer. In fact, this was the first indication that these genes play an essential role in the genesis of HPV-associated cancers.[3,4] Numerous experiments, both in tissue culture and experimental animal models demonstrate the immortalizing and transforming potential of E6 and E7[5,6]. The key to HPV's effects on cells is in these two virally encoded protein – E6 and E7. These proteins interact with two tumor suppressor genes, p53 and pRb. p53 activity is often lost in tumors usually by a combination of mutation and gene deletions. In cervical cancer, the p53 gene is intact and p53 protein is expressed in the transformed cell (Vousden).[7] HPV protein binds to p53 (a tumor suppressor gene) so that when the cells lose the protein (to E6) they can grow uncontrollably. In other words, p53 loses its function as an anti-oncogene. Previous studies have indicated that HPV infection alone does not always lead to cervical cancer suggesting that certain co-factors may be involved in the genesis of cervical cancer.

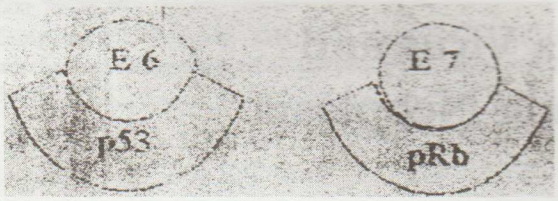


HPV genome map

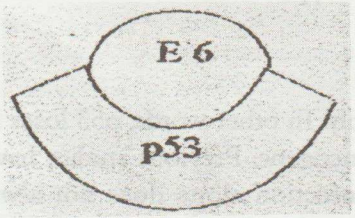


HPV capsids (Galloway. 1998)

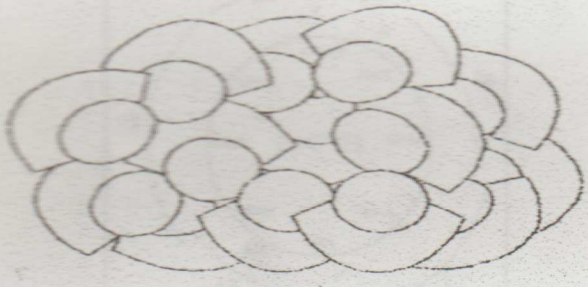
Mechanism of Action of HPV



Mechanism of Action of HPV



Mechanism of Action of HPV



Classification of HPV

There are more than 200 types of HPV identified. About 40 of these affect the anogenital tract. Anogenital HPV's have been classified into high risk (HR) for the development of cervical cancer. HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82, and low risk (LR) HPV's – types 6, 11, 34, 40, 42, 43, 44, 54, 55, 61, 62. The most common HPV types are 16, 18, 45 and 31. HPV types 6 and 11 are associated with 90 percent of genital warts. Epidemiologic studies revealed that HPV types 6 and 11 are associated with a low potential risk for the development of cancer.[8,9]

HPV Infection

Tiny cuts in the skin surface allows entrance of HPV which infect stratified squamous epithelial cells (keratinocytes). The virus spreads to the deep basal layer of the epithelim and stimulates the growth of the infected cell. The accumulated or mounds of infected cells become recognized as warts. In the deep basal layers of the epithelium there is little replication, no cell lysis occurs so that there is very little exposure of the antigen (HPV) to the immune system. Thus, the HPV can remain there for long perioa of time without inciting inflammation. It is only during the natural desquamation of mature epithelial cells that a large number of viruses are shed.[10]

HPV infections are among the most common sexually transmitted infections. The estimated prevalence of HPV ranges from 15 to 20 percent in many European countries to 70 percent in the United States or 95 percent in high risk population in Africa.[11] In the Philippines, the prevalence of HPV noted on a cohort study done in the Philippine General Hospital among cervical cancer patients and among controls is 93.8 percent and 9.2 percent, respectively.[12, 13]

HPV infection is usually transient, clears in 7 to 8 months to 2 years. HPV peaks at 20-46 percent between ages 20-25 after which it decreases to 6 percent for women older than 30 years, coinciding with the pattern of sexual behavior at corresponding ages.

HPV and Cervical Cancer

Epidemiologic evidence attesting to the association between cervical cancer is universally accepted. The evidence is strong, independent of other risk factors and consistent in several countries.[14] Ninety two point nine percent (92.9%) even as high as 99.7 percent of invasive cervical cancer are HPV DNA (+). HPV types 16 and 18 account for 2/3 of all cases of cervical cancer (Nubla Munoz). Data from screening programs from the Netherlands revealed age-specific prevalence of high risk (HR) HPV DNA to peak age 25-30 whereas cervical cancer peaks at age 40 years.

The potential risk of developing cercival cancer depends on:

1) HPV type-whether high or low risk
2) Persistence of infection especially beyond age 30 years

3) Viral load – a high viral load would have a greater risk potential
4) The patient's immune status may be an additional risk factor as immunosuppressed individuals would understandably be more susceptible to infection and progression of disease.[13]

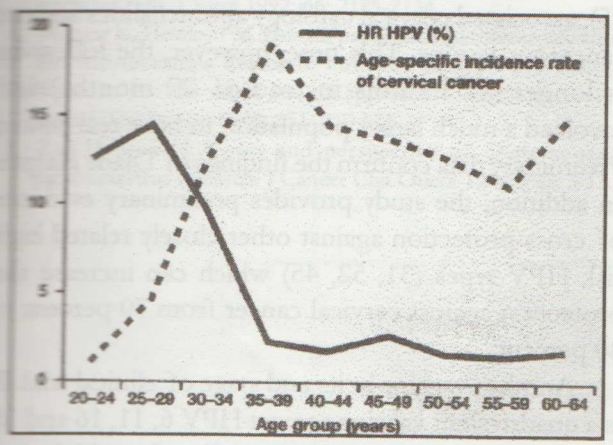


Figure 1. In the Netherlands, HPV infections peak at age 25-30 years, while cervical cancer peaks after 40 years.

It was widely accepted that cancer of the cervix is preventable since there is a long period of time (about 10-15 years) for the precursor lesion, CIN to develop into invasive disease, enough time to diagnose and treat it before it becomes cancer. The strategies which maybe used to prevent cervical cancer include:

1) Prevention of HPV infection
   a) changing one's lifestyle
   b) adapting a lifestyle that avoids the potential of contracting sexually transmitted disease
   c) prophylactic immunization using HPV vaccine

2) Screen for treatment of HPV/CIN with organized screening programs employing the
   a) Pap smear, HPV typing
   b) Visual inspection, aided or unaided, magnified or non-magnified in low resource setting

3) Immunotherapy for existing HPV infections.

Cervical cancer is still a major health problem globally. It is second leading cause of cancer – related deaths in women worldwide. Globally, there are 524,000 new cases yearly resulting in 234,000 deaths, 80 percent from developing countries. The age adjusted incidence rate (ASR) ranges from 10-40 / 100, 000 population. In the Philippines, cervical cancer is the second leading cancer in women, next to breast cancer. It is the leading cause of cancer-related deaths in Filipino women. The age standardized rate is 22.5 / 100,000 population – a rate which has not changed for many years now.

A cytology based screening program is very expensive so that only the developed nations are able to carry out organized and widespread screening. Inspite of attempts to use alternative methods of screening like visual inspection, aided or unaided national screening programs do not exist so that women frequently are at an advanced stage of the disease at the time of diagnosis. Treatment is more complex and expensive; survival rate is low.

The prospect of having a prophylactic vaccine that could reduce the incidence of cervical cancer by preventing HPV infection or having a therapeutic vaccine for treatment of existing HPV infections is truly exciting.

HPV Vaccine

The history of HPV vaccines is said to have its beginning when in 1983, Zur Hausen established HPV 16 as the leading candidate in the pathogenesis of pre-invasive and invasive cervical cancer. In 1991, the first generation HPV vaccine was created in the laboratory – the virus like particles (VLP) produced in yeast or insect cells. The VLPs do not contain the viral genome (no DNA) so that they are non-infectious. They, however, morphologically and anti-genetically resemble or mimic the natural structure of virions so that they can generate potent immune response.

In 1992, Koutsky, et al. reported on his phase II trial of HPV 16 VLPs. This is a randomized, double blind, multicenter study. Two thousand three hundred ninety two (2,392) women, age 16 to 23 (10/98 – 1/99) were randomized to receive three doses of placebo and HPV 16 VLP at day 0, mo2, mo6. Genital swabs (cervical and external genitalia) and cervico-vaginal lavage specimens for HPV 16 DNA were obtained at enrollment, one month after 3rd vaccination (mo7); 6 months after 3rd vaccination (mo12) and every six months, thereafter. The outcome measure is the

presence of persistent HPV infection (two or more positive (+) HPV DNA samples). The median follow-up was 17.4 months. The incidence of persistent HPV infection was: 3.8/100 woman years in the placebo groups vs. 0/100 woman years in the vaccine group giving a 100% efficacy at 95% confidence interval, 90-100; p <0.001. All nine cases of HPV 16 related CIN occurred in the placebo group.

DM Harper, et al. conducted a randomized double blind controlled trial in North America and Brazil to assess the efficacy, safety and immunogenicity of a bivalent L1 virus-like particle vaccine in the prevention of infection with incident on persistent HPV 16 and 18 in young women, associated cervical cytology abnormalities and precancerous lesions. One thousand one hundred thirteen women ages 15-25 were randomized to receive 3 doses of the vaccine formulated with AS04 adjuvant or placebo on a 0 month, 1 month and 6 months schedule. The women were assessed for HPV infection by cervical cytology and self obtained cervico vaginal samples for up to 27 months and for vaccine safety and immunogenicity. Results revealed:

1. According to protocol analysis, the vaccine efficacy was 91.6 percent (95 CI 64.5 – 98.0) against incident infection and 100 percent against persistent infection (47.0 – 100) with HPV 16 and 18.
2. In the intention to treat analysis, the efficacy was 95.1 percent (63.6 - 99.3%) against persistent cervical infection with HPV 16 and 18 and 92.9 percent (70.0%-98.3%) against cytological abnormalities associated with HPV 16 and 18 infections.
3. The vaccine was generally safe and well-tolerated and highly immunogenic. It was concluded that bivalent HPV vaccine was efficacious in the prevention of incident or persistent cervical infection of HPV 16 and 18 and associated cytological abnormalities and lesions. Vaccination against such infection could substantially reduce the incidence of cervical cancer.

Currently, prophylactic vaccine based on VLPs are in late phase clinical trials with evidence that they prevent HPV infection.

The Human **Papilloma Trial** against Cervical Cancer in young adults, is focused on the oncogenic HPV 16 and 18. The target enrollment is 18,000 women ages 15-25 for study regions (Asia Pacific-Europe, Latin America and North America). The Philippines is one of the countries in Asia Pacific region participating. The objectives are essentially the same as those of Diane Harper, et al. - that is to assess the efficacy, safety and immunogenicity of the candidate vaccine against HPV 16 and 18 infection in young women (ages 15-25), associated cervical cytology abnormalities and pre cancerous lesions. This time, however, the follow-up is longer (42 months instead of 27 months) and involved a much larger population to have real power. Preliminary data confirm the findings of Diane Harper. In addition, the study provides preliminary evidence of cross-protection against other closely related high risk HPV types (31, 52, 45) which can increase the protection against cervical cancer from 70 percent to 80 percent.

Another vaccine in its end stage of clinical trial. It is a quadrivalent vaccine against HPV 6, 11, 16 and 18 using alum as adjuvant. Early studies show high titer antibody to all four components. Thus, the vaccine is expected to prevent cervical cancer, and its precursor. It is expected to prevent genital warts as well.

Vaccine	MS	GSK
1. Bivalent		HPV 16, 18
2. Quadrivalent	HPV 6, 11, 16, 18	
3. Adjuvant	- alum	- $AS0_4$
4. will be available	late this year (2006)	- Early 2007

HPV 16 and 18 vaccines represent a major break through in cervical cancer prevention and if HPV vaccine will go the way of the Hepatitis B vaccine, cervical cancer would in our lifetime be a disease of the past.

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Non-Puerperal Uterine Inversion Associated with Malignant Mixed Mullerian Tumor of the Uterus

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Uterine inversion caused by a uterine malignancy is a rare condition. A 67-year old G12P11 (10-1-1-8) presented with a polypoid mass at the vagina accompanied by vaginal bleeding. Histopathologic report of the mass showed both sarcomatous and carcinomatous elements. Exploratory laparatomy revealed uterine inversion. Extrafascial hysterectomy and bilateral salpingooophorectomy with complete surgical staging were performed. Adjuvant treatment with radiotherapy and ifosfamide chemotherapy were recommended.

Key words: malignant mixed mullerian tumor, non-puerperal uterine inversion, surgical staging, radiotherapy, chemotherapy

Malignant mixed mullerian tumors (MMMTs) are rare but highly aggressive neoplasms comprising less than 1.5 percent of all malignant uterine tumors. Histologically, these tumors consist of both carcinomatous and sarcomatous components.

Uterine inversion is a rare complication during the third stage of labor. Reported incidence is one in 30,000 deliveries.[1] Non-puerperal inversion of the uterus is a much less frequent condition and is usually caused by benign tumors such as leiomyoma. For it to be caused by a malignant tumor makes the condition exceedingly rare. This condition is referred to as non-puerperal uterine inversion (NPUI). (Figure 1)

Non-puerperal uterine inversion is so rare that the author failed to find a reliable estimate of its incidence in the literature so far. From the Medline, Ichikawa[2] reported a series of 12 cases of uterine inversions brought about by uterine sarcomas from 1940 to 2000. In the review of Lupovitch[3], 17 cases of similar conditions were documented since 1887. Following exhaustive local literature search, no case of non-puerperal uterine inversion associated with a gynecologic malignancy was so far reported, hence, this case is probably the first locally.

This case is being presented to make the gynecologists aware of the occurrence of non puerperal uterine inversion in association with malignancy. Although it is extremely rare, there should be a high index of suspicion and should always be included in the differential diagnosis of patients presenting with vaginal mass. It is essential that a correct pre-operative diagnosis of the condition be made in order to provide optimal therapy to the patient and to reduce complications during surgery.

This presentation aims: 1) to present a rare case of non-puerperal uterine inversion associated with malignant mixed mullerian tumor in a 67-year old multipara and 2) to discuss its pathophysiology and

the diagnostic dilemma that it poses as well as its management strategies.

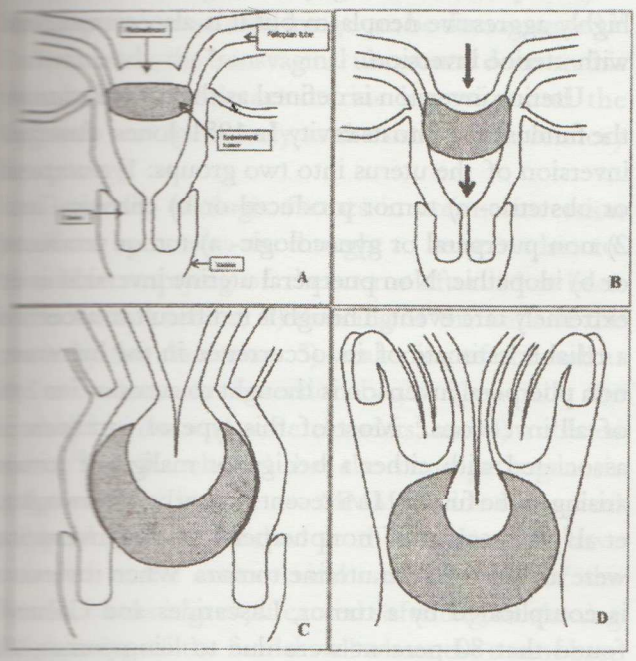

Figure 1. Mechanism of Uterine Inversion. (Case AS, et al. 2005). A Carcinosarcoma located at the uterine fundus B Myometrial contraction to expel the tumor. C The tumor is expelled through the cervix. D Uterine and tumor prolapse into the vagina with the adnexa being pulled into the inverted vagina.

Case Profile:

J.A. is a 67-year old, G12P11 (10-1-1-8), married, from Quezon City who presented with postmenopausal vaginal bleeding, which started two months prior to consultation, described as moderate, consuming two fully soaked pads per day, lasting for a week and associated with hypogastric discomfort. Consultation was done with a private doctor where transvaginal ultrasound revealed an enlarged anteverted uterus with thick (3.0 cm) endometrium, atrophic ovaries and cervix. Fractional curettage was performed which disclosed a malignant mixed mullerian tumor of the uterus and chronic cervicitis on histopathology. Surgery was advised.

She is a known hypertensive since age 65 with highest BP of 180/100 mmHg for which she takes Calcibloc 5 mg/tab irregularly. Her father and paternal aunts and uncles were also hypertensive. She is a widow who used to work as a cook. Menarche was at age 13 while menopause was at age 50. She is a G12 P11 (10-1-1-8).

Review of systems was unremarkable. On admission, she was conscious, coherent and not in any form of distress. BMI was 32. Pelvic examination revealed a 10.0 x 9.0 cm soft, polypoid, fleshy mass, filling up the upper half of the vaginal vault. The cervix could not be palpated because of the large mass. The corpus and adnexa were not properly assessed because of the flabby abdomen and voluntary muscle guarding during examination. Rectovaginal examination revealed smooth but shortened parametria.

Pre-operative tests that include CBC, urinalysis, blood chemistry, ECG and chest x-ray were normal and she was cleared for surgery. On exploratory laparotomy, no ascites was noted. All peritoneal and visceral surfaces were smooth. There were no palpable pelvic and paraaortic lymph nodes. Omentum was grossly normal. The uterine fundus was invaginated pulling the round ligaments and the adnexa with it measuring 12 x 7 x 7 cm. Extrafascial hysterectomy, bilateral salpingooophorectomy, bilateral pelvic lymph node dissection and peritoneal fluid sampling were performed.

The endometrial cavity was 7.5 cm in length, 4.0 cm of which was the endocervical canal. A 6.5 cm x 7 cm tan-gray, friable mass was noted occupying the entire endometrial cavity with point of attachment at the posterofundal area, with a base measuring 6 x 5.5 cm. Bulk of the friable mass was noted to prolapse through the internal os, cut section of which showed less than 50 percent myometrial invasion. The lowermost border of the tumor was 3 cm from the level of the internal os. The cervix was dilated mechanically by the protruding mass with thinned out smooth endocervix. The fallopian tubes and ovaries were grossly normal. All lymph nodes were tan-pink and smooth with no areas of hemorrhages and necrosis seen.

The postoperative diagnosis was malignant mixed mullerian tumor, uterus, stage IB. This was later confirmed by the final histopathological result.

She tolerated the procedure well. The postoperative course was unremarkable.

Pending histopathology result, the plan was to give adjuvant treatment with complete radiation therapy and chemotherapy using ifosfamide.

Discussion

Malignant mixed mullerian tumor, also termed carcinosarcoma, sarcomatoid carcinomas or malignant mixed mesodermal tumors are rare gynecological tumors that constitute less than 1.5 percent of all uterine malignancies.[4] This tumor usually occurs in postmenopausal women age 55 to 65 years old. It may also arise in the ovary, fallopian tube, cervix, or peritoneum, although with a much lower frequency than in the uterus.

Specific preoperative diagnosis of the disease is often difficult to establish. Many authors have reported that a definite histological diagnosis from curettings can be established in only 60-70 percent of cases[5], the small tissues obtained, the frequent necrosis and inflammation of the tumor surface being the limiting factor. It is also not uncommon that the result of the uterine curettings are ambiguous and misleading, such that, either only the carcinoma or only the sarcoma component is seen and the true histologic nature of the tumor becomes apparent only after the entire specimen has been available for study. Fortunately, this patient presented with prolapsing mass. This enabled us to obtain a large tissue for histopathological examination, which aided in establishing the diagnosis preoperatively.

Tumor spread occurs by direct extension to the cervix and vagina followed by other pelvic organs including the bladder and rectum. Lymphatic spread to local and regional lymph nodes occur at an early stage of the disease. Hematogenous spread is also common usually to the lungs, liver and bone.

The tumor is highly aggressive, hence the prognosis is poor. Since they arise within the myometrium where they have immediate access to the vascular and lymphatic channels, they tend to metastasize early.

Majority of the studies and most authors agree that the most important prognostic factor for MMMT is the stage of disease at presentation and that prognoses are poor when the tumor extended beyond the uterus. FIGO staging of MMMT of the uterus is the same as for endometrial carcinoma. Peters, et al. documented that the 5 year survival in patients with stage I is 58%, 33% in stage II, 13% in stage III, and no survivors in those with disease outside the pelvis (Stage IV).[6] Standard treatment for this tumor is surgery followed by adjuvant radiation therapy with or without chemotherapy.

This patient is not only afflicted with a rare and highly aggressive neoplasm but it is also complicated with uterine inversion.

Uterine inversion is defined as the invagination of the fundus uteri into its cavity. In 1951, Jones[7] classified inversion of the uterus into two groups: 1) puerperal or obstetric- a) tumor produced or b) chronic- and 2) non puerperal or gynecologic- a) tumor produced or b) idopathic. Non puerperal uterine inversion is an extremely rare event. Though is it difficult to ascertain a reliable estimate of its occurrence in the literature, non puerperal inversion is thought to account for 1/6 of all inversions.[8] Most of this type of inversion is associated with either a benign or malignant tumor arising in the fundus. In a recent review by Mwinyoglee, et al.[9], 97 percent of nonpuerperal uterine inversions were associated with uterine tumors. When inversion is complicated by a tumor, Lascarides and Cohen[10] found that 80 percent were due to leiomyomas, 10 percent to sarcomas, 7 percent to carcinomas and 3 percent to idiopathic causes.

The diagnosis of uterine inversion has not been clearly apparent in this case. On initial examination, the considerations were tumor of cervical origin versus a tumor arising from the corpus that is prolapsing through the cervix. But since the initial biopsy result revealed MMMT in addition to its characteristic clinical presentation, a primary corpus malignancy was favored.

Because of the rarity of uterine inversion and a clinical finding not consistent with it, this condition was not suspected initially. The classic presentation of uterine inversion is a prolapsed tumor in the vagina and a non-palpable uterine fundus, or the presence of fundal depression on pelvic examination. Lascaraides, et al.[10] proposed two criteria in diagnosing uterine inversion: 1) inability to palpate the uterine corpus on bimanual examination; and 2) non-visualization of the cervix after excision of the vaginal mass.

In most instances, ultrasound can detect the presence of uterine inversion. It can be seen as an indentation of the fundal area on longitudinal scan of the uterus. Alternatively, a depressed longitudinal groove extending from the fundus to the center of the inverted portion can be identified on abdominal ultrasound. Another useful imaging tool in the

diagnosis is a contrast-enhanced MRI wherein a u-shaped uterine cavity with thickened and inverted fundus on a sagittal image and a "bull's eye" configuration on an axial image can be demonstrated.[11] Unfortunately, the transvaginal ultrasound done on this patient failed to detect uterine inversion and the diagnosis was made only at the time of exploratory laparotomy.

Generally, etiologic factors in uterine inversion produced by tumors are thought to be secondary to: 1) sudden emptying of the uterus after it has been distended by a tumor, 2) thinning of the walls of the uterus by this distention 3) weakening of the wall at the site where the inversion begins (generally the fundus) by noncontractile elements; and 4) a dilated cervix.[12] It is believed that the same pathogenesis occurred in this case — MMMT with its typical polypoid growth attached to the fundus may have extruded to the endocervical canal and out of the cervical os. As it grew, it caused softening, weakening and thinning of the fundal wall where the tumor base was attached. Sensed as a form of irritation, the uterine wall started contracting to expel the tumor. The growing weight and size of the tumor place additional traction to the thinned out wall furthering the process of inversion.

After noting for the presence of uterine inversion at the time of laparotomy, thorough assessment of the degree of inversion was made. Uterine repositioning was attempted however was not successful, hence the author immediately proceeded with the planned hysterectomy and complete surgical staging. Several authors however, believed that even in cases of malignancy, the first maneuver that should be done is to return the uterus to its normal anatomic position followed by hysterectomy.[13] This will relatively make the operation easier. If preoperatively diagnosed, repositioning can be done either abdominally or vaginally. Vaginal approaches have been described by Kustner and Spinelli.[14] In both procedures, the uterus is split and everted to its normal position. In the Kustner procedure, the uterus is posteriorly incised, while in the Spinelli procedure, the uterus is incised anteriorly. After uterine repositioning has been done by either method, hysterectomy can be performed. Abdominal approach have been described by Huntington and Haultain.[15] In Haultain procedure, cervical constriction ring is incised anteriorly and traction on the fundus is applied until the uterus has been normally positioned. In Huntington procedure, normal anatomy is restored by gradually everting the uterus without incising it, by applying gentle traction on progressively medial portions of the round ligaments using allis clamps. Surgical treatment of uterine inversion depends on the preoperative diagnosis. Therefore, preoperative diagnosis is of paramount importance. When uterine inversion is associated with benign disease, vaginal and abdominal approach is recommended. When inversion is associated with malignancy, as in this case, abdominal approach is suggested since a friable tumor may fill up the vagina. In addition, an abdominal incision will be needed for complete surgical staging.

Uterine inversion in association with malignant mixed mullerian tumor is an extremely rare event. Though rare as it is, it should always be included in the differential diagnosis of patients with vaginal tumor and corpus not palpable on pelvic examination. Recognizing the condition preoperatively will make the oncologists aware of the distortions in normal tissue planes and normal course of the ureter during surgery and would hence facilitate performance of the operation.

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Malignant Transformation of an Ovarian Endometriotic Cyst

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A 54 year old multigravid underwent a total hysterectomy and bilateral salpingooophorectomy for myoma uteri. Incidental finding was an ovarian cyst, assessed intra-operatively to be endometriotic. Histopathology showed endometrioid carcinoma arising from endometriosis. A review of literature shows a strong association between ovarian cancer and endometriosis and that in a small percentage of women with endometriosis, the lesions may undergo malignant transformation. Endometriosis-associated ovarian cancer appears to have a better prognosis that those not associated with endometriosis.

Key words: endometriosis carcinoma, endometriosis, ovarian cancer

In 1925, when Sampson first ventured a possible association between endometriosis and cancer of the ovary, he outlined three criteria for diagnosing malignant transformation of endometriosis:

1. The cancer and endometriosis must be demonstrated in the same ovary.
2. The cancer must arise in the tissue and not invade it from another site.
3. It must be possible to recognize the characteristic histological structure of endometriosis with both glands and surrounding stroma.

Later, in 1953, Scott added another criterion, a more stringent one: the demonstration of transition between endometriosis and malignant epithelium. Since then, the literature has pegged the incidence of malignant transformation of endometriosis at 0.7 percent to 1.0 percent of all patients with endometriosis.[1]

Case

A.C., a 54 year old multigravid consulted for vaginal bleeding. She was hypertensive and was maintained on beta-blockers for 14 years. Menarche was at 11. She had regular menstrual periods subsequently, at one-month intervals, which usually lasted 4 days and soaked an average of three pads per day. Through 1978 to 1987, she carried four pregnancies to term and delivered them vaginally, with no complications. She did not use any means of contraception.

Four months prior to admission, after being amenorrheic for six months, she experienced vaginal spotting. She sought no consult until two months prior to admission, when she had profuse vaginal bleeding, soaking five pads per day. This lasted for two weeks.

On internal examination, the corpus uteri was enlarged to 12 weeks gestation size. There were no adnexal masses or tenderness. The initial consideration was a myoma uteri. A Pap smear revealed "atypical

squamous cells of undertemined significance" (ASCUS) and bacterial vaginosis. Subsequent colposcopy done showed normal results. The transvaginal ultrasound (Figure 1) showed:

Multiple myoma uteri (subserous, intramural)
Right ovarian cyst, physiologic vs. pathologic
Para-ovarian adhesions on the right

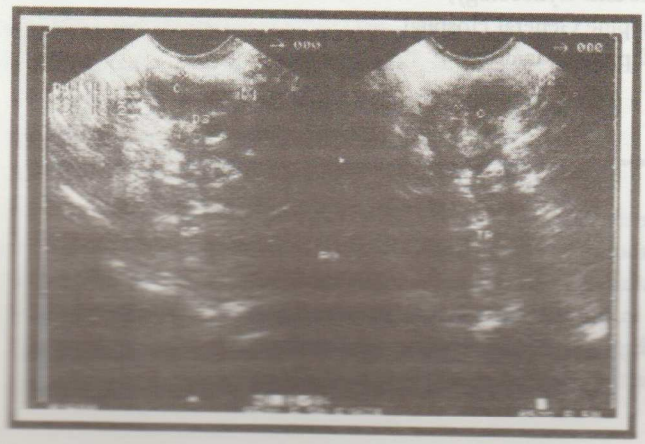

Figure 1. Transvaginal ultrasound.

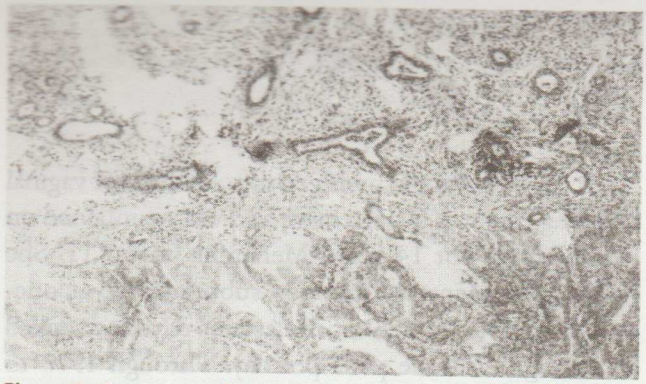

Figure 2. Low-power view.

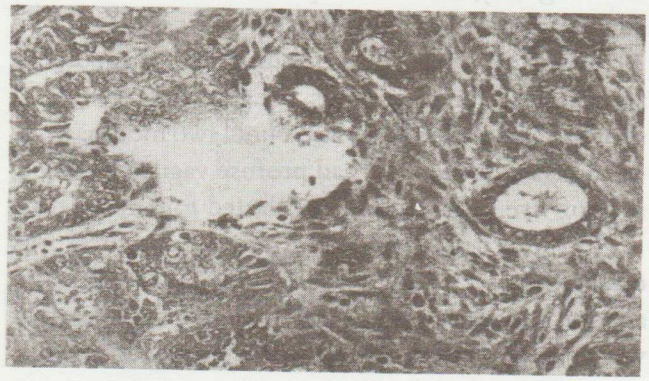

Figure 3. High-power view.

She underwent a total hysterectomy with bilateral salpingooophorectomy. Intraoperatively, there was no ascites. The liver, spleen, subdiaphragmatic surfaces, kidneys and intestinal surfaces were smooth. The uterus had a smooth, tan serosal surface and measured 14 x 11 x 9 centimeters. On cut section, the myometrium measured 4.5 centimeters anteriorly and posteriorly. The endometrium was 0.3 cm thick. There where two polypoid fleshly masses attached to the fundal wall, which measured 5.5 x 2.0 x 1.0 centimeters and 4.0 x 2.0 x 1.0 centimeters. The cervix was 3.0 x 3.0 centimeters and appeared grossly normal. The uterine cavity measured 12 centimeters, 2.5 centimeters of which was endocervical. The right and the left ovaries measured 3.0 x 2.0 x 0.5 and 2.5 x 2.0 x 0.5 centimeters respectively. On cut section, both ovaries contained chocolate colored fluid with identifiable normal ovarian tissue. The intraoperative assessment was adenomyosis, endometrial polyps and bilateral endometriotic cysts. However, the histopathologic report revealed:

"Endometrioid carcinoma, arising from a endometriotic cyst of the right ovary (Figures 2, 3)
Adenomyoma,
Endometrial polyps,
Proliferation endometrium,
Chronic cervicitis,
Normal left ovary and both fallopian tubes

Endometriosis

Endometriosis is a progressive disease that is found in approximately 10 percent of women.[2] It is a common problem, yet its exact etiology and pathogenesis remain unclear. The popular theories of metaplastic transformation of pelvic peritoneum and transplantation of uterine endometrium to ectopic locations are only two of the many theories regarding its development. By far, the most widely accepted theory on pathogenesis is that of retrograde menstruation. The presence of the disease is attributed to the attachment of endometrial fragments to the epithelium of the peritoneum, its invasion and establishment of a blood supply, and generation of a suboptimal immune response that does not adequately clear the disease.[3]

Although generally accepted to be a benign disease entity, endometriotic lesions do exhibit certain features similar to malignancies. Endometriosis is progressive and invasive. It recurs and metastasizes. To date, a number of investigative studies have shown an

association between endometriosis and malignant disease, most notably ovarian cancer.

Ovarian Cancer

Unlike endometriosis, ovarian cancer is less common, occurring in only 1-3 percent of women. Among the histologic subtypes, epithelial cancer is the most common, accounting for 90 percent of all ovarian malignancies.[6] Its pathogenesis is similarly unclear. The two strongest theories revolve around incessant ovulation and increased gonadotropin production.[7] Another theory has proposed that retrograde menstruation has a role in ovarian cancer, as in endometriosis. The pelvic contamination with menstrual products might induce ovarian cancer.[8]

Endometriosis as a Predisposing Factor to Malignancy

Since 1925, several studies have reported the coexistence of malignancy and endometriosis. In a pooled analysis of 8 case-controlled studies, Ness, et al. have found that endometriosis was linked with a significantly increased ovarian cancer risk with an odds ratio of 1.73 (93% CI 1.10-2.71). In 1997, Brinton, et al. in the cohort study investigating cancer risk after hospitalization for endometriosis, found that overall cancer risk was significantly increased.[9] There was a significant incidence of ovarian cancer (RR 1.92, 95% CI 1.3-2.8) of breast cancer (1.27 CI 1.1-1.4), and of hematopoietic cancers (RR 1.35, 95% CI 1.0-1.8). Notably, the relative risk of developing an ovarian malignancy rose to 2.51 percent for subjects with more than 10 years of follow-up and even higher to 4.20 percent when the endometriosis was confined to the ovary. The investigators suggested possible hormonal and immunologic reasons for these excess risks.

Use of oral contraceptive pills, increased parity and lactation are associated with a reduced risk for ovarian cancer[10] primarily by decreasing ovulation. By decreasing menstrual flow (oral contraceptives) or inducing absence of menstruation altogether (pregnancy), and decreasing outflow tract resistance by permanent cervical dilatation (increased parity), the incidence of retrograde menstruation and therefore the likelihood of endometriosis, is also markedly reduced. The index patient is a multigravid with no history of use of any contraceptive method.

Tubal ligation and hysterectomy are also reported to be protective against ovarian cancer. Initially ascribed to the benefit of screening during the time of surgery, the protection that was observed to span even 20 years after was later proposed to be because of the pro-inflammatory exposures (to include endometriotic implants) prevented from reaching the ovarian epithelium by cutting off the pathway between the lower and the upper parts of the genital tract.[11]

The explanation for these shared protective factors lies in the purported relationship between inflammation and carcinogenesis. Inflammatory cells release toxic oxidants that cause DNA injury. Chronic inflammation results in necrosis and compensatory cell division. This can ultimately lead to replication errors and susceptibility to mutagenesis and eventually carcinogenesis. In addition, inflammatory cells release cytokines and growth factors that can be critical in progression of malignancies. There are several documented associations of inflammatory condition and carcinomas to date, namely viral hepatitis and hepatocellular cancer, inflammatory bowel disease and colon cancer and closer to home, HPV and cervical cancer.[12]

Ness, et al. reported on the role of ovarian inflammation in ovarian cancer. He stressed that inflammation may predispose to the occurrence of ovarian cancer in endometriosis, since the latter generates a chronic inflammatory state that may enhance the pathophysiologic conditions that lead to cancer initiation and progression. However, since not all women with endometriosis develop ovarian cancer, there may be other factors at play, most probably genetic.

Endometriosis in Ovarian Cancer

Analyzing 29 retrospective studies since 1973, Van Gorp, et al. calculated the prevalence of endometriosis in the major subtypes of epithelial ovarian cancer. They classified coexistence of endometriosis in three categories, namely:

Category (A) consisted only of ovarian cancers with histological proof of transition from ovarian endometriosis cancer according to the definition of Scott.

Category (B) consisted of all ovarian cancers with endometriosis in the same ovary but without

histological proof of transition or without knowledge whether this transition was further investigated or not.

Category C consisted of all ovarian cancers with concomitant endometriosis at any location in the pelvis: endometriosis in the bilateral or contralateral ovary, extragonadal endometriosis or without specification about lateralization and/or localization of the lesion.

For category A, they calculated the prevalence of endometriosis as 9.1 percent and 8.5 percent of clear cell (n = 99) and of endometrioid types (n = 234), respectively. No association was seen in mucinous and serous types. Category B was documented in all ovarian cancer types. The prevalence was computed at 4.5, 1.4, 35.9 and 19.0 percent for serous, mucinous, clear cell and endometrioid cancers, respectively. Even higher prevalence rates were calculated for Category C. Furthermore, they found that the prevalence of endometriosis for Categories B and C was significantly more for clear cell and endometrioid types .The significance applies to the index patient, where an endometrioid carcinoma was found to arise from an endometriotic cyst.

Ovarian Cancer in Endometriosis

Establishing the prevalence of ovarian cancer in endometriosis is limited by the nature of management. Not all endometriotic lesions are treated surgically while others are only partially resected, making it difficult to perform extensive sampling for histologic studies. The actual prevalence of malignant degeneration of endometriosis may be higher than earlier reported.

Pathogenesis

In the end, the question remains: why do endometriotic lesions predispose to malignancy? More than just shared risk factors, the answer seem to lie in similarities at the molecular level. The synchronous occurrence of endometriosis with ovarian clear cell and endometrioid carcinoma suggests transformation of endometriotic constituents into malignant cells.[13]

Stepwise molecular and histological transition has been well-described in colon cancer and is seen to involve germ line (inherited) and somatic (acquired) mutations of specific genes, namely: tumor suppressor genes and oncogenes that lead to predictable precancerous and cancerous lesions. Oncogenes are dominant genes that activate cellular proliferation when functioning normally but may lead to hyperactive growth when abnormal. Tumor suppressor genes are recessive genes that normally inhibit growth by controlling proliferation. When abnormal, deleted or mutated, they fail to retard growth.[13]

What recent molecular studies are suggesting is that for the case of ovarian epithelial cancers, namely endometrioid and clear-cell, endometriosis may actually be a premalignant lesion in predisposed individuals.

Loss of heterozygosity (LoH) demonstrated by microsatellite analysis represent a mutation in one allele of the tumor suppressor gene that often leads to its inactivation and tumorgenesis. Jiang, et al. studied 11 cases of adjacent endometriotic lesions with clear cell or endometrioid carcinomas. They detected 17 common LoH events on the chromosome arms 4q, 5q, 6q, 9p, 11q, and 22q in the endometriotic components and the adjacent carcinoma in 9 out of 11 tumors. In four of the cases, where the malignant component arose from within the endometriosis, at least two microsatellites were lost.[14] It is noteworthy to add that two chromosomal locations correspond to those implicated in endometrioid carcinoma of the ovary. Another study has observed that the patterns of inactivation are different in cases where endometriosis and epithelial ovarian cancer occurred in opposite ovaries.[15]

Studies on Bcl-2 and p53 expression in benign endometriotic cyst and cysts associated with endometrioid and clear-cell carcinomas have hinted on the malignant transformation of such cysts. Bcl-2 is an oncogene in chromosome 18, whose proteins promote cell division and play a role in whether a cell will irreversibly commit to apoptosis. p53 is a tumor suppressor gene found in chromosome 17. Nezhat and colleagues have found that while the benign cyst does not stain for these genes, endometriotic cysts associated with clear cell and endometrioid tumors do. Therefore, alterations in these genes may be associated with malignant transformation.

The PTEN gene, located on chromosome 10q23.3, has been investigated and found mutated in various types of cancer. It is common in endometrial cancers of endometrioid histology. Obata, et al. also identified PTEN somatic mutations in ovarian endometrioid tumors. Recently, the LoH patterns of this chromosome have been identified in endometrial

cysts.[17] This suggests a common carcinogesis for eutopic and ectopic endometrial tissue to atypical endometrium and endometriosis, and further to endometrioid and clear cell cancer.

Prognosis

Cuesta, et al. purported that endometrioid adenocarcinoma coexisting with endometriosis has a favorable prognosis. Suggestive evidence indicates that endometriotic lesion might serve as a negative influence on the intraperitoneal spread of ovarian cancer cells.

McMeekin found that endometriosis-associated ovarian cancer (EAOC) was associated with a younger age of diagnosis (<55 years), nulliparity, stage I or II disease and a longer disease-free survival. He studied 91 endometrioid cancer cases, of which 28 were EAOC. Toki, et al. studied 235 ovarian carcinomas of different types and found that patients with EAOC tended to be younger. Komiyama and colleagues studied 53 clear-cell carcinomas, 20 were endometriosis-associated, and found a statistical difference in 5 year-survival for stage I disease but not for stage III. In a study of 290 ovarian tumors, with each EAOC matched with four NEAOC, Erzen and colleagues found no difference in stage-specific survival but attributed this to the predominance of early stage disease in EAOC.

The data at hand support the view that EAOC behaves in a different manner. The tumors are generally well-differentiated, low stage carcinomas, which tend to occur in younger patients. This probably explains the better prognosis observed in patients with EAOC.

Management

It appears that ovarian endometriosis, especially in perimenopausal and postmenopausal women, is not always a harmless lesion. Molecular studies seem to support the link between simple endometriosis and ovarian cancer. Complete excision of endometriosis should be attempted if fertility is not desired in the perimenopausal patients.

Transvaginal ultrasonography has dramatically improved gynecologic examination. High resolution scanning has led to earlier detection of ovarian cysts as well as offered prognostication. Unilocular and echo-free cysts are generally regarded to be benign while multi-loculated, complex cysts are likely to be malignant. However, age appears to influence prognostication. Ekervohd and colleagues reported that simple unilocular cysts were malignant in 1.6 percent (4/247) in postmenopausal women only 0.7 percent in premenopausal women (3/413).

Serum CA 125 is a useful predictor of ovarian cancer and endometriosis. In the literature, when serum CA 125 level was more than 1000 U/ml, 89 percent of patients had gynecologic cancer, 7 percent had non-gynecologic cancers, and 3 percent had benign conditions. Some cases have been reported with serum CA125 levels over 1000 U/ml in women without ovarian cancer but with a diagnosis of endometriosis. It is essential to follow aggressively patients with endometriosis of the ovary who have a high level of CA 125.

The index patient neither had the benefit of a CA 125 determination nor of the knowledge that she had an ovarian malignancy at the time of the operation. She had undergone total hysterectomy with bilateral salpingo-oophorectomy for other indications. This would still have been the procedure of choice had she been known to be a case of ovarian cancer at the time of operation. Additional staging procedures, namely peritoneal fluid cytology and infracolic omentectomy, would have been ideal as well as assessment of the pelvic and para-aortic nodes for metastasis.

Summary and Conclusions

Endometriotic lesions may undergo malignant transformation. However, the incidence appears small. This may be because not all endometriotic lesions are treated surgically and histologic sampling is not adequate or not done at all. The actual prevalence may be higher.

The prognosis is generally accepted to be better for endometriosis associated ovarian cancers as the patients are young and the cancers well-differentiated and of low stage. Still, complete surgery, as well as extensive resection of endometriotic implants, is encouraged for cases of endometriosis in patients with completed family size.

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