Tumor Ploidy in Epithelial Ovarian Tumors: An Interim Analysis

Maria Margarita V. Manalang-Montecillo, MD; Leedah L. Ranola, MD; Marie O. Almira-Andal, MD; Jericho Thaddeus P. Luna, MD, FPGS and Efren J. Domingo, MD, PhD, FPGS

Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines Manila

Background: Epithelial ovarian cancer remains to be the leading cause of death from gynecologic malignancy. Survival is influenced primarily by FIGO stage, amount of residual disease and histologic type. Unfortunately, such prognostic factors still fail to account fully for the biologic behavior of ovarian carcinomas. It is of interest therefore to identify new prognostic factors which are more objective, quantifiable and reproducible. DNA ploidy has been shown to be an independent prognostic factor in epithelial ovarian malignancies.

Objective: The general objective of the study was to determine the ploidy characteristics of epithelial tumors of the ovary. The specific objectives were to determine the association of age and aneuploidy, the association of tumor size and aneuploidy and the association of stage and aneuploidy.

Methods: Patients who underwent surgical staging and/or tumor debulking for ovarian cancer with final histopathologic results of epithelial ovarian carcinoma were included in the study. Exclusion criteria included previous treatment with chemotherapy or radiotherapy and previous or concomitant malignant diseases. DNA ploidy was determined using flow cytometry of paraffin embedded blocks.

Results: DNA ploidy was obtained in 109 paraffin-embedded blocks of epithelial cancers of the ovary. Aneuploidy was established in 14 of the total 109 samples (12.8%) as follows: 2 from 24 mucinous cystadenocarcinoma (14.2%), 2 from 24 mucinous tumor of low malignant potential (14.2 %), 5 from 29 serous cystadenocarcinoma (17%), and 5 from 30 endometriod carcinoma (16%).

Conclusion: The prevalence of aneuploidy in epithelial ovarian cancer is 12.8% and aneuploidy is higher for serous adenocarcinoma and endometrioid adenocarcinoma compared to mucinous tumors of low malignant potential and mucinous cystadenocarcinoma.

Key words: Epithelial ovarian cancer, tumor ploidy, flow cytometry
to determine if flow cytometry plays a role in separating potentially aggressive tumors from those which pursue a more innocuous course. DNA ploidy analysis may prove useful in determining the risk of progression, especially in stage I invasive mucinous carcinomas.

This finding of Gaweski, et al. is also consistent with the findings of previous investigators. In his study, flow cytometric analysis was done from paraffin-embedded tumor blocks of 87 patients. The goal was to define high risk patients with early-stage disease who might benefit from adjuvant therapy. The finding is noteworthy since the dilemma in treatment regarding adjuvant therapy and aggressiveness is highly debated for this group (Stages I & II). In another study, flow cytometric DNA quantification was the main independent prognostic factor of relapse and survival in women with Stages I – II epithelial ovarian cancers.\(^4\) Clinical management of patients with these diseases may be aided by studying their tumors for these objective markers of biological aggressiveness.

Ploidy is usually assessed by a technique called flow cytometry. This can be used to measure the number of cells in the S-phase of the mitotic cycle. This measurement is, however, best considered under the heading of “proliferation indices” and only the use of flow cytometry for ploidy determination is usually employed. Ploidy and proliferative activity are the two properties commonly measured by DNA content flow cytometric study. These two properties were used as biologic predictors of aggressive behavior in a variety of ovarian carcinomas. Both abnormalities are associated with poor outcome in all stages of ovarian cancer.

Ploidy can also be evaluated by the less commonly used technique of static image cytometry in which the DNA content of Feulgen-stained nuclei in histological sections of touch preparations is measured via an image analysis system. Although there is a good correlation between ploidy results obtained from flow and static image cytometry, the static image technique allows for the identification of small subpopulations of aneuploid tumor cells that may be missed on flow cytometry; static cytometry also has the advantage that tissue morphology is retained. It is possible that static image cytometry will be more widely utilized in the future but most reported studies of ploidy in gynecological tumors have been based upon flow cytometric data.\(^6,7,8\)

Flow cytometry is a relatively simple and rapid technique for the measurement of cellular DNA content which can be used on both fresh and archival tissue and allows for tumors to be classed, in general terms, as either diploid or aneuploid. In essence, either cells are dissociated from tumors by mechanical or enzymatic techniques or recovered from paraffin blocks, stained with a fluorochrome dye that binds specifically and stoichiometrically with nucleic acids and then passed through a flow cytometer in a liquid suspension medium as a laminar flow jet. Flow cytometers measure and record fluorescence and light scatter in the cells and the fluorescence of the stained cells is converted into a digital electronic signal: the results are shown as a histogram in which the number of stained cells is plotted as a function of the intensity of the fluorescence. If the main peak of the DNA histogram centers around the 2C region and the overall DNA distribution is comparable to that of normal somatic cells the tumor is classified as diploid. Populations of cells with a DNA content dissimilar to that of normal cells are classed as aneuploid and these may be hypodiploid, hyperdiploid or tetraploid. The DNA index (DI) is calculated by dividing the modal DNA content of the tumor cells in G0/G1 phases of the mitotic cycle: diploid cells will therefore have a DI of 1 while aneuploid cells will have a DI of less than 1, more than 1 or, if tetraploid, 2.

The technique is not, however, without its pitfalls and difficulties and can detect DNA aneuploidy only if a significant proportion of the tumor cells have lost or duplicated several chromosomes. Other variables that have to be taken into consideration are the method of extraction and staining of the nuclei, delays in tissue fixation, intra- and inter-laboratory variability, the minimum number and proportion of tumor cells analyzed, the choice of the reference cell population, the program for debris correction and, very importantly, tumor heterogeneity.\(^9\)

**MATERIALS AND METHODS**

**Patient Population**

Patients who underwent surgical staging and/or tumor debulking for ovarian cancer with final histopathologic results of epithelial ovarian carcinoma were included in the study. The availability of representative paraffin blocks for flow cytometry analysis was added as an inclusion criterion. Other exclusion criteria were previous treatment with chemotherapy or radiotherapy and previous or concomitant malignant diseases.
Data Collection

The list and registry of epithelial ovarian cancer cases from January 2004 to June 2010 were obtained and reviewed from the surgico-pathologic census and weekly ward reports of the Department of Obstetrics and Gynecology. Tumor type was documented with the World Health Organization classification. Clinical data were obtained from the Medical Records Section, files from the Cancer Institute and files from the Surgical Pathology Census of the Department of Obstetrics and Gynecology. Clinical data were retrospectively analyzed and recorded. The patient characteristics retrieved were age, tumor size, intraoperative and final stage according to the International Federation of Gynecology and Obstetrics. Histopathologic reports, archival paraffin blocks and corresponding slides were retrieved from the Surgical Pathology Section. These were sent to the Histopathology/Immunology Section of another institution for review and tumor ploidy test using flow cytometry.

DNA Ploidy by Flow Cytometry and Analysis

A monodispersed cell suspension was prepared from physical and chemical disruption of 5 strips of 50 micron section from paraffin embedded tissue, previously microdissected for tumor cell enrichment. The resulting cell suspension was incubated simultaneously with RNAse to remove RNA and Propidium iodide for DNA staining. The tissue sections were deparaffinized using 3 cycles of xylene incubation and rehydrated with decreasing strengths of ethanol and final incubation in distilled water. The rehydrated sections were enzymatically digested with pepsin incubation at 37ºC for 45 minutes after mechanical disaggregation with a glass pestle. The sample was resuspended in RPMI, filtered using a membrane filter and stained with Bauer’s stain solution at 37ºC for 20 minutes. Room temperature Bauer’s salt solution was added and the sample was vortexed and stored at 4ºC until flow cytometric analysis.

Flow cytometric analysis of the cell suspension was performed with an excitation wavelength of 342-514nm and the resultant emission was measured at 610nm. DNA histograms were generated and analyzed for diploid and aneuploid peaks. Criteria for aneuploidy included the following:

1. Two or more distinct G0/G1 peaks with the second peak having a DNA index of 0.95 to 1.05.
2. Single G0/G1 peak with right-sided shoulder.
3. G2M peak over 10% of the total population.

Sample Size

To determine the required sample size for a proportion, three items were specified:

1. The desired level of confidence, usually 95% (Z = 1.645 for one tailed; Z = 1.96 for two tailed test) or 99% (Z = 2.326 for one tailed; Z = 2.576 for two tailed test)
2. The margin of error in the population proportion that is required.
3. An estimate of the population proportion.
   Formula: \[ n = \frac{p \times (1-p) \times \{ \frac{Z}{E} \}^2}{p \times (1-p) \times \{ \frac{Z}{E} \}^2} \]
   Where:
   \( p \) is the estimated proportion based on the pilot study/survey (70%)
   \( Z \) is the z score associated with the degree of confidence selected (95% = Z 1.96)
   \( E \) is the allowable error (E = 0.05).
   \[ n = 0.70 \times (1-0.70) \times (1.96/0.05)^2 \]
   \[ n = 0.21 \times (39.20)^2 \]
   \[ n = 0.21 \times (1536.64) \]
   \[ n = 322.69 \]
   \[ n = 323 \]

Thus, the study required 323 patients based on the incidence of aneuploidy in epithelial ovarian cancers of 70%, margin of error of 0.05 and confidence level of 95%.

Statistical Analysis

Descriptive statistics were used for the demographic data of the patient population and for the computation of the prevalence. A univariate and multivariate analysis were used to assess the factors (age, histologic type, stage, tumor size) with probable association with aneuploidy in epithelial ovarian cancers. Logistics regression analysis was performed to establish a predictive model for tumor ploidy.
This study was approved by the institutional technical and ethical review boards and the study was partially funded by the Philippine Obstetrical and Gynecological Society and National Institutes of Health.

RESULTS

The interim analysis of the study population consisted of 109 paraffin blocks divided as follows: 24 mucinous cystadenocarcinoma of low malignant potential (LMP), 24 mucinous cystadenocarcinoma, 2 serous cystadenocarcinoma of LMP, 24 serous cystadenocarcinoma and 25 endometrioid adenocarcinoma.

For the 24 patients with a final histopathologic result of mucinous cystadenocarcinoma, the mean age of patients was 39.05 years (range = 13 - 72 years of age). The most common symptom was an abdominal mass (100%) and increase in abdominal girth (100%). Other signs and symptoms experienced were as follows in decreasing order of incidence: anorexia and abdominal pain (31.25 %), weight loss (14.6 %), ascites (12.25 %), and edema (6.25%). Most of the cases had an intraoperative and final stage of IA (79.1 %). The remaining had a final stage of 1C (10.4%), IIIB (4.2%), IIIC (6.25%). The largest tumor size was 60cm in its widest diameter and the smallest was 12cm.

For the 26 patients with a final histopathologic result of serous cystadenocarcinoma, the average age of patients was 48.04. The range was from 27 to 69 years of age. The most common symptoms were abdominal mass (38.4%) and increase in abdominal girth (38.4%). Other signs and symptoms experienced were abdominal pain (19.2%) and gastrointestinal symptoms (3.8%). Most of the cases had an intraoperative and final stage of IC (30.7%). The remaining had a final stage of IC (10.4%), IIIA (2.1%), IIIB (4.2%), IIIIC (6.25%). The largest tumor size was 60cm in its widest diameter and the smallest was 12cm.

For the 25 patients with a final histopathologic result of serous endometrioid carcinoma, the average age of patients was 45.08. The range was from 29 to 64 years of age. The most common symptom was increase in abdominal girth (48%). Other signs and symptoms experienced were abdominal mass (36%), abdominal pain (12%) and gastrointestinal symptoms (4%). Most of the cases had an intraoperative and final stage of IC (40%). The remaining had a final stage of IA (4%), IIIC (12%), IIIB (8%), IIIIC (24% and IV (12%). The tumor size for < 10cm was 20%, 11-20cm, 60% and for >20cm, 20%.

DNA ploidy was obtained in all of the 109 paraffin-embedded blocks of epithelial cancers of the ovary (Table 1). Aneuploidy was established in 14 of the total 109 samples (12.8%) as follows: 2 from 24 mucinous cystadenocarcinoma (14.2%), 2 from 24 mucinous tumor of low malignant potential (14.2%), 5 from 29 serous cystadenocarcinoma (17%), and 5 from 30 endometrioid carcinoma (16%).

Table 1. DNA ploidy classification.

<table>
<thead>
<tr>
<th>Histopathologic Type</th>
<th>DNA Ploidy Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>22</td>
</tr>
<tr>
<td>Mucinous tumor of low malignant potential</td>
<td>22</td>
</tr>
<tr>
<td>Serous cystadenocarcinoma</td>
<td>24</td>
</tr>
<tr>
<td>Serous tumor of low malignant potential</td>
<td>2</td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>DNA Ploidy Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>59</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>25</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
</tr>
</tbody>
</table>

DISCUSSION

This is a study in which flow cytometric DNA analysis was carried out on epithelial tumors of the ovary in this tertiary institution. In this study, we investigated the DNA ploidy pattern in 109 epithelial tumors of the ovary (24 mucinous cystadenocarcinoma, 24 mucinous tumor of low malignant potential, 2 serous tumor of low malignant potential, 29 serous cystadenocarcinoma and 30 endometrioid adenocarcinoma. Though we have a small study population, our results have shown that patients with aneuploid tumors were older than those with diploid tumors. This finding was of no surprise, because ovarian cancer is most common in menopausal women over 45 years of age.11 Findings were also similar to that of the studies of Zangwill and Klemi, wherein patients with ovarian cancers with aneuploidy were older than those patients with diploid DNA.8,12

Our results also showed that the incidence of aneuploidy was higher in patients with serous
cystadenocarcinoma (17%) and endometrioid carcinoma (16%) compared to both mucinous cystadenocarcinoma (8.3%) and mucinous tumor of low malignant potential (8.3%). No aneuploidy was seen in the 2 patients with serous tumor of low malignant potential. This finding was not consistent with the study of Harlow, wherein the author concluded that only less than a third of patients with mucinous tumors of low malignant potential had aneuploidy. Patients with aneuploid type of mucinous tumor of low malignant potential had a poor survival rate than did those with their diploid counterparts and should be treated like a low grade epithelial ovarian cancer as mentioned in the study made by Ehen, et al.

According to Trope, nearly 80% of patients with advanced ovarian carcinoma are aneuploid and that aneuploidy was more frequent in tumors with poorly differentiated histologic type or nuclear atypia. The aneuploidy was seen in Stage IC (20%), IIC (20%), IIIIC (20%) and IV (20%). Majority of the advanced ovarian carcinoma did not demonstrate aneuploidy (IIIC- 31% and IV – 9.8%) With the limited population, aneuploidy cannot be associated yet with the variables on tumor size with aneuploidy. Several studies state that tumor aneuploidy has been seen to correlate with a poor prognosis of ovarian cancer both in advanced and early stage disease. It is therefore recommended that continuation of the study be done to correlate the DNA ploidy findings with patient survival to further confirm these findings in the local setting.

CONCLUSION

The interim analysis results of the study on tumor ploidy of epithelial tumors of the ovary revealed a prevalence of 12.8%. Results showed that the incidence of aneuploidy is higher for serous adenocarcinoma and endometrioid adenocarcinoma compared to mucinous tumors of low malignant potential and mucinous cystadenocarcinoma. No further association between clinicopathologic factors and tumor ploidy can yet be determined pending the recommended completion of this study.

REFERENCES

Occurrence of Pregnancy-Induced Hypertension Among Patients with Gestational Diabetes Mellitus: A Retrospective Review

MARIA YVETTE P. APOSTOL, MD AND BRENDA BERNADETTE P. BAUTISTA-ZAMORA, MD, FPOGS

Department of Obstetrics and Gynecology, Delos Santos-STI Medical Center

Gestational diabetes mellitus (GDM) and pregnancy-induced hypertension (PIH) are common but their correlation is not well understood.

Objective: Our objective was to determine the association of the occurrence of PIH among patients with GDM.

Methods: This was a retrospective study conducted among pregnant patients diagnosed with GDM. Chart review was done noting the occurrence of PIH, maternal characteristics including details on family history of hypertension and family history of diabetes and neonatal outcomes. Comparisons of the different variables under study were statistically analyzed.

Results: A total of 93 patients of 6,248 deliveries were diagnosed with GDM (0.015%) in which 16 women also developed PIH (17.2%). There was no significant difference in the age, gravidity, parity, age of gestation at diagnosis of GDM, and age of gestation on admission. There was a significant association between a patient’s family history of hypertension with the occurrence of PIH among GDM cases (OR 3.89, 95%CI 1.19-12.76, P=0.01). There was no significant difference in the manner of delivery (P=0.66), comparison of the APGAR scores, birthweight, and birthlength (P >0.05). However, there was a significantly greater proportion of small for gestational age (SGA) neonates among those with PIH and GDM (P=0.03). There was likewise a significantly longer NICU stay of neonates born of mothers with PIH and GDM (P=0.05).

Conclusion: The incidence of PIH among GDM patients is higher than the general population. Family history of hypertension predisposed a GDM patient to develop PIH. PIH in GDM predisposes to adverse neonatal outcomes.

Key words: gestational diabetes mellitus, pregnancy induced hypertension

Gestational diabetes mellitus (GDM) is a very common problem encountered in pregnant women. It occurs in 7% of all pregnancies.¹ It is a state of glucose intolerance and hyperinsulinemia.

Pregnancy induced hypertension (PIH), on the other hand, is another common disease entity encountered in pregnant women. It is a state of elevated blood pressure occurring in pregnancy, which may or may not be accompanied by proteinuria.

Glucose intolerance and high blood pressure during pregnancy are common and frequently occur together, and have been labeled as markers of vascular dysfunction.² Women with pre-existing alterations in insulin metabolism have exaggerated response to changes in angiogenic factors which may increase risk for pre-eclampsia.¹

GDM alone brings with it an array of consequences detrimental to both maternal and fetal well-being. This becomes more pronounced when it is coupled with PIH. Identifying risk factors involved in the development of PIH in GDM patients will go a long way in alerting the clinician for the probability of disease development. Therefore, complications, maternal and fetal, immediate and long-term, may be lessened, if not totally eliminated.

Objectives of the Study

General Objective

To determine the association of the occurrence of pregnancy induced hypertension among patients with gestational diabetes mellitus at a tertiary care private hospital.
**Specific Objectives**

1. To determine the incidence of pregnancy induced hypertension among patients diagnosed with gestational diabetes mellitus
2. To identify significant risk factors associated with the occurrence of pregnancy induced hypertension among patients diagnosed with gestational diabetes mellitus
3. To compare maternal and neonatal outcomes of patients with gestational diabetes mellitus, with and without pregnancy induced hypertension

**MATERIALS AND METHODS**

**Methodology**

This was a retrospective cohort study conducted among pregnant patients admitted and who delivered at a tertiary care private hospital from 2001 to 2006 with a diagnosis of gestational diabetes mellitus, as determined during prenatal care or upon admission. Patients included in the study were those diagnosed with GDM by 100g OGGT during prenatal check-up. Patients who have overt DM and/or chronic hypertensive vascular disease were excluded from the study. Also excluded from the study were pregnancies with other medical complications (e.g. thyroid disease, pulmonary disease, endocrine disorders).

Chart reviews were done, taking into account the following maternal characteristics: 1) age, 2) gravidity, 3) parity, 4) age of gestation on admission and delivery, and 5) age of gestation at diagnosis of GDM. The occurrence of PIH was noted in all cases of GDM in pregnancy. The type of PIH was likewise noted i.e. gestational hypertension, mild preeclampsia or severe preeclampsia. Details on family history of hypertension and family history of diabetes were also tabulated. Maternal outcome as to manner of delivery, cesarean or vaginal, was compared. Noted also were the following maternal outcomes 1) highest recorded systolic blood pressure, 2) highest recorded diastolic blood pressure and 3) protein spillage on urinalysis. Neonatal outcomes were recorded and these included 1) first minute APGAR score, 2) fifth minute APGAR score, 3) birthweight, 4) birthlength, 5) appropriateness for gestational age and 6) length of NICU stay.

Data were encoded and tallied in SPSS version 10 for windows. Descriptive statistics were generated for all variables. For nominal data, frequencies and percentages were computed. For numerical data, mean ± SD, the median and the range were generated. Comparison of the different variables under study was done using the following test statistics: 1) Mann Whitney U Test – a non-parametric equivalent of the t-test, comparing medians, instead of means of the two groups; 2) T-test–used to compare 2 independent measurements; 3) Chi-square test – used to compare/associate data; 4) Fisher’s exact test – a modification of chi-square test used to compare/associate nominal data in a 2x2 contingency table; and 5) Pearson correlation.

**RESULTS**

During the study period, 93 patients had gestational diabetes mellitus (GDM) among the 6,248 total deliveries giving an incidence of 0.015%. Among the patients with GDM, 16 patients (17.2%) developed pregnancy induced hypertension (PIH) while the rest of the 77 patients had no hypertensive complications of pregnancy.

Age range of the patients included in this study was at 21-43 years old, majority of whom were in the 30’s age group (64.5%). A quarter of the population (25.8%) was in their 20’s while a minority (9.68%) was in their 40’s. Forty six (49%) were primiparas, while the other half, 47 (51%) were multiparas. Most of the patients were term admissions (86%).

Table 1 shows the comparison of the different maternal characteristics/variables among GDM patients with or without PIH. The results showed that there was no significant difference in the comparison of the variables as proven by all P values >0.05. There was no significant difference in the age, gravidity, parity, age of gestation at diagnosis of GDM, and age of gestation on admission among patients with or without PIH.

Fifty nine (53%) of the patients were diagnosed with GDM at 24-28 weeks AOG, while 4 (4%) of the individuals included in the study were diagnosed earlier at ≤ 23 weeks AOG. Forty three percent of patients were diagnosed with GDM after their 28th week AOG. As to those who developed PIH, majority of the patients were diagnosed at ≥ 24 weeks AOG.

Table 2 shows that 17.2% of the patients with GDM developed PIH during pregnancy. Half of the PIH cases were severe preeclampsia followed by mild preeclampsia in 37% of cases and the rest were...
Table 1. Maternal characteristics of GDM patients with and without PIH.

<table>
<thead>
<tr>
<th>Maternal Characteristics</th>
<th>Pregnancy Induced Hypertension (PIH)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With PIH n=16</td>
<td>Without PIH n=77</td>
</tr>
<tr>
<td>Age</td>
<td>Mean ± SD 33.68 ± 6.29</td>
<td>32.54 ± 4.52</td>
</tr>
<tr>
<td>Gravida</td>
<td>Mean ± SD 2.62 ± 2.09</td>
<td>2.20 ± 1.48</td>
</tr>
<tr>
<td>Parity</td>
<td>Mean ± SD 1.18 ± 1.28</td>
<td>0.94 ± 1.29</td>
</tr>
<tr>
<td>AOG on Admission (weeks)</td>
<td>Mean ± SD 37.83 ± 2.31</td>
<td>38.47 ± 2.02</td>
</tr>
<tr>
<td>AOG at Diagnosis of GDM (weeks)</td>
<td>Mean ± SD 28.62 ± 4.38</td>
<td>28.64 ± 4.28</td>
</tr>
</tbody>
</table>

Table 2. Distribution of pregnant patients according to PIH.

<table>
<thead>
<tr>
<th>Occurrence of PIH, n=93</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>With PIH</td>
<td>16</td>
<td>17.2</td>
</tr>
<tr>
<td>Without PIH</td>
<td>77</td>
<td>82.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of PIH, n=16</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational HPN</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Pre-eclampsia, mild</td>
<td>6</td>
<td>37.5</td>
</tr>
<tr>
<td>Pre-eclampsia, severe</td>
<td>8</td>
<td>50.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AOG at diagnosis of PIH (weeks), n=16</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 weeks</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>21 - 25 weeks</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>26 - 30 weeks</td>
<td>8</td>
<td>50.0</td>
</tr>
<tr>
<td>31 - 36 weeks</td>
<td>3</td>
<td>18.8</td>
</tr>
<tr>
<td>&gt;36 weeks</td>
<td>1</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Mean ± SD = 27.56 ± 5.15

A family history of hypertension was noted in 49 (53%) of GDM cases and family history of diabetes was noted in 40 (43%) of GDM cases. Family history of both hypertension and diabetes was noted in 20 patients (22%).

Table 3 shows the association of the family history of hypertension and/or diabetes among GDM patients with and without PIH. Results showed that there was a significant association between a patient’s family history of hypertension with the occurrence of PIH among GDM cases (P=0.01). A patient with GDM has almost 4 times increased risk of developing PIH if there is maternal family history of hypertension, OR 3.89, 95%CI 1.19-12.76.

Of the 93 patients included in the study, 42 (45%) delivered operatively, the rest (55%) were able to deliver vaginally. Reasons for operative delivery included oligohydramnios, uncontrolled severe preeclampsia, macrosomia, fetal distress, poor obstetric history, repeat cesarean section, and other indications i.e. infertility, elderly primigravid, tumor previa, and malpresentation.

Table 3. Maternal characteristics of GDM patients with and without PIH.

<table>
<thead>
<tr>
<th>Family History</th>
<th>Pregnancy Induced Hypertension</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With PIH n=16</td>
<td>Without PIH n=77</td>
<td></td>
</tr>
<tr>
<td>Family History of HPN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With hypertension</td>
<td>13 (26.5%)</td>
<td>36 (73.5%)</td>
<td>49</td>
</tr>
<tr>
<td>Without hypertension</td>
<td>3 (6.8%)</td>
<td>41 (93.2%)</td>
<td>44</td>
</tr>
<tr>
<td>Family History of Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With diabetes</td>
<td>5 (12.5%)</td>
<td>35 (87.5%)</td>
<td>40</td>
</tr>
<tr>
<td>Without diabetes</td>
<td>11 (20.8%)</td>
<td>42 (79.2%)</td>
<td>53</td>
</tr>
</tbody>
</table>
Table 4 shows the comparison of the maternal outcome of GDM patients with or without PIH. Results showed that there was no significant difference in the proportion of mothers who delivered via cesarean delivery or vaginal delivery (P=0.66). The highest systolic and diastolic BP of mothers with PIH was 159.38 and 100.00, respectively. Among the 16 GDM patients with PIH, 13 (81.25%) had protein spillage, 2 (12.5%) had trace and 1 (6.3%) did not have protein spillage.

Table 5 shows the comparison of the neonatal outcomes among GDM patients with or without PIH. Results showed that there was no significant difference in the comparison of the APGAR scores at

<table>
<thead>
<tr>
<th>Maternal Outcome</th>
<th>Pregnancy Induced Hypertension</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With PIH n=16</td>
<td>Without PIH n=77</td>
<td></td>
</tr>
<tr>
<td>Manner of Delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean Delivery</td>
<td>8 (50%)</td>
<td>34 (44.2%)</td>
<td>42</td>
</tr>
<tr>
<td>Vaginal Delivery</td>
<td>8 (50%)</td>
<td>43 (55.8%)</td>
<td>51</td>
</tr>
<tr>
<td>Highest Systolic BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>159.38 ± 17.30</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Highest Diastolic BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>100.00 ± 10.32</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Protein Spillage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 (18.8%)</td>
<td>---</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>5 (31.2%)</td>
<td>---</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>5 (31.2%)</td>
<td>---</td>
<td>5</td>
</tr>
<tr>
<td>Trace</td>
<td>2 (12.5%)</td>
<td>---</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1 (  6.3%)</td>
<td>---</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonatal Outcome</th>
<th>Pregnancy Induced Hypertension</th>
<th>Without PIH n=77</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With PIH n=16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APGAR 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>7.86 ± 0.83</td>
<td>7.97 ± 0.90</td>
<td>0.67 (NS)</td>
</tr>
<tr>
<td>APGAR 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>9.20 ± 0.56</td>
<td>9.06 ± 0.41</td>
<td>0.29 (NS)</td>
</tr>
<tr>
<td>Birthweight (grams)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3123 ± 838</td>
<td>3170 ± 617</td>
<td>0.79 (NS)</td>
</tr>
<tr>
<td>Birthlength (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>48.33 ± 5.04</td>
<td>49.42 ± 2.72</td>
<td>0.44 (NS)</td>
</tr>
<tr>
<td>Appropriateness for gestational age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGA</td>
<td>3 (30.0%)</td>
<td>7 (70.0%)</td>
<td></td>
</tr>
<tr>
<td>AGA</td>
<td>9 (11.8%)</td>
<td>67 (88.2%)</td>
<td>0.03 (S)*</td>
</tr>
<tr>
<td>SGA</td>
<td>3 (60.0%)</td>
<td>2 (40.0%)</td>
<td></td>
</tr>
<tr>
<td>Length of NICU stay (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>4.94 ± 8.72</td>
<td>2.74 ± 4.05</td>
<td>0.05 (S)</td>
</tr>
</tbody>
</table>

* includes 2 cases of intrauterine fetal demise
Based on this study, the incidence of pregnancy-induced hypertension (PIH) among gestational diabetes mellitus (GDM) patients was remarkably higher than that reported as 0.012% only and likewise with an increasing trend for the past five years (2003-2007). In our institution, the incidence of GDM was doubly higher at 0.015%. Hypertension, on the other hand, complicated pregnancy in 5%-10% of cases. The local incidence of hypertensive complications in pregnancy was 0.012% only and likewise with an increasing trend from 2003-2007.

Gestational diabetes mellitus (GDM) complicates at least 7% of pregnancies. Local data based on the POGS Committee on National Statistics show that for the past five years (2003-2007), GDM was recorded in 0.007% of all deliveries only although with note of an increasing trend. In our institution, the incidence of GDM was doubly higher at 0.015%. Hypertension, on the other hand, complicated pregnancy in 5%-10% of cases. The local incidence of hypertensive complications in pregnancy was 0.012% only and likewise with an increasing trend from 2003-2007. Gestational diabetes and pregnancy-induced hypertension are common but their relation is not well understood. Joffe, et al. (1998) described women with GDM to have significantly increased risk of preeclampsia, RR 1.67, 95%CI 0.92-3.05 and pregnancy-induced hypertension complications, RR 1.48, 95%CI 0.99-2.22. Bryson, et al. (2004) reported that after adjustment for BMI, age, ethnicity, parity and prenatal care, GDM was associated with increased risk of severe preeclampsia (OR 1.5, 95%CI 1.1-2.1), mild preeclampsia (OR 1.5, 95%CI 1.3-1.8) and gestational hypertension (OR 1.4, 95%CI 1.2-1.6). Review of literature shows that the incidence of pregnancy-induced hypertension or PIH among GDM patients ranges from 6.1% to 19% with one report to be as high as 43%. Based on this study, in our institution for the same time period, the incidence of pregnancy induced hypertension complication GDM pregnancies was 17.2%. Earlier reports showed that the incidence of preeclampsia in GDM was similar to the rate in the general population at 9.6% and 9.2%, respectively. However, in more recent years the incidence became doubly higher among GDM cases than that in the general population at 6.1% vs 2.8%. In our study, the incidence of PIH among GDM patients was remarkably higher than that reported as the local incidence for the general population, 17.2% vs 0.012%, and about twice to three times higher than that reported in literature, 17.2% vs 5-10%.

An increase in insulin secretion and resistance are normal during pregnancy but the contribution of these factors to the pathophysiologic features of hypertension in pregnancy remains unknown. Although it is well known that GDM predisposes to subsequent NIDDM and that NIDDM is associated with a high incidence of essential hypertension, there is no direct clinical evidence that shows that GDM predisposes to future hypertension. In a prospective cohort study by Montoro, et al. (2005), they found out that women with GDM who developed preeclampsia had blood pressure levels that were significantly higher, although still in the normal range, than those who did not develop preeclampsia. Further explained that GDM and PIH are gestational disorders that are markers of vascular dysfunction for among women who have had transient diabetes during pregnancy and later redeveloped overt diabetes, cardiovascular risk was already elevated nearly four-fold before diagnosis, suggesting that a vascular risk in such women is at least partly independent of overt hyperglycemia.

On the other hand, there is growing evidence that hypertensive complications in pregnancy are related to insulin resistance and carbohydrate intolerance such as GDM. According to Thadani, et al. (2004), women with pre-existing alterations in insulin metabolism have exaggerated response to changes in angiogenic factors which increase the risk for preeclampsia. Roberts and Gamill (2006) explained that elevated insulin increases sympathetic tone and muscle blood flow and increases vascular smooth muscle growth, all of which work hand-in-hand, to cause vascular insults relevant to the development of hypertension in pregnancy. Increased insulin resistance can activate the sympathetic nervous system and lead to an increase in expression of receptors for endothelin, both of which can lead to increased blood pressure. Hyperinsulinemia can also induce hypertriglyceridemia causing endothelial dysfunction and reduction of prostacyclin production. Moreover, hyperglycemia is a unique metabolic state that attenuates endothelium-dependent vasodilation and can interfere with the nitric oxide availability. It can enhance vascular tone resulting in abnormal flow and hypertension.

Several clinical characteristics and variables have been evaluated in determining the association of pregnancy-induced hypertension and gestational diabetes mellitus. In a prospective study by Joffe, et
al. (1998), they reported that women with abnormal glucose tolerance or gestational diabetes had greater body mass index (BMI), upper arm circumference, and mean arterial blood pressure. These data were consistent with previous reports by other investigators who have demonstrated a positive correlation between increasing BMI and abnormalities in glucose metabolism in pregnancy. Moreover, the observation that blood pressure was increased at enrollment in women with elevated BMI was consistent with syndrome X in pregnancy.\(^7\)

Initially, Langer, et al. (2001) concluded that the incidence of preeclampsia in the GDM and non-GDM groups were similar and that based on their logistic regression analysis, there was no significant difference for the net effect of obesity, parity, insulin dose, maternal age and treatment modality.\(^13\)

However, in the succeeding years, Bryson, et al. (2003) reported that gestational diabetes was more strongly associated with PIH among women who received less prenatal care (OR 4.2 for eclampsia and OR 3.1 for severe preeclampsia, P<0.05 for both) and among black women (OR for eclampsia and preeclampsia together 3.9, P<0.05).\(^5\)

Further studies by Yogev, et al. (2004) showed that the GDM subjects who developed preeclampsia were significantly younger, had a higher nulliparity rate, were more obese, and gained significantly more weight during pregnancy. A comparison between patients with fasting plasma glucose (FPG) < 105 and FPG > 105 revealed that the rate of preeclampsia increased significantly (7.8% vs 13.8%; OR 1.81, 95%CI 1.3-2.51). In the logistic regression analysis, only pre-pregnancy BMI (OR 2.3, 95%CI 1.16-2.30) and severity of GDM (OR 1.7, 95%CI 1.21-2.38) were independently and significantly associated with an increased risk of preeclampsia.\(^18\)

According to Montoro, et al. (2005), those with preeclampsia were significantly taller (61.5±2.4 vs 60.1±2.3 in, P=0.003), were more often nulliparous (38% vs 16%, P=0.01) and had higher entry systolic blood pressure (112±10 vs 103±6.9 mmHg, P<0.0001) and diastolic blood pressure (64±9 vs 59±5 mmHg, P=0.002).\(^10\)

Phaloprakarn and Tangjitgamol (2009) developed a clinical model to assess the risk of preeclampsia in women with GDM. Based on their multivariate analysis, first trimester body mass index (BMI) ≥ 27kg/m^2 (P<0.001), GDM diagnosed within 20 weeks of gestation (P<0.001) and poor glycemic control (P<0.001) were associated with preeclampsia. When these three factors were incorporated into a risk-scoring model, the sensitivity, specificity and accuracy were high at 76.9% (95%CI 69.0-85.2), 92.8% (95%CI 85.9-98.1) and 84.9% (95%CI 79.2-90.5) respectively.\(^8\)

While GDM is a known risk factor for preeclampsia, based on a retrospective cohort study by Carr, et al. (2007) women with higher 1-hour OGCT results that are below the threshold for GDM testing and those with one abnormal OGTT value that does not meet GDM criteria also have a greater risk of preeclampsia suggesting an important role for maternal metabolic condition in the pathophysiology of preeclampsia.\(^19\)

In this investigative study, age, parity and age of gestation on diagnosis of GDM were the clinical factors initially evaluated. Results showed that none of them were statistically significant risk factors in the development of pregnancy induced hypertension among GDM patients. In contrast to the findings of Yogev, et al. and Montoro, et al. but similar to the findings of Langer, et al. age and parity were not significant risk factors in the development of preeclampsia among GDM patients. As to age of diagnosis of PIH among GDM patients, as compared to the study of Phaloprakarn and Tangjitgamol where it was significantly evident within 20 weeks age of gestation, our results showed that about half of the cases were diagnosed with PIH at a later gestation, 26 to 30 weeks. Only 12.5% of cases were diagnosed at less than 20 weeks age of gestation. It was a limitation of this retrospective review that not all records reviewed had complete data on the BMI, OGCT and OGTT results, glycemic status monitoring and other blood chemistry examinations.

Barden, et al. (2004) prospectively evaluated the factors predisposing women with GDM to preeclampsia. Their results showed that those who developed preeclampsia had elevated BMI, blood pressure, fasting glucose, insulin, uric acid, and C-reactive protein (CRP) which have all been linked with the “metabolic syndrome”. They had a greater degree of microalbuminuria and more frequently reported a family history of hypertension and maternal gestational diabetes. After logistic regression analysis, the significant independent factors for developing preeclampsia were fasting glucose, CRP, a family history of hypertension and the proband’s mother having gestational diabetes. The results suggest that, in GDM, increased severity of insulin resistance and related features of the “metabolic syndrome”, rather than lipid abnormalities, are precursors to the development of...
Pregnancy-Induced Hypertension Among Patients with Gestational Diabetes Mellitus / Apostol and Zamora

Complications of hypertensive disorders in pregnancy include preterm delivery, fetal growth restriction, placental abruption, and cesarean delivery, as well as increased risk for development of preeclampsia in a subsequent pregnancy, and development of chronic hypertension, postpartum. On the other hand, complications of GDM are fetal macrosomia, unexplained pregnancy losses in early gestation, intrauterine fetal demise, polyhydramnios, cesarean delivery, brachial plexus injury, and fetal malformations. In the neonate, it may predispose to respiratory distress, hypoglycemia, hypocalcemia, hyperbilirubinemia, and hypertrophic cardiomyopathy. Operative delivery for cephalopelvic disproportion, metabolic syndrome, persistent diabetes postpartum and its subsequent complications, preeclampsia, and infections make up the roster of maternal complications of gestational diabetes mellitus.

Perinatal outcome of hypertensive complications and GDM are well established but their combined effect on pregnancy outcome remains under investigated.

Stella, et al. (2004) studied the outcomes of pregnancies complicated by gestational hypertension alone, GDM alone and combined gestational hypertension and GDM compared with controls. After controlling for covariates, gestational hypertension significantly increased cesarean section rate (OR 1.62, 95%CI 1.47-1.78), rates of admittance to the neonatal intensive care (NICU) and birth of large for gestational age (LGA) infants. GDM significantly increased cesarean section rate (OR 1.42, 95%CI 1.21-1.66), rate of NICU admission (OR 1.32, 95%CI 1.0-1.75), birth of LGA infants (OR 1.51, 95%CI 1.14-1.98) and macrosomic infants (OR 1.53, 95%CI 1.12-2.08). Rates of LGA infants (OR 1.85, 95%CI 1.19-2.86) and cesarean section rate (OR 2.03, 95%CI 1.52-2.71) were significantly increased with gestational hypertension and GDM. They concluded that coexistence of gestational hypertension and GDM further increases adverse perinatal outcomes.

Contrary to Stella, et al. in this study, the comparison of the maternal outcome of GDM patients with or without PIH showed no significant difference in the proportion of mothers who delivered via cesarean delivery and vaginal delivery (P=0.66). There was no increase in cesarean rate. As to neonatal outcome, there was no significant difference in the comparison of the APGAR scores at 1 minute, APGAR scores at 5 minutes, birthweight, and birthlength (P>0.05). Remarkably opposite the results of Stella et al, in this study, there was significantly a greater proportion of neonatal outcomes small for gestational age (SGA) among those with PIH and GDM (P=0.03). There was likewise a significantly longer NICU stay of neonates born of mothers with PIH and GDM (P=0.05).

As compared to the outcomes in the study by Stella, et al., where there was an increased incidence of LGA infants, our study showed that there were more SGA infants among GDM patients with PIH. Glycemic control, hypertension control and vascular dysfunction through Doppler flow evaluation may explain such contrast. Poorer glycemic control often leads to increased LGA outcomes while inadequate hypertension control and increased vascular resistance lead to increased SGA outcomes.

CONCLUSION

In this investigative study, there were 93 patients with gestational diabetes mellitus (GDM) among the 6,248 total deliveries giving an incidence of 0.015%. Among the patients with GDM, 16 patients (17.2%) developed pregnancy induced hypertension (PIH). The incidence of PIH among GDM patients was remarkably higher than that locally-reported incidence for the general population, 17.2% vs 0.012%, and about twice to three times higher than that reported in literature, 17.2% vs 5-10%.

There was no significant difference in the age, gravidity, parity, age of gestation at diagnosis of GDM, and age of gestation on admission among patients with or without PIH. Results showed that there was a significant association between a patient’s family history of hypertension with the occurrence of PIH among GDM cases (P=0.01). A patient with GDM has almost 4 times increased risk of developing PIH if there is maternal family history of hypertension, OR 3.89, 95%CI 1.19-12.76.

As to maternal outcome, there was no significant difference in the proportion of mothers who delivered via cesarean delivery or vaginal delivery (P=0.66).
As to neonatal outcome, there was no significant difference in the comparison of the APGAR scores at 1 minute, APGAR scores at 5 minutes, birthweight, and birthlength (P>0.05). However, there was a significantly greater proportion of small for gestational age (SGA) neonates among those with PIH and GDM (P=0.03). There was likewise a significantly longer NICU stay of neonates born of mothers with PIH and GDM (P=0.05).

**RECOMMENDATIONS**

The investigators recommend that a prospective validation of the findings in this study be conducted in a multicenter local set-up so as to compare our results with those published in international literature. It is suggested that diagnostics be standardized, bases for diagnosis be recorded and glycemic and blood pressure monitoring be noted. Interestingly, blood chemistry and other serum markers should likewise be evaluated to correlate with the “metabolic syndrome.” A long-term post partum follow-up of both maternal and neonatal outcomes would eventually be warranted. Future results in such collaboration may lead to modifying identifiable risk factors and emphasize closer monitoring on specific markers to decrease maternal and neonatal morbidity.

**REFERENCES**

Clinical Variables Associated with Neonatal Infection After Prelabor Rupture of Membranes at Term: A Retrospective Review

RIN Y EMMYLENE KALALO, MD AND BRENADETTE P. BAUTISTA-ZAMORA, MD, FPOGS

Department of Obstetrics and Gynecology, Delos Santos-STI Medical Center

Objective: To determine the significant clinical variables associated with neonatal infection in prelabor rupture of membranes at term.

Methods: This was a retrospective cohort study of all patients with prelabor rupture of membranes at term. Inclusion criteria were as follows: singleton gestation, cephalic presentation, gestational age > 37 weeks, and ruptured membranes. Clinical variables evaluated included the following: cervical dilatation on admission, Bishop’s score, amniotic fluid characteristic during labor, use of antibiotics, use of oxytocin for induction/augmentation of labor, electronic fetal monitoring during labor, total number of internal examinations (IE) done, time interval from PROM to delivery, time interval from active labor to delivery, and manner of delivery. Outcome measure was neonatal infection, both probable and definitive neonatal infection.

Results: The incidence of neonatal infection among the 28 cases of term PROM in this study was 39%. Bishop’s score, total number of internal examinations done, time interval from PROM to delivery and time interval from active labor to delivery showed nearly statistically significant association with neonatal infection in the background that all cases underwent labor induction or augmentation and were given antibiotic prophylaxis. On multiple logistic regression analysis, only time interval from PROM to delivery showed statistically significant association with neonatal infection, OR 1.58, 95%CI 1.01-2.47.

Conclusion: When the clinical variables are analyzed all together, only the time interval from PROM to delivery showed statistically significant association with neonatal infection, suggesting that a time interval of >24 hours from PROM to delivery renders the neonate at about 1.58 times at increased risk of neonatal infection.

Key words: term, prelabor rupture of membranes, neonatal infection

Premature rupture of the membranes (PROM) at term poses a clinical problem, and management of this condition remains a matter of debate. Premature rupture of membranes results in an increase in pregnancy complications in both term and preterm gestations. The risk of infection after premature rupture of the membranes is of concern for both mother and fetus or neonate. The incidence of neonatal infection after membrane rupture of more than 24 hours is approximately 1%, and when clinical chorioamnionitis is present, the risk increases to 3% and 5%. According to Gerden, a 10-fold increase in neonatal infection has been noted in uncomplicated cases of premature rupture of the membranes.

There is a wide spectrum of clinical appearance in infants with infection, and the early and efficient diagnosis of neonatal bacteria sepsis remains difficult. Therefore, it is reasonable to determine among which neonates will infection most likely develop after premature rupture of the membranes, so that effective management of labor and delivery can minimize subsequent neonatal infection and allow a reduction in inappropriate use of antibiotics in the neonatal period.

Spontaneous prelabor rupture of membranes at term occurs in approximately 10%. The management of patients with PROM remains controversial. Induction of labor is undertaken after spontaneous amniorrhesis to prevent chorioamnionitis and neonatal sepsis, which occur with increased frequency with PROM existent more than 24 hours before delivery.
Objective

To determine the significant clinical variables associated with neonatal infection in prelabor rupture of membranes at term.

MATERIALS AND METHODS

This was a retrospective cohort study of all patients with prelabor rupture of membranes at term within the five-year study period from January 2003 to December 2007. Gestational age was determined according to the date of the last menstrual period preceded by regular cycles and confirmed by a physical examination and/or ultrasonography at less than 20 to 24 weeks if the last menstrual period was uncertain. All subjects were in-patients in the labor and delivery units of a tertiary hospital.

Inclusion criteria were as follows: 1) singleton gestation; 2) cephalic presentation; 3) gestational age > 37 weeks; 4) ruptured membranes confirmed by (a) gross pooling of amniotic fluid in the vaginal vault by sterile speculum examination, (b) positive nitrazine test; and (5) reactive fetal heart rate pattern on admission test.

Exclusion criteria included: 1) cervical dilatation in excess of 3cm; 2) documented regular uterine contractions or uterine contractions ≥ 4 in 20 minutes; 3) presence of any medical and perinatal complications e.g hypertension, diabetes, intrauterine growth restriction or macrosomia; 4) clinical evidence of cephalopelvic disproportion e.g. macrosomia or clinically contracted pelvis by clinical pelvimetry; 5) presence of contraindications to vaginal delivery e.g. placenta previa; 6) previous cesarean section or uterine surgery; 7) presence of meconium-stained amniotic fluid; 8) evidence of chorioamnionitis e.g maternal temperature of 100°F or higher or presence of uterine tenderness and/or foul-smelling amniotic fluid; 9) parity of 6 or more; and 10) use of epidural anesthesia for labor.

The admissions logbook, perinatal census and admission charts at the Department of Obstetrics and Gynecology were reviewed. A patient’s database form was filled up which included pertinent data such as maternal age, obstetric score, age of gestation on admission and both medical and obstetrical histories. Admitting physical examination findings and tocographic interpretation or assessment were likewise recorded. Data from the course of labor and the maternal and neonatal outcomes were extracted from the admissions chart.

The SPSS software package was used for statistical analysis. Categoric data were tested for significance using the chi squared or Fisher’s exact test. Continuous data were tested for significance using a 2-tailed Student t test. Multivariate logistic regression analysis was used to determine significant predictors of adverse perinatal outcomes. A P value of <0.05 indicates statistical significance. Odds ratios and 95% confidence intervals were calculated.

RESULTS

In this study, from January 2003 to December 2007, 28 cases of PROM at term were admitted at our institution. Eleven of the 28 cases or 39% had neonatal infection.

Among those admitted with a closed cervix, all three cases or 100% had neonatal infection on outcome. Among those admitted with 1-2cm cervical dilatation, 8 of 21 cases or 38% had neonatal infection. Among those admitted with 3cm cervical dilatation, all 4 cases or 100% had no neonatal infection on outcome. These differences were not statistically significant (P=0.106).

As to Bishop’s score on admission, among those with score <4, there were more cases with neonatal infection (7/13, 54% vs 6/13, 46%). Among those with score ≥5, there were more cases with no neonatal infection (11/15, 73% vs 4/15, 27%). The difference was nearly statistically significant (P=0.086).

When amniotic fluid characteristics during labor were compared, among those with clear amniotic fluid, neonatal outcomes were similar, 11/24 of cases or 46% had neonatal infection while 13/24 of cases or 54% had no neonatal infection. All four cases with thinly meconium-staining had no neonatal infection. This difference was not statistically significant (P=1.000).

There was use of antibiotics and use of oxytocin for induction or augmentation of labor for all cases.

There were near equal incidences of neonatal infection and no neonatal infection among those with reassuring fetal heart monitoring, 9/22 cases (41%) vs 13/22 cases (59%). Among those with non-reassuring fetal heart pattern there were still more cases with no neonatal infection, 4/6, 67% vs 2/6, 33%. This difference was not statistically significant (P=1.000).

As to total number of internal examinations done prior to delivery, among those with <3 to about
### Table 1. Univariate analysis

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>(+) Neonatal Infection (Definite &amp; Probable)</th>
<th>(-) Neonatal Infection</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical dilatation on admission</td>
<td></td>
<td></td>
<td>0.106</td>
</tr>
<tr>
<td>closed</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1-2cm</td>
<td>8</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>3cm</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bishop's score</td>
<td></td>
<td></td>
<td>0.086</td>
</tr>
<tr>
<td>&lt;4</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Amnitoic fluid characteristic during labor</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>clear</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Thinly meconium-stained</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Use of antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Use of oxytocin for induction/augmentation of labor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Electronic fetal monitoring during labor</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>&lt;3</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>5-6</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7-8</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;8</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Time of PROM to delivery</td>
<td></td>
<td></td>
<td>0.090</td>
</tr>
<tr>
<td>&lt;24 hours</td>
<td>7</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>&gt;24 hours</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Time of active labor to delivery</td>
<td></td>
<td></td>
<td>0.074</td>
</tr>
<tr>
<td>&lt;6 hours</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6-12 hours</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>&gt;12 hours</td>
<td>6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Manner of delivery</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Vaginal</td>
<td>7</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Multiple logistic regression analysis.

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Coef</th>
<th>St Dev</th>
<th>Z</th>
<th>P</th>
<th>Odds Ratio</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-2.466</td>
<td>6.498</td>
<td>-0.38</td>
<td>0.704</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bishop's score</td>
<td>-1.415</td>
<td>1.504</td>
<td>0.94</td>
<td>0.347</td>
<td>0.24</td>
<td>0.01</td>
<td>4.63</td>
</tr>
<tr>
<td>Number of IEs</td>
<td>0.2419</td>
<td>0.3590</td>
<td>0.67</td>
<td>0.500</td>
<td>1.27</td>
<td>0.63</td>
<td>2.57</td>
</tr>
<tr>
<td>Time of PROM to delivery</td>
<td>0.4582</td>
<td>0.2283</td>
<td>2.01</td>
<td>0.045</td>
<td>1.58</td>
<td>1.01</td>
<td>2.47</td>
</tr>
</tbody>
</table>

Log-Likelihood = -5.376
Test that all slopes are zero: G = 18.312, DF = 3, P-Value = 0.000
5-6 times, there were more cases with no neonatal infection on outcome, 60-83% vs 17-40%. Among those with 7 to >8 times total number of internal examinations, there were more cases with neonatal infection, 50-75% vs 25-50%. This difference was nearly statistically significant (P=0.100).

There were more cases with no neonatal infection among those with ≤24 hours time interval from PROM to delivery, 14/21, 67% vs 7/21, 33% as compared to more cases of neonatal infection among those with >24 hours time interval from PROM to delivery, 4/7, 57% vs 3/7, 43%. This difference was nearly statistically significant (P=0.090).

When the time intervals from active labor to delivery were compared, all cases <6 hours had neonatal infection while 5 of 7 cases or 71% of those with time interval of 6-12 hours and 14 of 21 cases or 67% of those >12 hours had no neonatal infection. These differences were nearly statistically significant (P=0.074).

As to manner of delivery, there remained to be more number of cases with no neonatal infection in both vaginal (11/18, 61%) and abdominal (6/10, 60%) deliveries.

Table 1 shows that by univariate analysis none of the clinical variable evaluated were statistically significant. Only the Bishop’s score on admission, total number of internal examinations done, time interval from PROM to delivery and time interval from active labor to delivery were nearly statistically significant.

Variables reaching near significance were entered into a logistic regression model to determine the independent predictors of neonatal infection. Four variables were initially included in the model, but stepwise regression analysis showed that the variable time interval from active labor to delivery did not improve the model and thus was dropped from the analysis. The final variables entered into the model were the following: 1) Bishop’s score, 2) total number of internal examinations done, and 3) time interval from PROM to delivery. All these variables were entered as continuous variables to allow more variations in their values.

Table 2 showed that after multivariate analysis or taking all variables into consideration at the same time, the time interval from PROM to delivery was the only significant clinical variable which predicted neonatal infection, P=0.045, with an odds ratio of 1.58, 95%CI 1.01-2.47.

DISCUSSION

Premature rupture of membranes (PROM) is fairly common occurring in 2%-18% of pregnancies. At the Philippine General Hospital, the annual incidence ranges from 2.1%-2.4% of obstetric admissions or about 125 cases per year. For 1995, the admission rate for PROM was 157 out of 5648 deliveries or a cumulative incidence of 2.8%. Data from the American College of Obstetricians and Gynecologists also state an increasing rate of about 17% through the years. PROM most frequently occurs at term (37 weeks age of gestation or more), with the overall incidence of PROM at term being 8%.

At term, labor follows PROM within 24 hours in 90% of cases. PROM also influences the duration and course of labor. Generally, there is a moderate shortening of the first stage but no effect on the duration of the second stage with rupture of membranes in contrast to labor with intact membranes.

PROM at term is known to be associated with over distension of the uterus due to multiple pregnancy, polyhydramnios, cigarette smoking, altered mechanical properties of the amniotic membranes, frequent digital examinations, coitus and infection although it is not clear if these are causally related. PROM may result in immediate risks such as cord prolapse, cord compression, placental abruption, use of interventions such as cesarean and instrumental vaginal delivery and later problems such as maternal or neonatal infections as well.

Expectant management of term PROM has been associated with maternal infections such as chorioamnionitis and endometritis. These infections may result in neonatal infection and mortality, chronic lung disease and cerebral palsy as well as serious morbidity for the mother.

In this study, the primary outcome measure was presence or absence of neonatal infection, be it a probable or definitive neonatal infection. The incidence of neonatal infection in this study among cases with PROM at term was 39%. Clinical variables such as cervical dilatation on admission, Bishop’s score, amniotic fluid characteristic, use of antibiotics, use of labor induction/augmentation, fetal heart rate monitoring, number of internal examinations done, time interval from PROM to delivery, time interval from active labor to delivery and manner of delivery were evaluated to determine which will be significantly associated with neonatal infection.
In a review of six trials where all women had an unfavorable cervix,\textsuperscript{21-24} with the remaining trials either having a mixture of women with unfavorable and favorable cervixes\textsuperscript{27,28} or not reporting cervical state,\textsuperscript{29,32} an insufficiently ripe cervix resulted in increased length of labor and failed induction requiring cesarean section. For the favorable cervix, there is a greater chance of success for vaginal delivery after induction and others have shown no benefit in delaying induction.\textsuperscript{31} A delayed induction > 24 hours or more is to be abandoned because it may be associated with increased maternal and neonatal infection.\textsuperscript{31}

In this study, all PROM at term cases underwent induction and/or augmentation of labor upon admission. Similar to the results of previous trials, those admitted with a closed cervix had neonatal infection while those with at least a 3 cm cervical dilatation did not manifest neonatal infection on outcome. As to Bishop’s score on admission, those with a more favorable cervix had lesser incidence of neonatal infection as compared to those with a more favorable score. This difference in Bishop’s score on admission was nearly statistically significant.

Hannah, et al. have found that intrapartum antibiotic chemoprophylaxis will decrease the risk of maternal-fetal transmission and the risk of symptomatic group B streptococci infection in the newborn.\textsuperscript{33} Hannah, et al. mentioned treatment of women and infants with antibiotics was left to the judgment of the clinician, but intrapartum maternal chemoprophylaxis was recommended if the mothers were known to have positive cultures for group B streptococci or if there were signs of clinical chorioamnionitis.\textsuperscript{12} Mercer and Artheart concluded that the use of prophylactic antibiotics in patients with PPROM resulted in a longer latent period and in reduction in maternal infection including both chorioamnionitis and endometritis. Fetal and neonatal benefit is also seen, including lower rates of sepsis, pneumonia and intraventricular hemorrhage.\textsuperscript{12} In this study, cultures for group B streptococci were not routinely done yet all cases of PROM were given prophylactic antibiotics.

All cases of PROM included in this study underwent induction and/or augmentation of labor upon admission. Oxytocin infusion was recommended as the gold standard management of PROM at term in a recent review.\textsuperscript{7} Planned management with methods such as oxytocin or prostaglandin reduces the risk of some maternal infectious morbidity without increasing cesarean sections and operative vaginal births. Fewer infants were admitted to neonatal intensive care under planned management although no differences were seen in neonatal infection rates between planned and expectant management.\textsuperscript{34} These results are in contrast to the findings of Guise, et al. who reported that induction of labor results in increased frequency of chorioamnionitis, neonatal sepsis, cesarean section and longer duration of hospitalization.\textsuperscript{35} On the other hand, Mozurkewich and Wolf highlighted the risks and benefits of induction of labor, with reduced rates of chorioamnionitis, endometritis and neonatal infection, but still with increased number of cesarean births.\textsuperscript{36} Results of this study however revealed that the manner of delivery did not affect the incidence of neonatal infection.

Hannah, et al. compared immediate induction of labor with either oxytocin or prostaglandin E\textsubscript{1} gel versus expectant management up to 4 days. There were no differences in the rates of cesarean section or neonatal sepsis among the groups. However, chorioamnionitis and postpartum fever were less likely in the group managed with immediate induction with oxytocin.\textsuperscript{33} Crane, et al. mentioned that oxytocin infusion was recommended as the gold standard management of PROM at term in a recent review.\textsuperscript{7} Oxytocin is the most commonly used agent for labor induction in patients with PROM although several studies have also demonstrated the safety of using prostaglandin compounds in the face of PROM.\textsuperscript{37} Zeevi, et al. studied the effect of PROM in fetal heart rate patterns and found that PROM was associated with increased fetal heart rate reactivity.\textsuperscript{38} Vintzeleos, et al. determined the value of NST in predicting infection in the outcome of pregnancy in PROM, as reflected by the development of clinical amnionitis and/or neonatal sepsis. The sensitivity and specificity of NST in predicting infection among patients with PROM were 78% and 86%, respectively. A non-reactive NST or fetal tachycardia had the most significant correlation with infection.\textsuperscript{39} Rousis, et al. also found a significant association between non-reactive NST and subsequent development of infection in patients with PROM.\textsuperscript{40} In a local study by Gonzales and Macaranas, NST had a 78% sensitivity and 86% specificity in predicting infection.\textsuperscript{41}

In this study, there were near equal incidences of neonatal infection and no neonatal infection among those with reassuring fetal heart monitoring. Among those with non-reassuring fetal heart pattern there were still more cases with no neonatal infection although this difference was not statistically significant.
Hannah, et al. mentioned in their study that the number of vaginal examinations and the duration of active labor are the most important predictors of clinical chorioamnionitis. Digital vaginal examinations should be avoided until labor is initiated; however, fetal presentation should be documented to avoid discovering malpresentation of the fetus long after admission for rupture of membranes. 

In this study, as to total number of internal examinations done prior to delivery, among those with <3 to about 5-6 times, there were more cases with no neonatal infection on outcome. Among those with 7 or more times total number of internal examinations, there were more cases with neonatal infection. Thus, the more internal examinations done during labor of PROM patients, at 7 times and more, the greater is the incidence of neonatal infection. This difference was nearly statistically significant.

Risk of neonatal infection increases as the duration of rupture of membranes becomes prolonged. Many clinicians have aggressively managed term patients by inducing labor with oxytocin shortly after PROM in an effort to shorten the interval between rupture and delivery. The risk of maternal and fetal infection increases proportionally with the time between membrane rupture and birth. 

The longer a woman remains undelivered with ruptured membranes, the higher the likelihood of chorioamnionitis and subsequent neonatal infection.

Mozurkewich and Wolf described the risks and benefits of induction of labor showing reduced rates of chorioamnionitis, endometritis and neonatal infection but with increased number of cesarean births. Kappy, et al. reported excessive or higher rates of cesarean delivery in such cases where active intervention was done compared with those managed by observation. Whether or not to induce labor may depend on the state of the cervix. An insufficiently ripe cervix results in increased length of labor and failed induction of labor requiring cesarean section.

Some reports have suggested that the risk of maternal and fetal infection increases proportionally with the time between membrane rupture and birth. Hallak, et al. found that with a longer interval from admission to the onset of labor, there is an increased incidence of neonatal intensive care unit admission, cesarean rates and more frequent maternal diarrhea and use of analgesia or anaesthesia.

Johnson, et al. reported increased perinatal mortality and intrapartum fever in women at term when there was delay of more than 72 hours between rupture of membranes and birth. The incidence of neonatal infection after membrane rupture of more than 24 hours is approximately 1% and when clinical chorioamnionitis is present, the risk increases to between 3% to 5%. A ten-fold increase in neonatal infection has been noted in uncomplicated cases of premature rupture of the membranes compared with the general neonatal population. According to Gerden, et al., risk factors that increase the risk of neonatal infection in a mother with group B streptococcal colonization include premature rupture of the membranes >18 hours, maternal fever during labor and prematurity.

Similar to review of literature, results of this study showed that there were more cases with no neonatal infection among those with ≤24 hours time interval from PROM to delivery as compared to more cases of neonatal infection among those with >24 hours time interval from PROM to delivery. This difference was nearly statistically significant. Moreover, on multiple logistic regression analysis, time interval from PROM to delivery was the only significant clinical variable which predicted neonatal infection (P=0.045) with an odds ratio of 1.58, 95%CI 1.01-2.47 suggesting that a time interval of >24 hours from PROM to delivery renders the neonate at about 1.58 times at increased risk of neonatal infection.

CONCLUSION

In this study, among the clinical variables evaluated in PROM at term cases only Bishop’s score, total number of internal examinations done, time interval from PROM to delivery and time interval from active labor to delivery showed nearly statistically significant association with neonatal infection in the background that all cases underwent labor induction or augmentation and were given antibiotic prophylaxis.

Among term PROM cases, the more favorable the cervix is on admission, the lesser the incidence of neonatal infection. The more internal examinations done during labor, at 7 times or more, the higher the incidence of neonatal infection. Time interval >24 hours from PROM to delivery showed increased incidence of neonatal infection as well. This suggests that the risk of intrauterine infection increases with the duration of PROM.

However, on multiple logistic regression analysis or when the clinical variables are analyzed all together, only the time interval from PROM to delivery showed
statistically significant association with neonatal infection, OR 1.58, 95% CI 1.01-2.47, suggesting that a time interval >24 hours from PROM to delivery renders the neonate at about 1.58 times at increased risk of neonatal infection.

**RECOMMENDATIONS**

Results of this study suggest that clinicians should carefully evaluate the Bishop’s score on admission of term PROM cases, be conscientious of the number of times internal examinations are done and take into consideration the time interval from PROM to expected time of delivery in correlation with other clinical findings.

The investigators would like to recommend a prospective multi-center validation of the findings in this study taking into consideration other maternal clinical variables as well such as antenatal course, smoking history, previous history of infection and Group B streptococcus culture. As to outcome measures, both maternal and neonatal outcomes in terms of infection may be evaluated. Based on the incidence of 39% neonatal infection in this study among term PROM cases, a greater number of subjects may be recruited to obtain a greater power of the study for a conclusive recommendation.

**REFERENCES**


34. Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more) (Review) Copyright © 2008 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.


The Terrible 3s: Three-Cell Type Malignant Mixed Germ Cell Ovarian Tumor in a Woman with Gonadal Dysgenesis*

MARNIE ANN ESPRITU-CONCEPCION, MD; SABRINA ANG-SY, MD, FP OGS AND AIDA J. BAUTISTA, MD, FP OGS

Department of Obstetrics and Gynecology, Manila Doctors Hospital

A three-cell type malignant mixed germ cell tumor of the ovary is very rare neoplasm. Presently, there has been no reported incidence of three-cell type mixed germ cell tumor in the literature. Malignant germ cell tumors comprise less than 5% of all ovarian neoplasms. Mixed germ cell tumors constitute 10% of these tumors, most of which have only two elements.

This is a case report of a 22-year old, nulligravid, who presented with hypogastric pain and increased abdominal girth. Clitoromegaly was noted at puberty. Patient has normal secondary sexual characteristics and menarche. A large multi-septated cystic abdominal pelvic mass was seen on ultrasound. Intraoperatively, the left ovary was transformed into a solid tumor measuring 13.5cm x 7cm x 7cm, dangling separately from the left fallopian tube, such that a left oophorectomy was performed instead of the usual salpingo-oophorectomy. The uterus was hypoplastic. A thin, white, fibrous tissue inferior to the right fallopian tube was seen, which may represent the right ovary, signifying gonadal dysgenesis. For the purpose of staging, peritoneal fluid cytology, bilateral lymph node dissection, infracolic omentectomy, liver and para-aortic lymph node palpation were also performed. Final histopathologic diagnosis was malignant mixed germ cell tumor comprising three elements, endodermal sinus tumor (70%), dysgerminoma (25%) and embryonal carcinoma (5%). Patient was diagnosed to have malignant mixed germ cell tumor, left ovary, stage IA; hypoplastic uterus; gonadal dysgenesis, right. Adjuvant chemotherapy was advised due to the aggressive nature of the predominant cell type. Reproductive function is further compromised in the presence of hypoplastic uterus and gonadal dysgenesis.

Key words: Malignant mixed germ cell tumor, dysgerminoma, embryonal carcinoma, endodermal sinus tumor, clitoromegaly, gonadal dysgenesis.

Malignant mixed germ cell tumor is combination of two or more histologic types. It occurs in 10 percent of patients with germ cell tumor. The most common components of a mixed malignancy was dysgerminoma, which occurred in 80%, followed by endodermal sinus tumor in 70%, immature teratoma in 53%, choriocarcinoma in 20%, and embryonal carcinoma in 16%. The most frequent combination was a dysgerminoma and an endodermal sinus tumor. Mixture of three elements is uncommon.

The combination of malignant mixed germ cell tumor of the ovary, gonadal dysgenesis and hypoplastic uterus is indeed a rare occurrence, compromising the reproductive function of a young nulligravid woman.

THE CASE

A 22 year old, female, nulligravid, from Batangas, was admitted to our institution for the first time on February 26, 2010, due to hypogastric pain.

Past medical and personal social histories were unremarkable. Patient has a 25-year old sibling, with hypoplastic uterus and with irregular menstruation. Menarche was at 13 years old. Patient has irregular menstruation occurring every two to three months, characterized as spotting, lasting 2 to 4 days, with no dysmenorrhea. Last menstrual period was during first week of December 2009, while previous menstrual period was in October 2009. Patient had her thelarche and pubarche at 11 and 12 years old, respectively. Patient started to have gradual clitoral enlargement at 13 years old.

Patient had her coitarche at 19 years old, with one partner whom she claimed to be monogamous. Patient has never experienced dyspareunia.
Six months prior to admission, patient started to have colicky, intermittent, non-radiating hypogastric pain, 5/10 in intensity, not related to menstruation. Patient also had increased abdominal girth as manifested by tightening of her clothes. There were neither complaints of pelvic heaviness, bloatedness, palpable mass nor bowel and bladder habit changes. No consultation was done nor medication taken.

Three weeks prior to admission, due to the persistence of symptoms, patient decided to seek consult with a general physician. Pelvic examination was not done. Pelvic ultrasound revealed a 7.7cm x 6.2cm cystic mass with multiple septations located on the right adnexa, superior to the uterus. The impression then was a right ovarian cyst so patient was advised gynecologic consult.

Two weeks prior to admission, patient consulted with a gynecologist. There was a palpable mass on internal examination, however, the size and the location were unknown to patient. Transvaginal ultrasound showed a multi-septated cystic mass measuring 11.5cm x 8.4cm x 8.6cm, located superoanterior to the uterus. It exhibited low to medium level echoes with papillary excrescences measuring 1.1cm x 0.9cm. Its capsule and septum measured 0.4 cm and 0.3 cm, respectively. It had a Sassone score of 10 and Lerner of 5. The impression was abdominopelvic cystic mass, to consider ovarian newgrowth of borderline malignancy. Patient was advised surgery but she opted to seek second opinion.

One week prior to admission, patient consulted at our outpatient department. Surgical management was recommended, hence she was admitted.

Review of systems was unremarkable.

On admission, vital signs were stable. Patient has normal breast development with single contour of breast and areola (Tanner stage 5). On abdominal examination, there was a palpable, slightly movable, non-tender hypogastric mass 12cm from the symphysis pubis, deviated to the right. Patient has clitoromegaly with normal pubic hair growth (Tanner stage 5) (Figures 1 & 2). Speculum examination showed that cervix was small, flushed to the wall, pink, smooth, with minimal, non-foul smelling whitish discharge. Internal examination revealed that the cervix was firm, small, flushed to the wall, non-tender, deviated to the left; corpus was small and non-tender, with a 10cm x10cm doughy to cystic, movable, non-tender abdominopelvic mass, anterior to the uterus, more on the right hemi-abdomen. There was no adnexal mass or tenderness on the left.

Transvaginal ultrasound showed a multi-septated cystic mass measuring 11.5cm x 8.4cm x 8.6cm, located superoanterior to the uterus. It had low to medium level echoes with papillary excrescences measuring 1.1cm x 0.9cm. Its capsule and septum measured 0.4 cm and 0.3 cm, respectively. It had a Sassone score of 10 and Lerner of 5. Both ovaries were not visualized. The uterus was anteverted, deviated to the right, measuring 5.5cm x 3.1cm x 3cm with homogenous echopattern. It had an endometrial stripe of 0.2 cm on Day 70 of the cycle with intact subendometrial halo. Impression was an abdominopelvic cystic mass probably ovarian new growth of borderline malignancy (Figure 3).

On exploration of the abdomen, there was approximately 30cc of serosanguinous fluid noted which was sent for cytology. The left ovary was converted into a large, predominantly solid, tan to
gray mass, bosselated, and intact capsule, measuring 13.5 cm x 7 cm x 7 cm, occupying the abdominopelvic cavity (Figure 4). There were filmy adhesions noted between the left ovarian mass and the omentum. The right ovary was not visualized; instead, a white thin fibrous tissue measuring 4 cm x 0.4 cm was seen inferior to the right fallopian tube. Both fallopian tubes were seen, both with fimbriated ends. The uterus was hypoplastic which measured 3 cm x 2 cm x 1 cm (Figure 4). Since the left ovarian tumor was dangling separately from the left fallopian tube, left oophorectomy was performed instead of the usual salpingo-oophorectomy (Figure 5). The specimen was then sent to histopathology for frozen section. On cut section, it contained partly solid and partly cystic areas. The solid component had focal necrotic portion, with areas of gritty calcification, while the cystic component contained serous fluid. Its capsule was 0.2 cm to 0.3 cm thick, with papillary excrescences on its inner wall (Figure 6). Frozen section revealed malignant mixed germ cell tumor vs sex cord stromal tumor. Due to this histopathologic finding, patient underwent bilateral pelvic lymph node dissection, infracolic omentectomy, liver and para-aortic lymph node palpation. Harvested lymph nodes were not suspicious of malignancy. The liver had smooth surface on palpation. There were no palpable para-aortic lymph nodes. Incidentally, patient had a 9 cm congested appendix so appendectomy was done (Figure 7).

Figure 3. Transvaginal ultrasound- A multi-septated cystic mass measuring 11.5 cm x 8.4 cm x 8.6 cm, located superoanterior to the uterus, with low to medium level echoes and papillary excresences measuring 1.1 cm x 0.9 cm, with its capsule 0.4 cm and its septum 0.3 cm. (Sassone score of 10 and Lerner of 5)

Figure 4. The right ovary is not visualized, instead a thin white fibrous tissue (gray arrow) measuring 4 cm x 0.4 cm is noted inferior to the right fallopian tube (white arrow). Left fallopian tube (slim arrow) is seen, with fimbriated end. The uterus (black arrow) is hypoplastic measuring 3 cm x 2 cm x 1 cm.

Figure 5. Left ovarian mass- A large, predominantly solid, tan to gray mass, with nodular surface, measuring 13.5 cm x 7 cm x 7 cm, occupying the abdominopelvic cavity. Left oophorectomy is done by triple clamping the infundibulopelvic ligament (black arrow).

Figure 6. Cut section of the left ovarian mass shows partly solid (white arrow) and partly cystic areas (gray arrow), with yellow white focally necrotic areas that have focal gritty calcification while the cystic component contains straw to somewhat watery fluid.
Microscopic examination of the left ovary revealed hemorrhagic and necrotic neoplasm consisting of microcystic spaces with pseudopapillary patterns and loose myxoid areas (Figure 8). In several areas, tumor cells were draped around central blood vessels known as the Schiller Duval bodies (Figure 9). Hyaline globules were also noted (Figure 10). These findings were consistent with endodermal sinus tumor comprising 70% of the ovarian tumor.

In a minority of areas, tumor cells were separated by thick fibrous septa infiltrated by chronic inflammatory cells, which were monotonous in appearance with abundant pale cytoplasm and fairly uniform nuclei. These findings were consistent with dysgerminoma comprising 25% of the ovarian tumor (Figure 11). Tumor cells with primitive-looking nuclei lining irregular gland-like spaces were also seen, consistent with embryonal carcinoma comprising 5% of the ovarian tumor (Figure 12). A combination of three germ cell types makes it a mixed germ cell tumor. All four lymph nodes (Figure 13), omentum (Figure 14) and peritoneal fluid cytology were negative for malignancy. Lymphoid hyperplasia was seen in the appendix (Figure 15).

The final diagnosis was malignant mixed germ cell tumor, left ovary, stage IA; hypoplastic uterus; gonadal dysgenesis, right ovary.

Patient had an unremarkable postoperative course. Levels of serum testosterone and Ca 125 were normal. Serum alpha fetoprotein was elevated at 3,340ng/ml (Table 1). Upon discharge, patient was advised adjuvant chemotherapy 5-day course of bleomycin, etoposide, and cisplatin (BEP). Karyotyping, serum FSH and estradiol were requested for further evaluation of the hypoplastic uterus and streaked right ovary. However, patient refused...
Figure 11. Tumor cells are separated by thick fibrous septa infiltrated by chronic inflammatory cells. The cells are monotonous in appearance with abundant pale cytoplasm and fairly uniform nuclei consistent with dysgerminoma.

Figure 12. Tumor cells with primitive-looking nuclei lining irregular gland-like spaces (arrow). Numerous mitotic figures are seen. (consistent with embryonal carcinoma).

Figure 13. Left external and internal iliac, right obturator and internal iliac lymph nodes with no malignant cells.

Figure 14. Omentum with no malignant cells identified.

Figure 15. Lymphoid hyperplasia is seen in the appendix.
further blood examinations and did not comply with chemotherapy. As of July 2010, five months after surgery, patient is asymptomatic but with no resumption of menstruation.

**DISCUSSION**

**Epidemiology**

Ovarian germ cell neoplasms are derived from the primitive germ cells of the embryonic gonad. They are the second most frequent ovarian neoplasm and account for approximately 15% to 20% of all ovarian tumors. Malignant germ cell tumors comprise less than 5% of all ovarian neoplasms. Among the malignant germ cell tumors, the most frequent is the dysgerminoma, which accounts for approximately 45%. The endodermal sinus tumor or yolk sac tumor, comprises 10% of the malignant germ cell tumors. Less common germ cell tumors are embryonal carcinoma, immature teratoma, choriocarcinoma, polyembryomas and mixed germ cell tumor. Mixed malignant germ cell tumors of the ovary are a combination of the different types, usually of 2-cell type. There is no reported incidence specific to a mixture of 3-cell type in the literature. In one series, the most common component of a mixed malignancy was dysgerminoma, which occurred in 80%, followed by endodermal sinus tumor in 70%, immature teratoma in 53%, choriocarcinoma in 20%, and embryonal carcinoma in 16%. The most frequent combination was a dysgerminoma and an endodermal sinus tumor, accounting for one third of the cases. In our case, the mixture was that of 3-cell type, predominantly endodermal sinus tumor (70%) with embryonal carcinoma (5%) and dysgerminoma (25%).

Malignant germ cell tumors are normally not hereditary, although familial cases have been reported rarely.

**Clinical Manifestations**

Majority of the patients with germ cell tumors present with abdominal pain, abdominal distention or a pelvic mass. In contrast to the relatively slow-growing epithelial ovarian tumors, germ cell malignancies grow rapidly. Subacute abdominal pain is the most common symptom and reflects the rapid growth of a large, unilateral tumor undergoing capsular distention, hemorrhage, or necrosis. This symptom was manifested in our patient.

In advanced disease, ascites may develop causing further abdominal distention. Menstrual irregularity may be present because of the hormonal changes that accompany these tumors. Embryonal carcinoma may secrete estrogen, causing signs of precocious pseudopuberty or irregular bleeding. Although most individuals note one or more of these symptoms, one quarter of individuals are asymptomatic, and a pelvic mass is noted incidentally during physical or sonographic examination.

**Diagnosis**

Human chorionic gonadotropin, lactate dehydrogenase and alpha fetoprotein are secreted by some germ cell malignancies, therefore their presence may prove useful in the diagnosis and the monitoring of the response to treatment. Human chorionic gonadotropin is secreted by pure choriocarcinoma and dysgerminoma. Measurement of lactate dehydrogenase is informative for patients with dysgerminomas. Alpha fetoprotein is high in patients with endodermal sinus tumor and some embryonal carcinoma. In our patient, serum alpha fetoprotein was elevated, which is consistent with the predominance of the endodermal sinus tumor.

Serum testosterone was normal in the patient. Pre-operative serum testosterone should have been taken especially in the presence of clitoromegaly to determine its cause. If it was elevated pre-operatively, virilizing ovarian tumor can be considered. In our patient, we ruled it out, since none of the identified components of the malignant mixed germ cell tumor caused testosterone secretion.

Preoperative karyotyping of young women with primary amenorrhea and a suspected germ cell tumor can clarify whether both ovaries should be removed, as in the case of women with gonadal dysgenesis. It is important to determine the presence of mosaicism or presence of Y chromosome which would signify increased risk for malignancy and would warrant examination of other siblings.

Dysgerminomas are bilateral in approximately 10% of cases. Endodermal sinus tumor are almost always unilateral. Embryonal carcinoma are confined to one ovary in two thirds of the cases. Most of the time, mixed germ cell tumors are unilateral unless dysgerminoma elements are involved. Our patient had unilateral ovarian involvement and had predominantly endodermal sinus tumor.
In ultrasonography and computed tomography, a multi-lobulated complex ovarian mass is the typical finding consistent with malignant germ cell tumor. Moreover, prominent blood flow in the fibrovascular septa may be seen using color flow Doppler sonography suggesting the likelihood of malignancy. On ultrasound, our patient had multi-septated, cystic mass with low to medium level echoes and papillary excrescences. Unfortunately, no Doppler sonography was done in our patient.

Pathology

A mixture of dysgerminoma and endodermal sinus tumor is the most common combination, accounting for one third of the cases. Grossly, endodermal sinus tumors form solid masses that are more yellow and friable than dysgerminomas. They are often focally necrotic and hemorrhagic, with cystic degeneration and rupture. The microscopic appearance of yolk sac tumor is often diverse. The most common appearance is the reticular pattern, reflecting extra-embryonic differentiation, with formation of a network of irregular, anastomosing spaces that are lined by primitive epithelial cells. Schiller-Duval body is a glomerulus-like structure composed of a central blood vessel surrounded by germ cells within a space similarly made up of germ cells. It is pathognomonic of endodermal sinus tumor when present.

The classic histology of dysgerminoma features a proliferation of epithelioid cells admixed with mature lymphocytes arranged in sheets or small clusters separated by thin, fibrous septae resembling alveoli. The neoplastic cells are large in size and have moderate to high nucleus-to-cytoplasm ratios.

Embryonal carcinoma is characterized by pleomorphic cells with glassy nuclei and prominent nuclei. Cellular borders are indistinct.

All these microscopic findings were noted in our patient.

Treatment

Due to the rapid progression of tumors, patients present at an early stage. Most of the tumors are unilateral and highly chemosensitive, therefore unilateral salpingo-oophorectomy with preservation of contralateral ovary and uterus is the appropriate treatment for most patients with malignant germ cell tumor. Due to relatively low toxicity and ease of treatment, chemotherapy has replaced radiation as the preferred surgical adjuvant even when fertility is not an issue. Treatment is determined by the non-dysgerminomatous component. In our patient, treatment is based on the endodermal sinus tumor.

Endodermal sinus tumors are the most deadly malignant ovarian germ cell type. All patients are treated with chemotherapy, regardless of stage. The treatment of the endodermal sinus tumor consists of unilateral salpingo-oophorectomy, and a frozen section for diagnosis. The addition of a hysterectomy and contralateral salpingo-oophorectomy does not alter outcome. This justifies our procedure of unilateral oophorectomy. Furthermore, our patient is classified under stage IA. Treatment is similar with sex cord stromal tumor which is a differential diagnosis during the frozen section.

The standard chemotherapy regimen is a 5-day course of bleomycin, etoposide, and cisplatin (BEP). This is the regimen appropriate to our patient. Due to the aggressive nature of the tumor, chemotherapy should be started shortly after surgery. After three courses of BEP, recurrence is prevented in women with accurate staging and completely resected ovarian germ cell tumor. Generally, most patients require three to four cycles of therapy. In 1990, Gershenson and coworkers reported that 25 of 26 patients treated with BEP for malignant germ cell tumors were in sustained remission 10-54 months from the start of chemotherapy. Subsequently, Williams and associates noted that 89 of 93 patients (96%) with completely resected stage I, II, or III disease remained continuously disease-free.

After completion of primary therapy, there is no standard surveillance for patients with malignant ovarian germ cell tumors. Serum tumor markers monthly for up to 2 years and then less frequently is recommended. Patients treated with fertility-sparing surgery should be closely followed with periodic transvaginal ultrasound and/or CT evaluations. Office visits with physical examination are generally recommended every 3 months for the first 2 years and gradually less frequently thereafter.

Prognosis

Malignant germ cell tumors have an excellent prognosis when managed appropriately. Histologic cell type, surgical stage, and the amount of residual disease at initial surgery are the major variables affecting prognosis. However, of the germ cell tumor group, dysgerminomas have a better prognosis overall than the non-dysgerminomatous types. The
most important prognostic features are the size of
the primary tumor and the relative size of its most
malignant component. For stage Ia lesions smaller
than 10cm, survival is 100%. Tumors composed
of less than one third endodermal sinus tumor,
choriocarcinoma, or grade 3 immature teratoma also
have an excellent prognosis, but it is less favorable
when these components constitute most of the mixed
lesions.

Endodermal sinus tumor is the predominant
cell type in our patient comprising 70% of the large
tumor which measured 13.5cm x 7cm x 7cm. It is
aggressive and carries a poor prognosis. The reported
mortality rate is >90% within 2 years of diagnosis if
without chemotherapy.\(^4\) Two thirds of the patients
with endodermal sinus tumor are classified under
stage I disease. Chemotherapy has dramatically
improved prognosis. In recent studies, patients
with stage I tumor who underwent surgery with
adjuvant chemotherapy, had 5 year survival rate of
92%. Our patient belongs to this stage so it is
imperative for her to undergo adjuvant chemotherapy.
Endodermal sinus tumors have a propensity for rapid
growth, peritoneal spread, and distant hematogenous
dissemination to the lungs. Individuals with stage
II–IV disease have a dismal survival rate of less than
10 percent. Patients die within 2 years of diagnosis
in greater than 90 percent of these more advanced
cases. Poor prognostic factors include an advanced
initial cancer stage, residual disease following surgical
staging, and ascites.

Reproductive Function After Conservative Treatment

With regard to ovarian function and fertility
after treatment, Gershenson reported that 68% of
women maintained regular menses after completion
of chemotherapy and 83% of them were having
regular menses at the time of follow-up.\(^6\) Perrin,
et al. reported seven normal pregnancies with
healthy babies among 29 women who had received
chemotherapy for germ cell tumors.\(^7\) Ezzat, et al.
described 44 women who retained their fertility after
treatment for germ cell tumors, and they reported
that no abnormality was observed in 16 pregnancies.\(^8\)
Brewer, et al. observed that 71% of young women
who were treated with bleomycin, etoposide, and
cisplatin after fertility-sparing surgery for pure
dysgerminoma maintained their normal menstrual
function during and after chemotherapy. With a
median follow-up of 89 months, five pregnancies
were recorded in 14 patients.\(^9\) The study of Zanetta,
et al. confirmed that normal gonadal function and
fertility are possible after conservative surgery and
chemotherapy. Fertility seems to be only marginally
affected by treatments. Gonadal function recovers few
months after treatment.\(^10,11\) In a study by Low, et al.
62% undergoing chemotherapy were amenorrheic
during treatment, but 92% resumed regular menses
on completing chemotherapy.\(^12\)

Although temporary ovarian dysfunction or
failure is common with platinum-based chemotherapy,
most women will resume normal ovarian function,
and childbearing is usually preserved. Factors such
as older age at initiation of chemotherapy, greater
cumulative drug dose, and longer duration of therapy
all have an adverse effect on future gonadal function.\(^1\)

The prognosis of our patient may improve if
she complies with chemotherapy. The reproductive
function of our patient is compromised since the
remaining right ovary is a streak ovary and the
uterus is hypoplastic. As of July 2010, patient
still has no menstruation five months after surgery.
Determination of serum FSH level is needed to know
whether or not she has undergone premature ovarian
failure.

Unilateral Ovarian Agenesis and Dysgenesis

Ovarian agenesis is defined as failure of
development of the ovary in contrast to ovarian
dysgenesis wherein there is defect in the development
of the ovary. A progressive loss of primordial
germ cells on the developing ovary of the embryo
is noted, which leads to an extremely hypoplastic
and dysfunctioning ovary. The ovary is reduced to
atrophic fibrous strands, devoid of ova and follicles.\(^13\)
In our patient, this dysgenetic gonad is represented by
the white fibrous tissue measuring 4cm x 0.4cm, seen
inferior to the right fallopian tube. However, we can
only be certain if a biopsy of that tissue was obtained.
Histopathological picture of a dysgenetic gonad
will show the absence of follicular structures while
the stroma is in a form resembling ovarian structure.
In retrospect, the white fibrous tissue noted in our
patient should have been removed for confirmation
and moreover, for prevention of malignancy since
there is high risk of neoplasm in dysgenetic gonads.\(^14\)
The incidence of neoplasia in patients with gonadal
dysgenesis is higher than reported.\(^15\) In 50 reported
cases, there were 11 malignancy, 15 adenoma and 10
benign cases, with a 22% incidence of malignancy
and a 52% incidence of neoplasia.\(^15\) Slowikowska
reported that neoplasia may occur in 16.7% to 23.1%
of patients with gonadal dysgenesis. According to Speroff, the propensity for tumor development of dysgenetic gonad is 20% to 30%. Thus, prophylactic removal of a dysgenetic ovary is recommended. Intraoperatively, the relatives were informed regarding the need to remove the streak ovary, however, they refused.

Gonadal dysgenesis is a pathologic syndrome characterized by lack of germ cells in a patient with external and internal features of the female sex. The classic form of gonadal dysgenesis was described by Turner in 1938. This syndrome is characterized by 45 XO karyotype, short stature, absence of secondary sexual characteristics and amenorrhea. Several new variants have been described since then. The term “pure gonadal dysgenesis” was first coined by Harnden and Stewart in 1959. It has bilateral streak gonads associated with normal 46 XX or 46 XY, normal stature and primary amenorrhea. The gonads are usually streaks, but there may be some development of secondary sexual characteristics with some episodes of uterine bleeding. Sohval coined the term “mixed gonadal dysgenesis” which is described as having mosaicism, 45 X or a 46 XY cell line, a unilateral testis and a contralateral streak gonad. A syndrome characterized by a unilateral streak ovary associated with a contralateral hypoplastic ovary in a phenotypic female has been described as the Slotnick-Goldfarb’s syndrome. The streak ovary probably results from unknown congenital factors and the hypoplastic ovary from suspected viral factors in postnatal life. Hypoplastic ovaries have follicles that may grow sporadically. However, follicular waves are irregular and follicles may not mature beyond 6 mm. Estrone levels are lower than in women with normal ovarian follicles. These individuals have enough gonadal function to initiate puberty and obtain sexual maturation. The gonadal reserve is limited. Thus, these individuals have breast, axillary and pubic hair development. As a result of the limited gonadal reserve, estrogen production fails resulting in amenorrhea and elevated gonadotropin levels.

Our patient had normal development of secondary sexual characteristics which would signify estrogen production prior to the surgery. She had her menarche at 13 years old but has oligomenorrhea, with spotting occurring every 2 to 3 months. She had her thelarche and pubarche at appropriate ages. These are all consistent with Slotnick Goldfarb syndrome; however, we cannot be certain on the presence of the hypoplastic ovary since it was complicated by a malignancy. There was also no identifiable viral illness in our patient which may lead to hypoplastic ovary. Five months after the surgery, patient still has no resumption of menstruation. The patient may already have undergone premature ovarian failure since her functioning left ovary was removed and a dysgenetic right ovary was left behind. Measurement of hormones is important to determine if the patient has premature ovarian failure. A low estrogen with high FSH must be detected on at least three separate occasions at least one month apart to confirm the diagnosis. Chromosomal analysis is essential for women experiencing ovarian failure before 30 years old. Serum FSH, estrogen and karyotyping were requested in our patient, however, she refused further blood examination. In the presence of premature ovarian failure, hormone replacement therapy has to be started, together with intake of calcium and vitamin D.

The term “gonadal dysgenesis” is frequently used to describe all subjects with female genitalia, normal mullerian structures and streak gonads with either 46 XX, or 46 XY karyotypes. There are different diseases manifesting with gonadal dysgenesis, each with different manner of inheritance and some with no established hereditary pattern. In 46 XX, gonad dysgenesis, there is a mutation in an autosomal gene which is the likely etiologic factor, inherited in autosomal recessive fashion. The etiology of 46, XY gonadal dysgenesis is thought to be a short arm Y chromosome deletion involving SRY. Our patient lacks karyotyping so it is difficult to classify her in a specific syndrome. However, due to presence of hypoplastic uterus and irregular menstruation in her sister aged 25 years old, our patient’s disease may be hereditary. It is therefore important to do karyotyping on the patient and her sister. Another important information that can be achieved from karyotyping is whether or not Y chromosome is present. The presence of a Y chromosome component in a phenotypic female requires removal of the streak gonad due to the increased propensity for tumor development.

**Hypoplastic Uterus**

The etiology of uterine hypoplasia is unclear except for in utero exposure to diethylstilbestrol. Hormonal dysfunction may be also be postulated as a cause. There are three types of uterine hypoplasia. Simple hypoplasia has a normal uterine morphology but size is small-scaled. Elongated hypoplasia has
a narrow fundus with a normal or elongated length. Malformative hypoplasia has an arcuate fundus or T and Y configuration of the uterus, which is the most unfavorable. Hysterosalpingogram remains to play a significant role in diagnosing diethylstilbestrol uterus, however, other uterine anomalies are best seen by magnetic resonance imaging and ultrasonography. For simple hypoplasia, hormonal treatment can be given to produce adequate endometrial lining. With other types of hypoplasia, hysteroscopic metroplasty can be done to cause enlargement of the uterine size and improvement of the uterine shape.\textsuperscript{18}

Our patient has simple hypoplasia based on gross and ultrasonographic findings. Hormone replacement with donor in-vitro fertilization can be an option for the patient to get pregnant.

**Clitoromegaly**

Clitoromegaly can be classified as congenital and acquired. Clitoral hypertrophy is usually seen as a congenital malformation, specifically in intersexual stages of hormonal expression. Acquired clitoral hypertrophy is a relatively rare condition, and data in the literature concerning this problem are sparse. The causes can be classified into hormonal and non-hormonal conditions, pseudoclitorteomegaly and idiopathic.\textsuperscript{19} Endocrinopathies, masculinizing tumors, exposure to androgens and various syndromes are the main hormonal causes of clitoromegaly. Congenital adrenal hyperplasia or androgenital syndrome is due to the defect in pathway of steroid biosynthesis. Patients may have precocious puberty, hirsutism and hypertension which were not present in our patient. Virilizing tumors of the ovary and adrenals can cause clitoral enlargement due to increased level of serum testosterone which was not seen in our patient. Malignant mixed germ cell tumor was the final histopathologic diagnosis and not a sex cord stromal tumor. Non-hormonal causes include neurofibromatosis, epidermoid cysts and nevus lipomatosus cutaneous superficialis. Various syndromes such as Turner syndrome, Fraser and congenital generalized lipodystrophy can also cause clitoromegaly. Pseudohypertrophy can be due to repeated mechanical trauma caused by manipulation of the skin of the prepuce.

Our patient noted clitoral enlargement when she was only 13 years old so it is classified as acquired. There is no identifiable cause of her symptom so it is classified under idiopathic.

The first step in correcting acquired clitoral enlargement must be to determine and stop the cause of the hypertrophy, followed by a period of simple observation. If clitoral enlargement does not disappear over time, surgical correction can be offered. Clitoropectoplasty with preservation of the neurovascular pedicle can be done for preservation of sexual arousal function, sensation and cosmetic.\textsuperscript{19}

**CONCLUSION**

This is a case report of a young adult who presented with hypogastric pain and a palpable mass, which was seen on ultrasound as a large ovarian tumor. Patient underwent left oophorectomy, bilateral lymph node dissection and infracolic omentectomy, and the final diagnosis was three-cell type mixed malignant germ cell tumor, stage IA. Early diagnosis, prompt treatment with surgery followed by adjuvant chemotherapy can greatly improve prognosis of these patients. However, the patient has doubtful reproductive function due to the presence of dysgenetic right ovary. It is also important to screen siblings of patients with gonadal dysgenesis and similar abnormalities because of the tendency of gonadal dysgenesis to be hereditary and to manifest with malignant potential especially in the presence of a Y chromosome.

**REFERENCES**

Dysgerminoma in a Nineteen-Year-Old Patient with Swyer’s Syndrome

MARIE FAITH B. VILLARUZ, MD, FPOGS; REY FELICISIMO SP. CASTILLO, MD, FPOGS AND ARNOLD P. LIWAG, MD, FPOGS

Department of Obstetrics and Gynecology, Western Visayas State University Medical Center

Dysgerminomas are the most common type of malignant germ cell tumor. It primarily occurs in women under age thirty. Five percent of cases occur in phenotypic females with dysgenetic gonads.

This paper presents a phenotypically female patient with hypogastric mass and primary amenorrhea. Eight months prior, patient underwent left salpingo-oophorectomy. Physical examination showed absent secondary sexual characteristics along with normal external female genitalia. Intra-operative findings at that time confirmed the presence of a uterus along with absent right ovary. Hormonal studies revealed increased gonadotropin levels, decreased estrogen and female testosterone levels. Serum LDH was elevated. Karyotyping revealed XY chromosome. Pure gonadal dysgenesis is characterized by abnormal testicular determination. The syndrome, as described by Swyer in 1955, represents the complete form of “pure” gonadal dysgenesis. This involves the association of the female phenotype, female internal genitalia, normal or tall stature and sexual infantilism with primary amenorrhea. These patients have streak gonads that do not secrete testosterone or Mullerian inhibiting factor, and therefore Mullerian derivatives develop.

Key words: Swyer’s syndrome, dysgerminoma

During embryogenesis, the human reproductive system is intrinsically conditioned to give rise to a female reproductive organization. As a result, if a gonad cannot express its sexual identity via its hormones, then the affected person, whether genetically male or female, will develop both internal and external female genitalia. The first known step in the sexual differentiation of a normal XY fetus is the development of testes. This requires the action of several genes, the earliest and most important of which is the SRY gene, which is the sex-determining portion of the Y chromosome. The development of such gonad into a testis depends upon the presence of the Y chromosome, whereas the absence of the Y chromosome will result in female development, irrespective of the number of X chromosomes.

Genetic sex is established at the time of fecundation by the nature of the chromosomal composition of the spermatozoon, whether it contains a Y chromosome which has a dominant effect (23,Y constitution), or an X chromosome (23,X constitution). In a first step, which is independent from the genetic sex, the gonadal primordium is colonized by the primordial germ cells originating from the allantoid sac. When these cells have reached the gonadal primordium, they form with the epithelium the “gonadal ridge”. The differentiation of the gonadal ridge into a testis is a rapid phenomenon, which contrasts with the slow and late development of the ovary. Inside the seminiferous tubules, germ cells are large. They divide actively but do not enter meiosis. Sertoli cells are smaller than the germ cells. They tend to surround the germ cells and prepare the future seminiferous tubules. The individualization of tubules and the synthesis of the anti-Mullerian hormone precede Leydig cells differentiation. Leydig cells differentiate from interstitial tissue and spread progressively in the intertubular spaces. They secrete testosterone and levels are comparable to those observed in adult males.

* 2nd Prize Winner, POGS-Multicare Interesting Case Contest, POGS Midyear Convention, Cagayan de Oro City.
Dysgerminoma in a Nineteen-Year-Old Patient with Swyer's Syndrome / Villaruz, et al.

After 20 weeks of gestation, Leydig cells involute, and circulating testosterone levels decrease progressively to levels observed in female fetuses. The internal genitalia derives from the differentiation of two pairs of ducts: the Wolffian ducts and the Mullerian ducts. Both ducts develop from the part of the mesonephros which does not participate in the formation of the fetal gonad. They both end in the urogenital sinus which opens to the perineum at the level of the urogenital orifice, located at the base of the genital tubercle. Wolffian ducts serve as the excreting duct to the mesonephros. When the definitive kidney becomes functional, the Wolffian duct that is dependent of the presence of androgens becomes the vas deferens system. In the female fetus, the Wolffian ducts degenerate. In the male fetus, the anterior part of the Wolffian ducts communicates with the seminiferous tubules, the posterior part forms the vas deferens and the seminal vesicle. This differentiation is dependent of high local concentration of testosterone, which is only active during a “critical” period during which the Wolffian duct is sensitive. Testosterone, and not dihydrotestosterone, is the active hormone as the Wolffian duct does not contain 5α-reductase activity at this stage of development. In the female embryo, Mullerian ducts differentiate into fallopian tubes, the uterus and the upper part of the vagina. The uterine cervix develops later. In the male fetus, Mullerian ducts later begin to regress. This regression is due to the presence of the anti-Mullerian hormone (AMH). The Mullerian duct is sensitive to AMH during a limited period of fetal development (up to 8 weeks in the human fetus) and acts only locally.

In Swyer’s syndrome, the defective SRY gene causes failure of the primitive gonads to differentiate into testes. With the absence of testosterone necessary for the development of male external genitalia and anti-Mullerian hormone, afflicted individuals have female internal and external genitalia.

Several authors have documented malignant transformation in a dysgenetic gonad with incidences as high as 20 to 30%. They are usually associated with Turner’s syndrome with 45,X karyotype or in a phenotypic female with a Y chromosome. The most frequent type of tumor arising from a dysgenetic gonad is dysgerminoma, accounting for almost 20% of such cases.

This paper presents the first diagnosed and documented case of Swyer’s syndrome with dysgerminoma in this institution, and probably in this locality. This paper also presents how the patient was diagnosed after a detailed and complete history taking, physical examination and a series of diagnostic and ancillary procedures and the treatment schema employed. It takes into consideration not only the biological aspect of the case but as well as the psychological and social impact of the diagnosis to the patient.

THE CASE

This is the case of E.J., 19 years old, single, who consulted because of hypogastric mass and primary amenorrhea.

The patient had no history of childhood illnesses. She was non-asthmatic, non-hypertensive and non-diabetic.

There were no familial diseases noted in the patient’s family. No other family member has the same complaint such as amenorrhea and hypogastric mass nor a history of genital tract tumor.

The patient is the second in a brood of 4. She is a non-smoker and non-alcoholic beverage drinker. She was employed as a household help.

She had a boyfriend at 18 years old but denied sexual contact. She never had menses.

History of present illness revealed that ten months prior, the patient sought consult at a different local hospital because of hypogastric mass and primary amenorrhea. Pelvic and KUB ultrasound were requested and revealed a complex pelvic mass superior to the urinary bladder measuring 10.2cm x 9.4cm x 8.8cm; uterus aplasia considered; normal kidneys and urinary bladder. The patient was admitted and underwent pelvic laparotomy, with a pre-operative diagnosis of left ovarian cyst, probably dermoid cyst. Intraoperative findings revealed a left ovarian mass, measuring 10cm x 8cm x 8cm, smooth, predominantly solid without adhesions. There was note of an infantile uterus with two fallopian tubes attached. The right ovary was not visualized. No ascites noted. The patient had no history of childhood illnesses. The patient underwent left salpingo-oophorectomy and was subsequently discharged. Patient was not able to secure the histopathologic result and was lost to follow up. Two months prior, the patient came back for follow-up in the same institution. An ultrasound was requested which revealed a complex adnexal mass measuring 11.7cm x 6.6cm x 9.5cm, mostly solid and located posterior to the uterus. The uterus was normal measuring 4.4cm x 2.0cm x 2.8cm. The patient was advised to have further work-up regarding the mass, but did not comply. A month prior, the patient noticed that the hypogastric mass was progressively enlarging...
and was now noted at the level of the umbilicus. It was associated with recurrent but vague abdominal pain and was relieved by NSAIDs. A week prior, there was a more intense abdominal pain prompting the patient to seek consult, this time in this institution. Review of systems revealed a 20% weight loss since 2 months PTA. No urinary or bowel changes, fever, anorexia and vomiting were noted.

On physical examination, the patient had stable vital signs. She weighed 65Kg and stood 5’3” tall. Her BMI (25.4) was within normal range. The patient was phenotypically female, medium-built (Figure 1), conscious, coherent, ambulatory with no signs of cardiopulmonary distress. There were no neck masses with no frontal and axillary hair and no neck webbing. The breasts were pre-pubertal with elevation of papilla noted (Tanner Stage I, Figures 2A & 2B). Chest findings were unremarkable. The abdomen was slightly globular with note of predominantly solid, fixed masses measuring approximately 10cm x 12cm x 8cm and 8cm x 6cm x 5cm, occupying the mid-abdomen, extending up to the level of the umbilicus. The patient’s extremities were grossly normal. On pelvic examination, inspection revealed prepubertal female external genitalia with no pubic hair (Figures 3A & 3B) and no vaginal discharge. Speculum internal and bimanual examinations were not done. Recto-abdominal examination revealed solid, slightly tender fixed masses measuring approximately 10cm x 12cm x 8cm and 8cm x 6cm x 5cm occupying the pelvo-abdominal cavity extending up to the level of umbilicus. There was good sphincter tone with no blood on examining finger. Admitting diagnosis was Abdominopelvic Mass, consider Ovarian New Growth, probably Malignant; Primary Amenorrhea; S/P Salpingo-oophorectomy, Left (2009). Patient was admitted for work-up and possible exploratory laparotomy.

CT scan of the whole abdomen revealed abdominopelvic and retroperitoneal masses measuring 12.2cm x 16.8cm x 7.0cm, solid and lobulated located posterior to the urinary bladder and extending to the pouch of Douglas and inseparable from the rectum. Similar smaller masses are noted in the right paracolic gutter, right lower anterior abdomen and retroperitoneal space. Neoplastic process was considered. Baseline laboratory parameters (hematology, chemistry, etc) were normal. Serum LDH was increased at 546 U/L (NV = 117-213 U/L). FSH was increased at 60.23 mUI/mL (NV = 3.4-33.4 mUI/mL). LH was also elevated at 52.98 mUI/mL (NV = 1.9-16.9 mUI/mL). Testosterone levels were decreased at <0.10 ng/mL (NV = 0.10-10.6 ng/mL). Estrogen, likewise, was decreased at 16.44pg/mL (NV = 18-147 pg/mL). Karyotyping was requested and revealed 46,XY chromosome (Figure 4). It was also during this admission that the histopathologic result of the previous surgery was retrieved, which revealed dysgerminoma.

Figure 1. Whole-body picture of patient E.J. showing stature and body habitus.

Figure 2A. Image showing patient’s prepubertal breasts with elevated papilla.
She underwent exploratory laparotomy under epidural anesthesia. After induction of anesthesia, pelvic examination revealed a 3cm vaginal canal. Intraoperatively, there was a bosselated abdominopelvic mass, soft and fleshy measuring approximately 14cm x 13cm x 9cm, cream to tan colored and was densely adherent to the sigmoid colon, the bladder and aorta. Pelvic and para-aortic lymph nodes were enlarged. No ascites were present. Tissue samples were taken from the bladder, the para-colic and sigmoid areas and cystoscopy with bilateral stenting of the ureters was also performed.

Patient was discharged on the 6th postoperative day.

Histopathologic report revealed dysgerminoma.

Postoperative plan was for six cycles of chemotherapy with etoposide, bleomycin and cisplatin and tumor debulking after the 3rd cycle of chemotherapy. She was also referred to the Department of Psychiatry for counseling.

On the third day of her first course of chemotherapy, there was a significant decrease in the size of the hypogastric mass. From the level of umbilicus, the masses were now palpable at 3 fingerbreadths above the symphysis pubis. The
patient was then discharged and appraised for another 5 chemotherapy sessions. However, the patient was lost to follow-up. Final diagnosis was Dysgerminoma Stage IIIC arising from Dysgenetic Gonads; Swyer’s Syndrome; s/p Chemotherapy I (Etoposide, Bleomycin, Cisplatin); s/p Exploratory Laparotomy, Biopsy of Pelvic Masses, Cystoscopy with Bilateral Stenting of Ureters (2010); s/p Salpingo-oophorectomy, Left for Dysgerminoma (2009).

DISCUSSION

Swyer’s syndrome, or pure XY gonadal dysgenesis, is defined as a type of hypogonadism in a constitutionally female patient with a 46, XY karyotype. Gonadal dysgenesis is divided into 3 histologic categories. First is complete or pure gonadal dysgenesis or Swyer’s syndrome. The patients are phenotypic females with a 46,XY karyotype and histologic gonads without germ cells. They present most often with primary amenorrhea with normal stature. The gonads are usually streaks, but there may be some development of secondary sexual characteristics as well as few episodes of uterine bleeding. Next is mixed gonadal dysgenesis. Primary amenorrhea in this case is associated with various mosaic status, the most common of which is 45,X or 46,XX. They have tall statures and few abnormalities. Spontaneous menstruation occurs in approximately 20% of these patients. Lastly, partial gonadal dysgenesis, where patients have 46,XY karyotype with some testicular development. These patients present as newborns with ambiguous genitalia.

Since the first description of Swyer’s syndrome in 1955, a number of cases have been reported, but no large series exist in literature. The exact incidence of the condition is unknown but can be estimated at 1:80,000 births. Although numerous reports in the past decades revealed an unexpectedly high risk of neoplasms in cases with abnormal gonadal development, the true incidences of tumors in dysgenetic gonads have not been reported. However, the risk of its development in the female phenotype that has primary amenorrhea and a Y chromosome has been well-documented. In the Philippines, a case of a 33-year old phenotypically female patient with 46,XY karyotype who developed a rare case of mixed germ cell tumor with rare malignant elements in combination (embryonal carcinoma and endodermal sinus tumor) has been well-documented.

Prior to the onset of menses, a normal female goes through a series of changes. Hypothalamic expression of gonadotropin-releasing hormone is a known puberty trigger. GnRH signals the pituitary gland to release luteinizing hormone and follicle-stimulating hormone, signaling the primary sex organs to produce estrogen and androgen. This increase in hormone production initiates the development of secondary sexual characteristics. Abnormalities of the Y chromosomes such as in Swyer’s syndrome result in progressive loss of primordial germ cells on the developing gonads. This loss leads to extremely hypoplastic and dysfunctional gonads mainly composed of a band of fibrous tissue called gonadal streak. Both the estrogen and androgen production do not occur, thus development of secondary sexual characteristics and menstruation does not come about. The early stages of testicular formation in the second month of gestation requires the action of several genes and one of the earliest and most important is the SRY gene, the sex-determining region of the Y chromosome (Figure 5). Under the influence of the Y chromosome, the primitive sex cords continue to proliferate and penetrate deep into the medulla to form the testis. In patients with Swyer’s syndrome, the SRY gene is defective resulting to failure of indifferent gonads to differentiate into testes. No testosterone is produced resulting to failure of the external genitalia to virilize resulting to development of normal female external genitalia. No anti-Müllerian hormone is present resulting to the development of fallopian tubes, uterus and upper vagina (Figure 6).

The consequences of streak gonads to a patient with Swyer’s syndrome include:

1. Gonads cannot make estrogen, so the breasts will not develop until estrogen is administered in the form of hormone replacement therapy given on the long term.

Figure 5. The sex determining region of the Y chromosome.
2. Gonads cannot make progesterone, so menstrual periods will not be predictable until progestin is administered.

3. Streak gonads with Y chromosome-containing cells have a high likelihood of developing cancer, commonly gonadoblastoma and dysgerminoma. Streak gonads are usually removed surgically as a precautionary measure within a year or so of diagnosis. Postpubertal gonadectomy is recommended by some studies but delayed to allow secondary sexual characteristics to develop.

In a case series, dysgerminoma developed in 3 phenotypic female patients aged 17, 19 and 20 years with 46,XY pure gonadal dysgenesis. All these three patients presented first with an abdominopelvic mass and laparotomy was subsequently done. These patients then underwent gonadectomy. Histopathology results revealed streak gonads without evidence for malignancy in 1 patient and the other 2 patients having dysgerminoma. The patients with dysgerminoma received adjuvant chemotherapy with 6 cycles of bleomycin, etoposide and cisplatin. These patients were Stage IIB and IIIIC, respectively. Full metastatic work-up was done and was negative. All these patients were given long term hormone replacement therapy. Another case report established the spectrum of presentation, natural history and gynecological outcomes in women with Swyer's syndrome. A total of 29 women were enrolled in the study. Results revealed that 90 percent present with delayed puberty, with median age of diagnosis at 17 years. Median age of gonadectomy was 18 years. Histology of the gonad was available in 22 patients which demonstrated streak gonads with no evidence of malignancy in 12, no evidence of dysgerminoma in 7 and no evidence of gonadoblastoma in 3 patients. The uterine size and shape were assessed in eight women after completion of induction of puberty and found to be significantly lower than normal controls. Fertility was achieved with ovum donation in three women, all of whom had livebirths and one subsequently had a second pregnancy. Treatment of dysgerminoma involves fertility-sparing surgery with unilateral salpingo-oophorectomy in patients without known metastasis. For those who have completed childbearing, hysterectomy with bilateral salpingo-oophorectomy is appropriate. In either case, following removal of the affected ovary, surgical staging by laparotomy or laparoscopy proceeds. Preservation of the contralateral ovary, however, leads to “recurrent” dysgerminoma in 5 to 10 percent of retained gonads over the next 2 years. Despite this significant incidence of recurrent disease, a conservative surgical approach does not adversely affect long-term survival because of this cancer’s sensitivity to chemotherapy. For several decades, radiation therapy was the traditional postoperative treatment for patients with metastatic dysgerminoma. Although the cure rate with such treatment was excellent, irradiation usually produced ovarian failure. The standard chemotherapy regimen is a 5-day course of bleomycin, etoposide, and cisplatin. Modified 2- or 3-day BEP combinations also have been shown recently to be safe and effective in pilot studies but are not used routinely in practice. Carboplatin and etoposide, given in three cycles, have shown promising result as an alternative for selected patients, but it warrants further study before it can be considered standard treatment. Another regimen that is as effective but more toxic is the combination of cisplatin, vinblastine and bleomycin. Dysgerminomas have the best prognosis of all malignant ovarian germ cell tumor variant when managed appropriately. Histologic cell type, surgical stage, and the amount of residual disease at initial surgery are the major variables affecting prognosis.

Seventy five percent of patients are stage I at diagnosis, and the 5-year survival exceeds 95 percent. Even those with advanced disease have high survival rates following chemotherapy. Those with stage II-IV disease have an 85 to 90 percent survival rate with platinum-based agents. However, despite the good prognosis, it is unfortunate for this patient that she did not complete the treatment and was lost to follow-up.

Long term management of patients with Swyer’s syndrome includes hormone replacement therapy. Some studies have demonstrated successful induction of pregnancy through ovum donation. Early diagnosis is crucial and extremely important for a number of reasons: first, the risk of gonadal malignancy. Removal of the dysgenetic gonads by age 18 years is ideal as a prophylactic measure to prevent disease.
avoid development of dysgerminomas and the like. Second, the early institution of estrogen therapy for induction of puberty is vital in the proper sexual function of the patient. Third, to allow for adequate hormone replacement to improve bone mineral density.8

Aside from the medical and surgical aspect of this case, the patient’s psychological needs have to be addressed. Intersex is the term used for cases wherein the patient’s reproductive anatomy does not fit the true and exact definition of either being male or female. Medicine has undergone a considerable upheaval in the past years over the treatment of patients with intersex problems. For years, treatment of patients with intersex conditions was guided by the belief that gender identity results from social rearing. Although there have always been questions about this policy, anecdotal evidence generally suggested that it produced good outcome. Sex assignment is coupled with the complexity of gender identity, especially in modern times. Gender identity is definitely not just a result of one singular factor. In certain times and conditions, gender identity does not always agree with the sex of rearing. Sometimes, the biology and chemistry of gender identity does not coincide with the patient’s emotions and actuations. Thus, theoretically, mental health of intersex patients may be affected in a variety of ways. However, there is surprisingly a small amount of evidence about psychological outcomes of intersex patients. Studies often prove to be difficult due to problems of under sampling or sometimes, over-representation. Females with congenital adrenal hyperplasia have undergone systematic study regarding their mental health. Evidence suggests that, aside from minor issues such as problems with body image, their mental health is not different from individuals without intersex problems. Above results prove to be consistent with evidence from patients with debilitating diseases, trauma, and other adverse life events. They only suffer from temporary effects on adjustment, such as an immediate period of depression, but after a few weeks or months, most have coped well.10,11

**SUMMARY AND CONCLUSION**

We were presented with the first diagnosed case of Swyer’s syndrome with dysgerminoma in our institution and probably in our locality. The patient was diagnosed after a careful history and physical examination and complete laboratory and ancillary work-up.

Swyer’s syndrome, or pure gonadal dysgenesis present with phenotypically female patients but with a 46,XY karyotype. These patients usually have streak gonads which, histologically, do not contain germ cells. These patients often present with primary amenorrhea, as was seen in our patient.

Dysgerminomas are the most common germ cell tumors among reproductive age women. They have a tendency for bilateralism and may arise from dysgenetic gonads, as seen in our patient. It is highly responsive to chemotherapy and surgical management usually includes fertility-sparing procedures.

Early diagnosis of Swyer’s syndrome is crucial for a number of reasons: the risk of gonadal malignancy and the need for early institution of hormone replacement therapy for induction of puberty.

Aside from the medical and surgical aspects of this case, the patient’s psychological and social issues have to be addressed. Traditionally, gender identity was believed to be a result of the sex of rearing. However, in these modern times and with the recent developments in medicine, it has come to be known that gender identity is not a product of just one singular determinant. However, most patients with intersex problems have had good mental health and were able to cope with their condition.

**REFERENCES**

9. Michener MD. Obstetrics/ Gynecology and Women’s Health Institute, Section of Gynecologic Oncology, The Cleveland Clinic

Complete Uterine Septum with Bicollis (double cervix) and Complete Longitudinal Vaginal Septum: A Mullerian Anomaly with No Present Classification

Cherryl M. Torregosa, MD; Veronica M. Deniega, MD, FPOGS; Darleen S.J. Estuart, MD, FPOGS and Ma. Lourdes Z. Cabling, MD, FPOGS

Department of Obstetrics and Gynecology, Brokenshire Integrated Health Ministries, Inc., Davao City

A 27 year old woman presented for investigation of primary infertility. She was found to have complete longitudinal vaginal septum and cervical duplication with two endometrial cavities. Laparoscopy demonstrated a normal uterine contour. Saline infusion sonohysterography and diagnostic hysteroscopy revealed two completely separate uterine cavities, each communicating with its own cervix. This case sets sights on the contribution to the incidence of this inimitable mullerian anomaly, one that is inconsistent with our current understanding of Mullerian development. An alternative embryological mechanism is reviewed to account for this and other anomalies which do not fit into existing classification systems.

Key words: Uterine septum, bicollis (cervical duplication), longitudinal vaginal septum, embryology, Mullerian anomaly

Congenital uterine anomalies in the general population are estimated to have an incidence of 0.001%-10%. Differences in diagnostic methods, classification systems, patient selection factors and clinical experience all contribute to difficulties in estimating true prevalence of congenital uterine malformations. The septate uterus is the most common form of structural uterine anomalies. A rare developmental variant is a complete septate uterus with cervical duplication and a complete longitudinal vaginal septum. Since the description by McBean and Brumstead in 1994, published reports suggest that the true incidence is probably more frequent but under-reported. A paper by Ribiero, et al. published in 2010 summarizes the 44 cases, thus far reported worldwide.

A classification system exists to categorize the various types of Mullerian anomalies (American Fertility Society, 1994). We encountered a case, and reviewed others in the literature, which could not be accommodated by this system and are also incongruous with the accepted mechanism of Mullerian embryogenesis.

THE CASE

A 27 year old nulligravid presented with a 2 year history of primary infertility. She denied difficulty initiating intercourse but complained of deep dyspareunia. Her menstrual history was normal. She had her menarche at the age of 12 and had regular cycles since then with moderate flow for 3-4 days and occasional dysmenorrhea. Her history was otherwise unremarkable. She is married to a 39 year old seaman.

Past investigation for primary infertility included a normal sperm analysis and two transvaginal scans showing uterine didelphys versus septate versus bicornuate uterus. Saline Infusion Sonohysterogram showed 2 endometrial cavities and 2 cervical canals with a vaginal septum (Figure 1). A 3D-scan (Figure 2) confirmed a complete uterine septum and a complete longitudinal vaginal septum. A diagnostic laparoscopy and hysteroscopy with resection of the uterine and vaginal septum was then planned.

On admission, the general examination was normal. There was no thyroid swelling or galactorrhoea and no evidence of any signs
suggestive of hyperandrogenism. The abdomen was normal. External genitalia were essentially normal. Examination of the vaginal introitus showed a fleshy mass about 0.3cm thick longitudinally dividing the vagina from the level of the hymen extending up to the cervix. Two distinct cervices were noted on speculum exam. There was no difficulty performing bimanual examination, done through both vaginal canals; revealing a normal-sized anteverted, freely, mobile uterus.

Laparoscopy (Figures 3a-3c) confirmed the presence of a single, smooth uterine fundus without indentation. A 5 mm focus of endometriosis in the uterosacral ligament was fulgurated (Figure 3d). The tubes and ovaries were unremarkable. Chromotubation done through both cervices showed patent fallopian tubes. The longitudinal vaginal septum was totally excised prior to hysteroscopy.

Figure 1. Saline infusion sonography showed 2 endometrial (EMT) cavities with complete separation. Initial findings showed the left endometrial cavity is dilated with fluid with rapid spillage of the fluid through the left fallopian tube. The right endometrium did not distend. Another foley catheter is inserted into the right cervix to establish complete separation of the cavities. There was rapid spillage of fluid thru the right fallopian tube. Moderate fluid was noted at the posterior cul de sac.

Figure 2. 3D gynecology scan - revealed a thin endometrium, a complete uterine septum with an accompanying longitudinal vaginal septum. The septum measured 2.63cm interfundal width and 2.22cm in depth. The normally-sized anteverted uterus noted to have a concave contour of the fundus. The cervical canal is not distinctly seen due to the presence of a solid vertical structure with 0.3cm in thickness. It spans from the isthmus to the upper vagina dividing it longitudinally. Both ovaries were small.
(Figure 4). Hysteroscopic survey revealed a complete uterine septum, with patent ostia (Figure 5).

**DISCUSSION**

This case represents a unique Mullerian malformation and a very rare variant of the septate uterus in gynecologic practice. Since it was first described in 1994 (Table 1), published reports suggest that the true incidence of septate uterus with cervical duplication and a longitudinal vaginal septum is more common but under-reported.

There were reports of a septate uterus with cervical and vaginal duplication, a communicating septate uterus with a double cervix and normal vagina (Levtoaff, et al. 1992), and a double cervix with a normal vagina and uterus (Tavasolli, 1977) as well as the report of 9 new cases having the same clinical features. Two similar cases of cervical and vaginal duplication with a normal uterus have been

---

![Figure 3](image1.png)  
**Figure 3.** Image at laparoscopy- normal size and concave external fundal contour. Both tubes were patent. Normal ovaries. Endometriotic implants noted at the uterosacral ligament.
Complete Uterine Septum with Bicollis (double cervix) and Complete Longitudinal Vaginal Septum / Torregosa, et al.

Figure 4. After resection of vaginal septum.
previously described; however one cervical canal ended blindly and did not communicate with the uterus (Kletz, et al. 1994, Candiani, et al. 1996). Patton, et al.\(^5\) reported 16 patients with cervical duplication and a longitudinal uterine and vaginal septum. These anomalies do not conform to our classical understanding of Mullerian development (Crosby and Hill, 1962). Its features fall outside the current classification system of Mullerian anomalies (American Fertility Society, 1988) and suggest an alternative embryological mechanism.

Musset, et al.\(^6\) proposed that fusion first occurs at the level of the uterine isthmus and simultaneously proceeds in both cranial and caudal directions. Midline resorption also begins at the isthmus and is first directed caudally, unifying the cervix and vagina, and later cephalad to eliminate the uterine septum. This theory can account for the standard classifications of Mullerian anomalies. It is unknown whether it is the mechanism for normal Mullerian development or only an aberration, etiologically unique to these most unusual anatomical variants.\(^7\)

Location of fusion initiation may vary among individuals and this variability could explain the wide variety of uterine malformations observed.

Patients described in literature have presented a variety of symptoms, including severe dysmenorrhea and infertility; some have been asymptomatic (Table
Table 1 - Reported cases of septate uterus with cervical duplication and longitudinal vaginal septum (Ribiero, 2010).

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Main symptom(s)</th>
<th>Imaging Exams</th>
<th>Resection of vaginal septum</th>
<th>Resection of uterine septum</th>
<th>Cervix unified</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mc Bean, et al.</td>
<td>1</td>
<td>Menorrhagia, infertility, oligo-amenorrhea &amp; dysmenorrhea</td>
<td>US, US, IVP</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Balasch, et al.</td>
<td>3</td>
<td>Spontaneous abortion, dysmenorrhea &amp; dyspareunia</td>
<td>US, HSG, IVP</td>
<td>Yes</td>
<td>Hysteroscopic</td>
<td>Yes</td>
<td>Pregnancy &amp; cerclage</td>
</tr>
<tr>
<td>Sharara, et al.</td>
<td>1</td>
<td>Infertility</td>
<td>MRI, US, HSG</td>
<td>Yes</td>
<td>Hysteroscopic</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Giraldo, et al.</td>
<td>1</td>
<td>Infertility</td>
<td>MRI, US, HSG</td>
<td>Yes</td>
<td>Hysteroscopic</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Wai, et al.</td>
<td>1</td>
<td>No symptoms</td>
<td>MRI, IVP, H, L</td>
<td>Yes</td>
<td>Tompkins</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Hundley, et al.</td>
<td>1</td>
<td>Pelvic pain &amp; dyspareunia, dysmenorrhea</td>
<td>MRI</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Chang, et al.</td>
<td>5</td>
<td>Deficiency</td>
<td>US, IVP, MRI</td>
<td>1 case</td>
<td>No</td>
<td>No</td>
<td>Spontaneous pregnancy (1 case)</td>
</tr>
<tr>
<td>Patton, et al.</td>
<td>16</td>
<td>Dyspareunia &amp; obstetric complications</td>
<td>US, HSG (10), MRI(6)</td>
<td>Yes</td>
<td>Hysteroscopic (11), Tompkins (5)</td>
<td>No</td>
<td>2 patients: no attempt to conception; in 14 cases- 14 pregnancies: 3 abortions</td>
</tr>
<tr>
<td>Pavone, et al.</td>
<td>1</td>
<td>Infertility</td>
<td>MRI</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Spontaneous pregnancy</td>
</tr>
<tr>
<td>Hur, et al.</td>
<td>1</td>
<td>Malodorous vaginal discharge</td>
<td>US, MRI, IVP</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Badalotti, et al.</td>
<td>1</td>
<td>Dysmenorrhea</td>
<td>US</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Spontaneous pregnancy (IVF), No evidence of cervical incompetence</td>
</tr>
<tr>
<td>Caliskan, et al.</td>
<td>1</td>
<td>Infertility &amp; menorrhagia</td>
<td>US, HSG &amp; MRI</td>
<td>Yes</td>
<td>Hysteroscopic</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>Ribiero, et al.</td>
<td>1</td>
<td>Dyspareunia, Infertility, dysmenorrhea, dyspareunia</td>
<td>US, MRI, US, H, L</td>
<td>Yes</td>
<td>Hysteroscopic</td>
<td>No</td>
<td>?</td>
</tr>
</tbody>
</table>

N- Number of reported cases; US- Pelvic ultrasound; IVP- Intravenous pyelogram; HSG- Hysterosalpingography, MRI - Magnetic resonance imaging; H-Hysteroscopy; L-Laparoscopy; IVF-In vitro fertilization

1) Interestingly, the great majority of patients, such as in the case presented did not have difficulty with initiation of intercourse. Our patient’s main problems were infertility and dyspareunia. The latter was the reason why the vaginal septum was excised.

The succeeding discussion focuses on the uterine septum, which is more significantly associated with reproductive function. A comprehensive review of combined data from several studies that addressed reproductive outcomes of the septate uterus revealed the following outcomes: 1105 (75.7%) spontaneous abortions, 146 (10%) preterm deliveries, 90 (58.1%) live births, 3 (1.9%) ectopic. Despite these findings, this condition is not always associated with an unfavorable obstetric outcome, and its presence alone is not an indication for surgery (Amesse, et al. 2009).
Etiology of reproductive failure is unclear. Mahgoub believes that the presence of a uterine septum can lead to abortion because of diminished intrauterine space for fetal growth or implantation of the placenta on a poorly vascularized septum. Mizuno and associates have attached importance to the inadequacy of vascularization of the uterine septum, associated cervical incompetence, luteal phase insufficiency, distortion of the uterine milieu have all been implicated in the etiology of increased reproductive loss. However, it is as yet unexplained why some patients with a uterine anomaly have normal reproductive function, whereas others abort early in pregnancy. In one study, septa tissue obtained from 5 patients at hysteroscopic metroplasty was sent for pathologic review, and all specimens demonstrated smooth muscle, not fibrous tissue. In another study the septum was evaluated along with pathologic specimens. All partial septa contained myometrium while complete septa had evidence of myometrium in the upper segment of the septum and fibrous tissue in the lower segment. In another prospective study, septal and non-septal tissue samples were obtained from the posterior uterine wall at the time of Tompkin metroplasty. Multiple biopsies demonstrated increased amounts of muscular tissue and less connective tissue in the septum. The authors theorized that the decreased connective tissue may result in poor decidualization and implantation, increased muscular tissue may result in increased contractility of the tissue, thereby predisposing the patient to spontaneous abortion. In addition to the inherent deficiencies of the composition of the septum, the overlying endometrium has been shown to be defective. Interestingly, it has been reported that the chance for a liveborn child increases with each pregnancy loss. It is unknown whether this apparent conditioning of the uterus is due to better vascularisation, better myometrial stretching, accommodation or some other factor.

Diagnosis is made by careful examination, followed by imaging. Magnetic resonance provides good cervical imaging and is the best non-invasive method for differentiating septate, bicornuate and didelphys uterus. Transvaginal ultrasonography is a useful aid in diagnosing septate uterus. One study demonstrating a sensitivity of 100% and a specificity of 80%. Results from combining transvaginal ultrasonography with color doppler imaging show 95% sensitivity and 99.3% specificity for septate diagnose. In a prospective study of 40 women with history of recurrent reproductive failure, accuracy of physician interpretation of 3-dimensional sonograms is 92% for the diagnosis of septate uterus. Most physicians, however, still use a combined approach with hysteroscopy and laparoscopy to confirm the diagnosis, in the case presented. Although urinary tract anomalies are not commonly associated with septate uterus, renal ultrasonography and/or IVP should be performed to help exclude or detect any concomitant anomalies.

The best approach to management which should provide relief of symptoms and preserve reproductive ability is controversial (Table 1). Resection of the vaginal septum is easy and commonly performed such in this case. Hysteroscopic resection of a uterine septum using a minimally invasive approach (improving obstetric outcomes) is the gold standard according to most authorities. However, preoperative evaluation should be done. The decision to perform surgical correction of the septum should be based on the poor reproductive performance rather than the presence of a septate uterus. Candidates for surgery include women who had recurrent spontaneous abortions, a single second-trimester loss, or history of preterm delivery. None of these applies to the patient, hence resection of the uterine septum was not done.

In one study, Heinonen, et al. evaluated gynecologic complaints, fertility and obstetric outcomes in 67 patients with a complete septate uterus and longitudinal vaginal septum. They reported that complete septate uterus and longitudinal vaginal septum are not associated with primary infertility, and that pregnancy may progress successfully without surgical treatment. The results do not support elective hysteroscopic incision of the septum in asymptomatic patients or before the first pregnancy (William’s, 2008). Some investigators (Turk J Med Sci 2008) have reported better reproductive outcome among women with a septate uterus not subjected to surgical interventions in that patients with no history of a poor reproductive outcome, a conservative approach may be considered. For those who are indicated for a septum resection some authorities recommend preoperative pharmacologic therapies like progestins, danazol, or gonadotropin-releasing hormone agonists, to reduce the thickness of the endometrium and to aid visualization. Others schedule surgery during the early follicular phase of the menstrual cycle, when the endometrium is already minimized. The union of the two cervices is another area of controversy which was done in a case reported by Ribiero. Some authors believe...
that cervical manipulation increases risk of cervical incompetence and that there is a risk of problematic bleeding during surgery. Others prefer to unify the cervicis to facilitate surgery and decrease the likelihood of recurrent symptoms (Caliskan, 2008; Ergun, 1997). In patients with a complete uterine septum extending into the cervix, Parsanezhad et al. demonstrated that resection of the cervical septum made the hysteroscopic metroplasty easier, faster, and safer than preserving it.

In an observational study of 16 women with this variant who experienced pregnancy loss (9 patients) or dyspareunia (7 patients), both hysteroscopic metroplasty (11 patients) and transabdominal-modified Tomkins metroplasty (5 patients) were used to correct the uterine septal abnormality. None of the patients underwent incision of the cervical segment of the septum and postoperative reproductive outcomes were impressive. Postoperative management includes placement of an intrauterine device for a month that may prevent intrauterine adhesion formation. Conjugated estrogens 1.25 mg/d for 25 days and progesterone 10 mg/d added on days 21-25 are frequently prescribed after surgery to assist with epithelialization. However, results from Dabirashrafi and colleagues' randomized study indicated that estrogen offered no apparent benefit after hysteroscopic metroplasty. Perioperative prophylastic antibiotics are recommended particularly if the patient has a history of pelvic inflammatory disease. One-month postoperative follow-up examination is recommended. Either hysteroscopy or HSG can be performed to assess the status of the uterine cavity. HSG is useful for helping detect uterine perforations that may have resulted from hysteroscopy. Ultrasonography can also be performed. When findings on postoperative examination are normal, pregnancy can be attempted. Due to the rarity of this condition, there is no sufficient evidence to establish consensus regarding management. Establishing an accurate diagnosis is essential for planning treatment and management strategies. The surgical approach for correction is specific to the type of malformation and may vary in a specific group. For most surgical procedures, the critical test of the procedure's value is the patient's postoperative ability to have healthy sexual relations and achieve successful reproductive outcomes.

CONCLUSION

A case of a rare variant of a mullerian anomaly in a young nulligravid desirous of pregnancy has been presented. The vaginal septum was excised to relieve the dyspareunia. The uterine septum, however, was not resected. Foremost criterion for an elective resection of a complete uterine septum is a history of poor reproductive capacity, which our patient did not have. Since the association of septated uterus and primary infertility is not well-established, the chance of having a successful pregnancy in unresected uterine septum is the same as the general population.

For this couple, sperm and tubal factors for infertility were ruled out. As was suggested, the couple followed the recommendation of increasing sexual frequency. The patient was relieved of dyspareunia. Moreover, the patient conceived three months after surgery, and is now pregnant at 11 weeks Age of Gestation (Figure 7). As with other pregnancies, the patient may undergo trial of labor and cesarean section as route of delivery should be reserved for obstetrical indications.

REFERENCES

A Case of Dilated Cardiomyopathy with Severe Left Ventricular Dysfunction in a 38-year old Primigravid

JOANNA PAULINE CHUA-URSUA, MD AND EDELIZA AMORIN, MD

Department of Obstetrics and Gynecology, The Medical City

A multidisciplinary approach was undertaken in a case of a 38 year old G1P0 who came in at 33 1/7 weeks age of gestation with a chief complaint of persistent cough. Aside from persistent non-productive cough, the patient was otherwise asymptomatic despite a 2D echocardiogram of global hypokinesia and an ejection fraction of only 32 percent. Assessment was uterine pregnancy 33 1/7 weeks age of gestation, dilated cardiomyopathy with severe left ventricular dysfunction, congestive heart failure (CHF) Class 1A. Patient underwent primary low transverse cesarean section (vertical) with left uterine artery ligation and bilateral tubal ligation and delivered to a live baby boy with APGAR score of 6,9, birth weight of 1,581g, birth length of 42cm, maturity score of 35 weeks small for gestational age. This case attests to the importance of pre conceptional counselling and prenatal care with active contributions of a specialized obstetrician, cardiologist, internist and anesthesiologist.

Key words: global dyskinesia, ejection fraction, left ventricular dysfunction, congestive heart failure (CHF)

According to the 2004 US Census Bureau, International Database, cardiomyopathy in the Philippines is around 15,853 from an investigated population of 86,241,697. This is around 0.02%, similar to the incidence in the United States wherein cardiomyopathy occurs in 53,980 patients out of 293,655,405 population (0.02%). (US Census Bureau, Population Estimates, 2004)

Cardiac diseases of varying severity complicate 1%-4% of pregnancies in women without pre-existing cardiac abnormalities. Despite being rare in pregnancy, heart disease still contributes significantly to maternal mortality. Cardiomyopathy in pregnancy and the postpartum period, accounts for a rising proportion of reported pregnancy-related deaths in the United States.

During 1979 to 1984, 3% of reported pregnancy related deaths were caused by cardiomyopathy. Berg and colleagues (2003) reported that cardiomyopathy alone was responsible for 7.7 percent of 3,201 pregnancy-related deaths in the United States between 1991 and 1997. Cardiomyopathy is one of the few causes of pregnancy-related death that has risen since 1979.

Women with cardiac diseases are at higher risk for cardiovascular complications during pregnancy. Pregnancy complicates the diagnosis of cardiac diseases because of the physiologic cardiovascular changes that occur during pregnancy. Without accurate diagnosis and appropriate care, heart disease in pregnancy can be a significant cause of maternal mortality. However, under more optimal conditions, many women with significant disease can experience good outcomes and should not necessarily be discouraged from becoming pregnant.

Normal pregnant women may experience dyspnea, orthopnea (defined as shortness of breath while lying on supine position), easy fatigability and occasional syncope which are similar symptoms as those felt by patients with cardiac problems. On physical examination, pregnant women may have edema, rales in the lower lung fields, visible neck veins and cardiomegaly. Murmurs are not uncommon. These symptoms pose difficulty in diagnosing heart diseases in pregnant women since these are same features as would occur in patients with pre-existing cardiac diseases.
A multidisciplinary approach to monitoring and treatment of patients such as these are warranted. It involves the expertise of an obstetrician, internist, cardiologist and anesthesiologist.

The goal of this paper was to create an awareness on the importance of preconception counselling for women with cardiac diseases who are planning to be pregnant. Risks to the mother and baby should be spelled out. Some cardiac disorders are very serious in nature so that physiologic changes of a superimposed pregnancy pose a high mortality risk for the mother.

This paper also aimed to present management options once presented with a pregnancy complicated with cardiac disease.

THE CASE

This is a case of I.A., a 38 year old primigravid who came in at 33 1/7 weeks age of gestation with a chief complaint of persistent cough.

Four months prior to admission (November 2009), at 16 weeks age of gestation, the first prenatal consult was done. Patient was asymptomatic with no signs and symptoms. Patient had no vaginal bleeding, abdominal pain, easy fatigability, orthopnea, or paroxysmal nocturnal dyspnea. On physical examination, vitals were stable but the patient was noted to have a dynamic precordium, with a holosystolic murmur, grade 3/6, at the 6th left intercostal space anterior axillary line. A 2D echocardiogram was requested which showed a dilated left ventricular hypertrophy with and ejection fraction of 30%. Patient was advised to watch out for untoward signs and symptoms and advised to consult with a cardiologist.

Three months prior to admission (December 2010), the patient, still asymptomatic, sought consult with a cardiologist. Her 2dEcho was reviewed and patient was started on digoxin (Lanoxin) 0.25mg/tab, 1 tablet once a day. Patient was sent home and advised to watch out for episodes of difficulty/shortness of breathing, chest pain, easy fatigability or loss of consciousness.

Two months prior to admission (January 2010), patient experienced occasional, non-productive cough. There was no associated fever, dyspnea or weight loss. Patient was asymptomatic OB Gyne-wise, without signs of vaginal bleeding, contractions or watery vaginal discharge. There was note of good fetal movement. Patient consulted with her obstetrician. On physical examination, her vital signs were stable with no signs of tachypnea or fever. Patient had occasional rales on both lower lung fields. She was prescribed salbutamol sulphate 2mg plus guiafenesin 100mg (Ventolin expectorant) 1 capsule three times a day and co-amoxiclav 625mg/tab 1 tablet to be taken twice a day for 7 days. Patient completed the medication but there was persistence of cough. After a week, medication was shifted to erdosteine (Zertin) 300mg/cap which the patient took once without relief of cough. Patient was lost to follow up.

One month prior to admission (February 16, 2010), consult was done with her obstetrician. Patient still had occasional bouts of non-productive cough for which she would take butamirate citrate (Sinecod) 30 mg/tab 1 tablet thrice a day without relief. There was no associated difficulty of breathing or shortness of breath, fever, weight loss or night sweats. It was also at this time that a pelvic ultrasound was done which showed pregnancy uterine 29 weeks age of gestation, live singleton in cephalic presentation, with adequate amniotic fluid volume, male fetus. A congenital anomaly scan showed unremarkable findings. The baby had no congenital anomalies seen in the scan. Patient was given dexamethasone 6mg/IM every 12 hours for four doses to facilitate lung maturity.

Two days prior to admission, there was still persistence of patient’s non-productive cough. Consult was done with her obstetrician. A pelvic ultrasound was done requested which showed pregnancy uterine 31 weeks and 4 days age of gestation by fetal biometry, live singleton in cephalic presentation, adequate amniotic fluid, with a biophysical score of 10/10. Estimated fetal weight was 1,480g. There was no note of a nuchal cord. Non-stress test was reactive with a baseline heart rate of 130’s, mild to moderate variability (good beat to beat variability), many accelerations, no decelerations, many fetal movement with no contractions. Patient was advised admission for work-up and close monitoring.

For the maternal history, patient’s last menstrual period was on July 29, 2009. Her expected date of delivery was on April 24, 2010. Hepatitis screening was negative and oral glucose challenge test was normal.

For the past medical history, the patient underwent polypectomy in 2008 which revealed benign findings on histopath. She had no history of hypertension, diabetes, tuberculosis or cancer.
The patient was a college graduate and works at home as a housewife. She neither smokes nor drinks alcoholic beverages.

For the family medical history, the patient had a sister who passed away upon delivery due to an undiagnosed cardiac problem. She also has a brother who has an undiagnosed heart disease. The patient had no family history of hypertension, diabetes, tuberculosis or asthma.

On physical examination, the patient had unstable vital signs with a blood pressure of 90/60, irregular heart rate of 82 with skipped beats, respiratory rate of 22 cycles per minute and a temperature of 36°C. Patient had a Glasgow Coma Scale of 15, with pale palpebral conjunctiva, and anicteric sclerae. She weighs 47 kg, stands 1.52m tall and has a body mass index of 20. There was no note of alar flaring. Neck veins were not distended. Chest examination showed a dynamic precordium, with audible S1 heart sound. Apex beat was at the 6th LICS anterior axillary line. There was a holosystolic murmur at the base of the heart. Chest expansion was symmetrical with decreased breath sounds over both lower lung fields. On abdominal examination, the fundic height was 29cm and the fetal heart tones were at 140 beats per minute. Speculum and internal examination was unremarkable. There was minimal whitish non-foul smelling discharge on speculum examination and cervix was closed on internal examination. Pulses were full and equal, with grade I bipedal edema (edema extending up to the ankles). There was no cyanosis nor clubbing of fingers.

Initial assessment on admission was Pregnancy Uterine 33 1/7 weeks age of gestation, not in labor, G1P0, undiagnosed heart disease. The patient had no family history of hypertension, diabetes, tuberculosis or asthma. For the family medical history, the patient had a sister who passed away upon delivery due to an undiagnosed cardiac problem. She also has a brother who has an undiagnosed heart disease. The patient had no family history of hypertension, diabetes, tuberculosis or asthma.

The electrocardiogram (ECG) results showed sinus rhythm with occasional paroxysmal ventricular contractions in trigeminy. 2D Echo results showed global hypokinesia, dilated with a left ventricular ejection fraction of 32%. Patient had dilated left ventricular hypertrophy with decreased systolic function with Doppler evidence of decreased left ventricular cardiac compliance, evidence of mild pulmonary hypertension and pulmonary regurgitation. There was minimal pericardial effusion. B-type natriuretic peptide was elevated at 408.10 (<100pg/mL) indicating the severity of heart failure. Patient was transferred to Telemetry (Intensive Care Unit) for close monitoring under the supervision of a specialized ICU internist. Dobutamine drip was started 250mg in D5W 250mL to run at 3mcg/kg/min (10cc/hr) to act as an inotrope to the heart.

Impression was pregnancy uterine 33 1/7 weeks age of gestation, not in labor, G1P0, dilated cardiomyopathy with severe left ventricular dysfunction. At this time, the persistence of cough attributed to congestion versus upper respiratory tract infection, probably viral. There was evidence of mild pulmonary hypertension and minimal pericardial effusion which may cause bouts of cough. Dobutamine drip was decreased to 6cc/hr (2mcg/kg/min) and the patient was started on antibiotics namely cefuroxime 250mg/cap 1 capsule twice a day for seven days. Total fluid intake was restricted to 1L/day. Patient was placed on moderate back rest.

A cardiotocogram/non-stress test was requested which showed a reactive tracing, baseline fetal heart rate of 140’s, with mild to moderate variability (good beat to beat variability), many accelerations, no decelerations, good fetal movement, and no contractions.

Two hours on dobutamine drip, ECG showed an increase in the number of premature ventricular contractions (PVCs) in trigeminy. A digoxin assay (ionized calcium and magnesium) was requested and was found to be normal. Dobutamine drip was discontinued and the patient was hooked to oxygen 2 liters per minute via nasal cannula. Thyroid function tests were requested which revealed normal results.

On the first hospital day, patient was still with productive cough but otherwise asymptomatic with no other subjective complaints such as vaginal bleeding, vaginal discharge, or contractions. There was note of good fetal movement. Patient was monitored for any signs of contractions or bleeding. A family conference was held. Present at the meeting were the patient’s obstetrician, cardiologist, intensivist and anesthesiologist. The plan was to do cesarean section with bilateral tubal ligation. The
risk of arrhythmia and cardiovascular death were explained to patient’s mother and brother. Patient was advised that there is a 36% mortality rate within 6 months after delivery of baby. Swan Ganz insertion was suggested to monitor hemodynamics during the operation.

During Swan Ganz insertion, patient developed mild to moderate uterine contractions. Fetal heart tones were at 140-150 beats per minute. There was no vaginal bleeding. Consent for stat cesarean section with bilateral tubal ligation was obtained.

Patient delivered to a live baby boy with APGAR score of 6,9, birth weight of 1,581g, birth length of 42cm, maturity score of 35 weeks small for gestational age, via primary low transverse cesarean section (vertical) with left uterine artery ligation (due to persistent bleeding noted at the left lateral uterine incision) and bilateral tubal ligation under general anesthesia. Operative time was 25 minutes. Estimated blood loss was 300mL.

Head circumference was 30cm, chest circumference was 25cm and abdominal circumference was 23cm. The placenta implanted fundally with a three vessel umbilical cord measuring 33cm.

Preoperative diagnosis was Pregnancy uterine 33 2/7 weeks age of gestation, breech in preterm labor, G1P0; elderly primigravid; primary infertility; dilated cardiomyopathy with severe left ventricular dysfunction. Postoperative diagnosis was pregnancy uterine, breech delivered preterm live birth; elderly primigravid, primary infertility; dilated cardiomyopathy with severe left ventricular dysfunction, G1P1 (0-1-0-1).

Estimated blood loss was 300cc. Postoperative antibiotics included continuing cefuroxime 750mg/IV every 12 hours x 6 doses. A repeat CBC, creatinine, K, calcium, and magnesium were requested. Oral digoxin was shifted to 0.125/IV while on NPO.

On the first postoperative day, patient was stable with a blood pressure of 110/64, heart rate of 80bpm, respiratory rate of 22. There was note of minimal vaginal bleeding. Oxytocin drip was consumed. Urine output was clear and adequate. Gradual diet and ambulation was done. Patient had hypomagnesemia. Magnesium 1 gram via slow IV push was given.

On the second hospital stay, the foley catheter was removed. Fluid intake was still limited to 1to 1.2 L per day. Started with Acetylcysteine (Fluimucil) 600mg in ½ glass of water once a day. Antibiotics were continued. The patient was asymptomatic with stable vital signs for the rest of the hospital stay. She was eventually transferred to a regular room and discharged stable and improved.

**DISCUSSION**

Physiological Considerations Associated with Heart Disease in Pregnancy

As previously mentioned, the marked hemodynamic changes in pregnancy have a profound effect on underlying heart disease. Most important consideration is that cardiac output is increased by as much as 30-50 percent and 50% of this increase occurs at 8 weeks age of gestation. Cardiac output is the product of heart rate and stroke volume and is a measure of the functional capacity of the heart. A small decline in cardiac output is seen at the third trimester as evidenced by a fall in stroke volume. Aside from an increase in cardiac output, blood volume increases by 40-50 percent, reaching a maximal volume of 4,700 to 5,200mL, by the 32nd week of gestation. Also, heart rate increases 10-15 beats per minute by the 32nd week of gestation. Physiological changes in hemodynamics are summarized in Table 1.

A Swan-Ganz catheter was placed on our patient to monitor her heart’s hemodynamics during her operation. It is a special type of catheter placed into the pulmonary artery for measuring pressures in the heart. Fortunately for our patient, despite an ejection fraction of 32%, cardiac pressures remained unremarkable and patient remained stable.

Patient’s Signs and Symptoms and Anatomical Considerations Associated with Heart Disease in Pregnancy

Aside from the persistence of cough, the patient was comfortable and did not experience symptoms such as chest pain, easy fatigability, orthopnea, paroxysmal nocturnal dyspnea and orthopnea. According to the New York Heart Association (NYHA) 1979, this classifies our patient as Class I, with uncomplicated (no limitation of physical activity). These women do not have symptoms of cardiac insufficiency or experience any chest pain (See Appendix 1). The 1994 revisions to the Classification of Functional Capacity and Objective Assessment of Patients with Heart Disease further classify our patient as stage Ia wherein, through...
extensive laboratories and ancillaries, patient has no objective evidence of cardiovascular disease. (See Appendix 2)

Anatomic cardiovascular changes in normal pregnancy include an increase in ventricular mass during the first trimester and an increase in end diastolic volume during the second and early third trimesters. The internal dimensions of all the cardiac chambers are increased and slight regurgitation through the four valves are frequently observed. The ejection fraction (EF) and stroke volume are concomitantly larger and the cardiac output is increased.¹

In dilated cardiomyopathy, the chambers are severely dilated and the left ventricle is diffusely hypokinetic. This results to a decrease in cardiac output and filling pressures increase as evidenced by dyspnea, edema and fatigue.¹

Dilated cardiomyopathy is characterized by the development of pulmonary edema in the context of left ventricular dysfunction and dilatation. Patients usually present with signs and symptoms of pulmonary edema: dyspnea, cough, orthopnea, tachycardia and occasional hemoptysis.⁴

Our patient's 2D echo showed global hypokinesia, dilated with a left ventricular ejection fraction of 32 percent is diagnostic of dilated cardiomyopathy. However, the patient did not have any symptoms of heart failure.

Ejection Fraction in Patients with Dilated Cardiomyopathy

Ejection fraction is defined as that portion of blood that is pumped out of a filled ventricle as a result of a heartbeat. Normally, the ejection fraction at rest, sitting quietly, would be approximately 55 percent.

Diastolic dysfunction is the initial alteration in dilated cardiomyopathy (DCM). Although, systolic and diastolic dysfunctions generally coexist during the clinical course of DCM. It is the left ventricular ejection fraction (LV-EF), as an entirely systolic parameter, that is commonly used to assess LV(left ventricular) function. This parameter has greater correlation between clinical status and diastolic echocardiographic parameters.¹¹ In essence, it is the left ventricular ejection fraction that correlates to the patient’s signs and symptoms.

An ejection fraction less than 35 percent refers to moderate to severe left ventricular dysfunction which classifies the patient as being in severe heart failure. Ejection fractions less than 40 cause symptoms of orthopnea, easy fatigability and paroxysmal nocturnal dypnea.

Our patient has an ejection fraction of 32% which may have been causing the patient’s persistent cough. Ironically, despite having a very low ejection fraction, our patient is asymptomatic except for her symptom of cough.

Peripartum Cardiomyopathy and Idiopathic Cardiomyopathy

The National Heart, Lung, and Blood Institute and Office of Rare Diseases convened a workshop on the diagnostic criteria for peripartum cardiomyopathy.⁶

The diagnostic criteria for peripartum cardiomyopathy include: 1) Heart failure within the last month of pregnancy or 5 months after delivery, 2) Absence of identifiable cause for

---

**Table 1. Normal hemodynamic changes during pregnancy.**

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Change During Normal Pregnancy</th>
<th>Change During Labor and Delivery</th>
<th>Change During Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood volume</td>
<td>↑ 40%-50%</td>
<td>↑</td>
<td>↓ (auto diuresis)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑ 10-15 beats/min</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↑ 30%-50% above baseline</td>
<td>↑ Additional 50%</td>
<td>↓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↑ 10mmHg</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>↑ First and second trimesters;</td>
<td>↑ (300-500mL/contraction)</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>↓ third trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td></td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
cardiac failure, 3) Absence of recognizable heart disease prior to the last month of pregnancy, 4) Left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria such as depressed shortening fraction or ejection fraction. (Ejection fraction <45% or fractional shortening <30% or left ventricular end-diastolic dimension >2.7cm/m$^2$). Since the patient’s heart failure was diagnosed at 16 weeks age of gestation, peripartum cardiomyopathy is unlikely the cause of our patient’s cardiomyopathy. 

Idiopathic cardiomyopathy may be considered after exclusion of an underlying cause for heart failure. The hallmark finding of which is impressive cardiomegaly, an echocardiographic finding of an ejection fraction less than 45 percent, or a fractional shortening less than 30 percent, and an end diastolic dimension greater than 2.7cm/m$^2$. Our patient exhibited cardiomegaly and an ejection fraction of 32 percent which make idiopathic cardiomyopathy our likely diagnosis.

### Risk Factors for Dilated Cardiomyopathy

Studies now show that dilated cardiomyopathy may be inherited. It is estimated that 20% are genetic in origin. Our patient had a sister who questionably died of a cardiac problem after giving birth and a brother who was positive for an undiagnosed heart disease.

### Importance of Preconceptual Counselling in Women with Heart Disease

It was very vital to the baby’s and mother’s survival that the patient underwent a thorough prenatal check-up with her obstetrician and cardiologist early on in the pregnancy. An ejection fraction of 32 percent would classify the patient in severe heart failure. It was important that the patient was maintained on inotropic drugs, namely digoxin (Lanoxin) otherwise called as digitalis. This drug helped sustain a cardiac output enough to supply for the mother’s and baby’s hemodynamic and metabolic needs. Close monitoring of this patient was warranted. The patient could have anytime, whether at rest of during activity, gone into cardiovascular shock compromising not only herself but the baby as well.

It is essential for obstetricians to be fully aware of the fundamentals of cardiovascular changes during pregnancy and how to detect heart diseases. Clinical indicators of heart disease during pregnancy include signs of progressive dyspnea or orthopnea, nocturnal cough, hemoptysis, syncope and symptoms of cyanosis, clubbing of fingers, persistent neck vein distension, systolic murmur of grade 3/6 or greater, diastolic murmur, cardiomegaly, persistent arrhythmia, persistent split second sound and the criteria for pulmonary hypertension. It is imperative that an obstetrician is able to recognize this signs and symptoms during prenatal care and to be able to refer to a cardiologist for further work up and monitoring.

Upon admission, the patient was under constant watch of an ICU internist. The patient was constantly hooked to an ECG monitor to monitor for any signs of cardiac distress. It was also the internist who had planned the insertion of a Swan Ganz catheter central line which had monitored the patients hemodynamics. An anesthesiologist was also available to provide for adequate pain control for whatever mode of delivery the patient underwent. In this case, the patient underwent primary cesarean section with bilateral tubal ligation under general anesthesia. Our patient was seen by an obstetrician, cardiologist, internist and anesthesiologist. All specialists were active in the patient’s management.

### Management of Cardiomyopathy

The presence of heart failure limits physical activity which may warrant several or all of the following medical options: 1) Digoxin, an inotrope which is generally considered safe in pregnancy and breastfeeding, 2) Hydralazine which is thought to be a safe vasodilator both antepartum and in the postpartum period for the newborn who is breastfeeding, 3) Diuretics such as ACE inhibitors and angiotensin receptor antagonists, although these are contraindicated in pregnancy, and 4) Beta adrenergic blockers which is now found to delay progression of myocardial dysfunction in patients with idiopathic dilated cardiomyopathy.

If heart failure is diagnosed for the first time during pregnancy, as in our case, episodes of cardiac decompensations warrant admission to an intensive care unit for close monitoring and work-up. If the hemodynamic parameters and clinical conditions deteriorate, this may warrant emergency cesarean section. Close fetal monitoring is also warranted. Steroids, dexamethasone or betamethasone, are given to enhance fetal lung maturity so as to enhance fetal survival.
In a young woman with severe dilated cardiomyopathy, manifested by greatly impaired ventricular function and decreased exercise capacity, cardiac transplantation may be considered. 

Prognosis for Patients with Dilated Cardiomyopathy

The five year survival rate for patients with dilated cardiomyopathy and symptomatic heart failure is 50%. 

Cardiovascular diseases where pregnancy is contraindicated because of the risk of maternal death are: dilated cardiomyopathy or left ventricular dysfunction (EF <40%) of any cause, severe pulmonary hypertension of any cause, and Marfan's syndrome.

Patient's Follow-up

One month after discharge, patient was readmitted for a two day history of difficulty of breathing. Diagnosis of peripartum cardiomyopathy with severe left ventricular dysfunction, CHF Class IIB. Patient had slight limitation of activity but was comfortable at rest. There was objective evidence of minimal cardiovascular disease.

On admission, blood pressure was 98/55, heart rate was irregular at 66 bpm, respiratory rate was at 19 cycles per minute. Patient had pink palpebral conjunctiva and flat neck veins. On chest examination, patient had a dynamic precordium, apex beat was at the 6th left intercostal space, anterior axillary line with a holosystolic murmur heard at its base. There was symmetrical chest expansion with clear lung fields. Pulses were equal. There was no edema or cyanosis.

Laboratories were requested. 2D echogram showed global hypokinesia with an ejection fraction of 18%. ECG showed normal sinus rhythm and non-specific ST-T wave changes. There was no note of PVCs as with the previous admission.

Medications included: Aldactone 25mg/tab 1 tablet once a day, digoxin (Lanoxin) 0.25mg/tab 1 tablet once a day and captopril 25mg/tab 1/2 tablet twice a day, Warfarin 1mg/tab 1 tablet once a day, furosemide 40mg/tab 1/2 tablet once a day. Patient was placed in bed rest and low fat low salt diet. Fluid intake was limited to 1 to 1.5L per day. Patient was monitored for signs of heart failure. On the first hospital day, the patient was asymptomatic with clear breath sounds. Observation was done for three more hospital stays. The rest of the hospital stay was unremarkable and patient was discharged stable and improved.

In conclusion, pregnancy in patients with dilated cardiomyopathy can be extremely hazardous, resulting in cardiac failure and even death. A multidisciplinary approach including the participation of an obstetrician, cardiologist, intensivist and anesthesiologist is warranted.

REFERENCES

3. Cunningham FG, et al. Williams Obstetrics 22nd ed. (c) 2005
### Appendix 1. Classification of heart failure according to the New York Heart Association (NYHA) Functional Classification System.

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Mild)</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).</td>
</tr>
<tr>
<td>Class II (Mild)</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class III (Moderate)</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class IV (Severe)</td>
<td>Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>

### Appendix 2. 1994 revisions to classification of functional capacity and objective assessment of patients with diseases of the heart.

<table>
<thead>
<tr>
<th>Functional Capacity</th>
<th>Objective Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td>
<td>A. No objective evidence of cardiovascular disease.</td>
</tr>
<tr>
<td>Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td>
<td>B. Objective evidence of minimal cardiovascular disease.</td>
</tr>
<tr>
<td>Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.</td>
<td>C. Objective evidence of moderately severe cardiovascular disease.</td>
</tr>
<tr>
<td>Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td>
<td>D. Objective evidence of severe cardiovascular disease.</td>
</tr>
</tbody>
</table>
Hodgkin’s Lymphoma in Pregnancy

HELEN V. MADAMBA, MD AND AGNES S. ESTRELLA, MD, FPOGS

Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines Manila

Lymphoma is the fourth most frequent malignancy diagnosed during pregnancy, occurring in approximately 1:6000 deliveries.1 In managing pregnant patients with Hodgkin’s lymphoma, there are dilemmas to timely diagnosis and treatment, considering many of the diagnostic procedures and treatment options for the mother’s condition may be harmful to the developing fetus. A 27-year-old G3P1 (1011) pregnant patient with a four-month history of anterior mediastinal mass, non-productive cough and low-grade afternoon fever, was initially treated as a case of community-acquired pneumonia. The patient was later admitted at our institution due to the persistence of symptoms, accompanied by dyspnea and chest pain. Biopsy done at 29 4/7 weeks age of gestation showed Hodgkin’s disease, lymphocyte depleted type (responsive to chemotherapy). At 31-32 weeks age of gestation, the patient started to experience dyspnea with intermittent low-grade fever. Chemotherapy consisting of doxorubicin 25 mg/m², bleomycin 10u/m², vinblastine 6mg/m² and dacarbazine 375 mg/m² was started. Radiotherapy was deferred until after delivery. She underwent spontaneous vaginal delivery and delivered a live baby girl small for gestational age, with no congenital malformations. It is imperative that in pregnant patients presenting with anterior mediastinal masses, accompanied by systemic symptoms, timely histopathologic diagnosis through incision or excision biopsies should be obtained. Treatment options for these patients would differ based on the histology and stage of the disease and also the age of gestation of the pregnancy.

Key words: Hodgkin’s lymphoma, pregnancy, chemotherapy, radiotherapy

Cancer in pregnancy is uncommon, with an incidence of about one in 1000.2 The most common cancers are those more frequently seen during the reproductive age of a woman; breast cancer, cervical cancer, Hodgkin’s disease, malignant melanoma, and leukemias. Lymphoma is the fourth most frequent malignancy diagnosed during pregnancy, occurring in approximately 1:6000 deliveries.1

Concurrence of pregnancy and cancer raises complex therapeutic and ethical dilemmas, because the most appropriate and timely treatment for the mother may not be in the best interest of the fetus. Fetal cells divide and differentiate rapidly during the first trimester, and radiation and chemotherapy carry well-recognized risks to the fetus, including the risk of abortion, congenital abnormalities, or preterm birth.3 As a result, physicians may be reluctant to treat the mother aggressively at the time of initial diagnosis, deferring treatment for several weeks or months, until the potential risks for the fetus are minimal. This delay, however, may substantially reduce the mother’s chance of surviving the disease.

The aim of this report was to present a case of an anterior mediastinal mass diagnosed as Hodgkin’s lymphoma during pregnancy, the approach to its diagnosis and issues involved in decision-making regarding treatment options.

THE CASE

This is the case of R.M., a 27-year-old G3P1 (1011) from Bicutan, who was admitted at the Philippine General Hospital for the chief complaint of dyspnea. She has no known co-morbidities. The family medical history is non-contributory. The patient is a college undergraduate, a housewife married for the past seven years. She has no vices, has not used any form of contraception and has had no history of any sexually transmitted disease. She had her menarche at the age of 14 with subsequent menses coming at irregular intervals lasting 3 days using 5...
sanitary pads per day. She experiences dysmenorrhea. She is unsure of her last menstrual period. The patient is a G3P1 (1011). Her first pregnancy was an abortion for which she underwent a dilatation and curettage in 1996. Her second pregnancy ended in the birth of a live baby girl by normal spontaneous delivery at a government hospital in 1997. This is her third pregnancy.

History started four months prior to admission when the patient developed persistent, non-productive cough associated with low grade afternoon fever, weight loss and body weakness. Two months prior to admission, due to persistence of symptoms, she sought consult at a government hospital where the impression was community-acquired pneumonia. She was given antibiotic treatment, which afforded no relief. At that time, examination revealed an egg-sized, firm to hard anterior chest wall mass. An abdominal ultrasound was done which showed an intrauterine pregnancy of around 16 weeks and 5 days to 17 weeks and 5 days age of gestation.

One month prior to admission, she consulted another hospital. Chest CT scan showed a mass lesion at the superior mediastinum measuring 12.0 cm x 8.5 cm x 12 cm. Erosive changes were seen in the sternum, with extension of the mass into the extrathoracic region. No abnormal calcifications were seen. The mass was intimately related to the superior mediastinal structures and extended up to the left subclavian region displacing the superior vena cava laterally. Both lung fields were clear and the heart was not enlarged. Impression was an aggressive-looking superior mediastinal mass, consider a malignant thymoma versus a lymphoma. A biopsy of the mass showed eccrine adenoma, negative for malignancy. The patient was then advised consult at a tertiary hospital.

A few hours prior to admission, the patient experienced difficulty of breathing accompanied by chest pain, which prompted consultation and subsequent admission at our institution. There was no headache, loss of consciousness, dizziness, weakness, easy fatigability, vomiting, dysphagia, dysuria, bowel changes, joint pains, no history of vaginal bleeding or discharge and with note of good fetal movement.

On admission, vital signs were stable. Physical examination centered on the chest and abdomen. There was a 10 cm x 10 cm, firm to hard, fixed, non-tender mass at the sternal area. Abdominal examination showed evidence of a pregnancy with a fundic height of 19 cms, estimated fetal weight of 500-600 grams and note of good fetal heart tones at the suprapubic area. Internal examination and rectovaginal examination were unremarkable. Admitting impression was pregnancy uterine 24 5/7 to 25 5/7 weeks age of gestation by early ultrasound, not in labor; mediastinal mass probably malignant, consider malignant thymoma versus lymphoma. Fetal well-being studies and congenital anomaly scan showed no gross malformations and a biophysical profile score of 10/10.

At 26 1/7 weeks age of gestation, biopsy of the anterior chest mass was done (10th hospital day). Pathology showed atypical spindle cell lesion with necrosis, cannot rule out mesenchymal malignancy. Repeat biopsy was suggested. At 27 5/7 weeks age of gestation, heavy growth of Candida albicans was seen on sputum smear. Patient was referred to the Obstetrics and Gynecology Infectious Disease Service and oral fluconazole was given as 200 mg loading dose and 100 mg/cap 1 capsule once a day for 14 days. Repeat biopsy was done at 29 4/7 weeks age of gestation (on the patient’s 34th hospital day). This showed Hodgkin’s disease, lymphocyte depleted type (responsive to chemotherapy). Patient was staged IIb, based on the presence of the mediastinal mass, symptoms of fever, weight loss, night sweats and on the chest CT scan findings. At 31 6/7 weeks age of gestation, the patient started to experience dyspnea with intermittent low-grade fever. Chemotherapy consisting of doxorubicin 25 mg/m², bleomycin 10 u/m², vinblastine 6 mg/m² and dacarbazine 375 mg/m² was started at 31 6/7 weeks age of gestation (on the 51st hospital day, given intravenously every two weeks on days 1 and 15).

A day after the administration of the first course of chemotherapy, the patient reported subjective feeling of improvement with no dyspnea or fever. However, two days later, the patient complained of chest heaviness, hard productive cough and occasional episodes of fever at night. Physical examination revealed an erythematous wound over the biopsy site at the right supraclavicular area. The mediastinal mass was noted to have markedly increased in size and now measured 17 cm x 13 cm. The biophysical profile score was 10/10. Non-stress test was reactive. Impression at this point was Hodgkin’s lymphoma (lymphocyte depleted type) stage IIb with massive mediastinal disease, pregnancy uterine 32 6/7 to 33 6/7 weeks age of gestation cephalic not in labor. The need for radiotherapy was discussed with the patient and her family to bring about symptomatic relief and faster shrinkage of the mediastinal mass. Patient
Hodgkin's Lymphoma in Pregnancy / Madamba and Estrella

and her family were advised on the advantages and disadvantages of radiotherapy during pregnancy. The family decided to have the baby delivered first before undergoing radiotherapy. Consensus was to carry the pregnancy as close to term as possible, regardless of the risks to the mother. Dexamethasone was likewise given to hasten fetal lung maturity.

At 33 1/7 to 34 1/7 weeks, the patient complained of labor pains. She underwent spontaneous vaginal delivery with median episiotomy and repair and delivered a live baby girl 35 weeks by pediatric aging, weighing 1400g, small for gestational age, APGAR score 9 remaining 9. The rest of the hospital stay was unremarkable and the patient was discharged from the hospital stable and improved, with home instructions, medications and follow up schedule. Discharge diagnosis was Hodgkin's lymphoma, stage IIB (lymphocyte depletion type); status post cycle I chemotherapy (ABVD); hospital acquired pneumonia, resolved; pregnancy uterine delivered via spontaneous vaginal delivery cephalic preterm livebirth, small for gestational age. The long-term plan for the patient was to continue with combined chemotherapy and radiotherapy for treatment of Hodgkin's lymphoma. Within six months postpartum, the patient underwent one more cycle of chemotherapy and one dose of radiotherapy for superior vena cava syndrome before she was lost to follow up.

**DISCUSSION**

Cancer complicates approximately 1 in one thousand pregnancies. Lymphoma is the fourth most frequent malignancy diagnosed during pregnancy. In the Philippines, for the year 2005, the incidence of Hodgkin's disease was 133 out of 54,864 women diagnosed with cancer. This gives a crude rate of 0.2-0.3% per 100,000 women. The male:female ratio is 1.4:1. Hodgkin lymphoma (HL) is rare before age 10 and is most common between ages 15 and 40. The early peak of Hodgkin's lymphoma includes patients from their teens to 30 years old, thereby covering the prime childbearing years.

Lymphoma is a localized or disseminated malignant proliferation of cells of the lymphoreticular system, primarily involving the lymph node tissue, spleen, liver and bone marrow. Hodgkin's lymphoma, also known as Hodgkin's disease, is a type of lymphoma first described by Thomas Hodgkin in 1832. It is characterized clinically by the orderly spread of disease from one lymph node group to another and by the development of systemic symptoms with advanced disease. These symptoms include painless lymphadenopathy, sometimes with fever, night sweats, unintentional weight loss, pruritus, splenomegaly and hepatomegaly. Systemic symptoms such as fever, night sweats, and weight loss are known as B symptoms; thus, presence of fever, weight loss, and night sweats indicate that the patient's stage is, for example, 2B instead of 2A. More than half the patients will have mediastinal adenopathy at diagnosis, and this may be the initial manifestation.

Diagnosis of Hodgkin’s lymphoma requires a pathologic examination of a lymph node biopsy. This procedure can be done safely even in pregnant patients. In most cases, samples taken from a fine needle aspiration is insufficient to make a precise diagnosis. Pathologically, the disease is characterized by the presence of Reed-Sternberg cells, although this is not pathognomonic of the disease. Classical Hodgkin's lymphoma (excluding nodular lymphocyte predominant Hodgkin's) can be subclassified into 4 pathologic subtypes based upon Reed-Sternberg cell morphology and the composition of the reactive cell infiltrate seen in the lymph node biopsy specimen. Most patients would be classified as having nodular sclerosing Hodgkin's disease while lymphocyte-rich and lymphocyte-depleted Hodgkin's disease are rare. Mixed cellularity Hodgkin's disease and lymphocyte-depletion Hodgkin's disease are seen more frequently in patients infected by HIV.

Hodgkin's lymphoma is staged using the Ann Arbor Staging System. The routine staging process requires radiological evaluation usually using chest and abdominal computed tomography (CT). Fetal exposure to radiation during chest x-rays and CT is much lower than the threshold dose for adverse fetal effects and should therefore not present with any fetal risk. On the other hand, abdominal and pelvic CT is associated with higher fetal radiation exposure of up to 0.02Gy. Although this level is still below the threshold dose for severe congenital malformation other types of examinations that are not associated with radiation, such as ultrasonography or magnetic resonance imaging (MRI), may provide the desired diagnostic information without measurably increasing the risk of fetal malformations. Therefore, abdominal and pelvic CT should be avoided during pregnancy.

Since the vast majority of Hodgkin's lymphoma patients are currently treated initially with
chemotherapy, whatever the disease stage, staging of a pregnant patient with lymphoma should be limited based on the history, a thorough physical examination, routine blood tests, lymph node biopsy, chest x-ray with abdominal shielding and an ultrasound or MRI of the abdomen.

The current trend in the treatment of Hodgkin’s lymphoma is to administer chemotherapy for all stages. The most popular chemotherapy regimens used in the treatment of Hodgkin’s disease include doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and mechlorethamine, vincristine, procarbazine and prednisone (MOPP), or combination of the drugs in these two regimens. For women with advanced disease diagnosed in the early stage of pregnancy, a delay in therapy may adversely affect survival and suboptimal treatment places the patient at risk of recurrence. In such cases, treatment with an appropriate chemotherapy regimen (ABVD, BEA-COPP, etc) should be initiated promptly and a therapeutic abortion should be considered due to the potential teratogenic effects of chemotherapy in the first trimester. On the other hand, patients with early stage Hodgkin’s lymphoma diagnosed in the first trimester can be followed up at short intervals for signs of disease progression without any treatment. At the beginning of the second trimester, adequate treatment with ABVD should be administered promptly. Patients presenting in the second or third trimesters can be safely treated with chemotherapy similarly to non-pregnant women. Delivery should be avoided during the maternal nadir period, usually 2-3 weeks after treatment to give time for the bone marrow to recover. For this same reason, chemotherapy should not be given beyond 35 weeks gestation because spontaneous delivery can occur before the bone marrow has recovered. Iatrogenic preterm deliveries should be avoided, and preterm labor should be treated aggressively.

Most cytotoxic agents exert their effect by interfering with DNA and RNA synthesis, thereby interrupting essential metabolic pathways and eventually destroying actively dividing cells and tissues. This holds true not just for the tumor tissues but also for the normal tissues. Most chemotherapeutic agents with relatively low molecular weight cross the human placenta and reach the fetus. Teratogenicity of any drug depends on the timing of exposure, the dose and the characteristics affecting placental transfer. Genetic predispositions to teratogenicity might explain why people given the same agents have differing susceptibility.

The majority of information on the effects of in utero exposure to chemotherapy has been derived from retrospective reports and case series. Fetuses exposed during the first trimester carry the risk of spontaneous abortion and miscarriage as well as congenital abnormalities and minor malformations. Exposure during the second and third trimesters increases the risk of intrauterine growth restriction (IUGR) and low birthweight. Maternal nutritional deficiencies, caused by the tumor or by chemotherapy-induced anorexia, can also affect fetal growth and birthweight. The baby in the case presented was delivered preterm at 35 weeks and small for gestational age.

After organogenesis, the eyes, genitalia, the hemopoietic system and central nervous system remain vulnerable to continued exposure to chemotherapy. This has raised concerns regarding long-term neurodevelopmental outcome, risk of childhood malignancy and long-term fertility of children exposed in-utero to chemotherapy for the treatment of HL. However, available data regarding the late effects of chemotherapy suggest that chemotherapy does not have a significant impact on a child’s neurologic and sexual development. Also, recent studies suggest that the offspring’s risk of developing childhood cancer is no higher than that in the general population. In the local setting, a study conducted by Zalameda-Castro in 2003 reported no significant neurodevelopmental delay in children exposed to chemotherapy in-utero.

A number of maternal risks may be caused by the toxicities of anti-neoplastic drugs, which are exacerbated by maternal changes during pregnancy. Bleomycin is associated with pulmonary toxicity, which can be exacerbated by oxygen therapy. Pregnant patients exposed to bleomycin should not be given oxygen during labor because of possible aggravated pulmonary toxic effects. Chemotherapy-induced neutropenia and the generalized immunosuppression during pregnancy place the woman and possibly the fetus at risk of infection. In our patient, heavy growth of Candida species was noted on sputum culture, for which she was given intravenous fluconazole. Fluconazole, although a category C drug, would be safe to use beyond the period of organogenesis.

Hodgkin’s lymphoma was one of the first cancers to be cured by radiation. However, nowadays, patients with Hodgkin’s disease stage I and II are treated mainly with polychemotherapy followed by radiotherapy given only to the originally involved sites (involved-field radiotherapy). In stage III–IV
disease, radiotherapy seems to be of no benefit if given routinely in patients who show a complete remission after chemotherapy and could benefit patients with partial responses after chemotherapy.\textsuperscript{2}

When radiotherapy needs to be delivered during pregnancy, fetal exposure to radiation depends on several factors including the target dose, size of radiation fields and the distance from the edges of the fields to the fetus.\textsuperscript{1} Generally, when conventional doses of radiotherapy are administered, a distance of over 30 cm from the field edges will limit the total exposure of the fetus to only 4-20 cGy. Hence, radiotherapy can still be considered an appropriate treatment for stage I Hodgkin's lymphoma, especially in pregnant women with isolated involvement of neck or axillary lymph nodes\textsuperscript{1}. The use of supplemental shielding can substantially reduce the fetal exposure. In all other cases, however, pregnant women with malignant disease are advised to delay radiotherapy until after delivery.

Long term events related to radiotherapy include second malignancies and cardiac injury.\textsuperscript{5} Survivors treated with chest radiotherapy are at increased risk of cardiovascular events, particularly coronary artery disease and a variety of cardiovascular complications, including pericarditis, myocardial fibrosis, valvular abnormalities and conduction disturbances. The risk of cardiovascular events at 5 and 12 years is 5.5% and 14%, with median latent time of 67 months from the end of radiotherapy. All patients who developed pulmonary toxicity had received mediastinal irradiation (median dose 40 Gy; range: 36-44 Gy); and the median time from radiotherapy to pulmonary sequelae was 76 weeks.\textsuperscript{6} The risk of neoplasia at 5 years and 12 years was 4% and 8%, respectively, with no cases of leukemia. Patients treated with radiotherapy have a \textasciitilde{}25% risk of developing a second malignancy at 25 years, with no evidence of decreasing risk over time.\textsuperscript{6}

risks of radiation effects to the fetus are derived mostly from animal studies and from survivors of nuclear explosions, data from children exposed in utero to diagnostic x-rays, and data on children who were exposed to radiation from the Chernobyl accident in utero. Generally, the expected radiation effects are lethality, organ malformations, mental retardation and cancer induction.\textsuperscript{2} Radiation exposure during the second and third trimesters is associated with a carcinogenic effect that may include an increased risk for the development of leukemia and solid tumors within the first decade of life.\textsuperscript{1} Another concern is the increased risk of neurodevelopmental impairment, including a decrease in the intelligence quotient (IQ) and even severe mental retardation.

The decision to give radiotherapy to pregnant women with cancer should be considered by the patient after the radiation oncologist has counseled her adequately. For the case presented, radiotherapy was suggested when the patient developed superior vena cava syndrome. The patient and her family were well informed of the risks and benefits that may be derived from the treatment. Aware of the potential risks to the unborn fetus, they decided on postponing radiotherapy until after delivery of the baby.

A number of studies showed that Hodgkin's lymphoma and its treatment does not affect fertility and pregnancy outcome. Fertility was preserved in patients with Hodgkin's lymphoma, even after treatment with chemotherapy and radiotherapy with favorable pregnancy outcome in long-term survivors after therapy for Hodgkin's lymphoma. In the study by Brusamolino, et al. (2006), 10 women (17% of those potentially fertile) became pregnant in one or more occasions after completion of treatment. Infants born to women with Hodgkin's lymphoma during pregnancy did not have higher risk of prematurity or intrauterine growth retardation.\textsuperscript{1} There are no reports of Hodgkin's lymphoma metastases to the placenta or the fetus. There is no overall increased risk of adverse birth outcome (congenital abnormalities and stillbirths combined) for Hodgkin's disease patients and no increased risk associated with radiation treatment alone (supra- or infradiaphragmatic), whereas women treated with both chemotheraphy and radiation were more likely to have an adverse outcome.\textsuperscript{3} In a locally published report\textsuperscript{12} by Castillo-Cheng (2002), a case of Hodgkin's lymphoma diagnosed before pregnancy was presented. Prior to pregnancy, the patient had undergone four cycles of chemotherapy and 25 sessions of Cobalt therapy. She was able to conceive and despite being symptomatic, opted to delay treatment for her condition until the safe delivery of a baby boy with no gross congenital abnormalities. However, the possibility of an increased risk of congenital abnormalities in offspring of women diagnosed with Hodgkin's disease before pregnancy still cannot be ruled out.

For years, it was believed that pregnancy increased the relapse and mortality rates of patients with Hodgkin's lymphoma.\textsuperscript{1} However, when diagnosed during pregnancy, the natural course of
Hodgkin’s lymphoma is only affected by the possible delay in treatment, since the beneficial effects of chemotherapy to the mother might pose deleterious effects on the developing fetus. Therefore, it is most important for the attending physician to provide the pregnant patient and her family with all the available information regarding the disease and its prognosis, possible treatment alternatives and maternal and fetal risks. Every decision should be made together with the patient only after careful consideration of both risks and benefits.

CONCLUSION

Pregnancy complicated by Hodgkin's disease makes management difficult for the physician because treatment for the malignancy by chemotherapy and radiotherapy would have deleterious effects on the growing fetus. We presented a case of pregnant patient who was diagnosed with Hodgkin's lymphoma at 34-35 weeks age of gestation. A single course of multiagent chemotherapy was given prior to delivering a preterm baby. We reviewed literature on the diagnosis of Hodgkin's lymphoma in pregnancy, the role of chemotherapy and radiotherapy in its treatment along with their effects on the developing fetus. Most important in the management of pregnant patient with Hodgkin's lymphoma is the proper education and appropriate counseling of the patient and her family regarding the disease, its treatment and prognosis. It is essential for the attending physician to involve the patient and her family in every decision-making process during the course of treatment.

REFERENCES