Association Between Ovarian Volume and Endometrial Malignancy in Women with Postmenopausal Bleeding

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Objective: This is a prospective case control study which aimed to determine the correlation of ovarian volume measurements with endometrial tissue diagnosis such as benign, premalignant and malignant conditions in women with postmenopausal bleeding.

Methods: Thirty four postmenopausal women with bleeding underwent transvaginal ultrasound for ovarian volume measurements prior to dilatation and curettage. The presence of benign (Group I), premalignant and malignant endometrial conditions (Group II) were correlated with ovarian volume.

Results: Mean endometrial stripe thickness for group I (N = 19; 1.16ml +/- SD 0.88ml) was not significantly different from group II (N = 15; 1.58ml +/- SD 0.53ml). Mean ovarian volume among patients with premalignant and malignant histology (5.70ml +/- SD 1.91ml) was significantly higher than those with benign histology (2.04ml +/- SD 1.10ml) (P = 0.023). Linear regression analysis showed an association between ovarian volume and premalignant and malignant endometrial conditions (P=0.000). Using the mean ovarian volume cut-off of 5.8ml for postmenopausal women with bleeding, the sensitivity, specificity, positive predictive value and negative predictive value for premalignant and malignant endometrial conditions were 100%, 67.87%, 40% and 100%, respectively.

Conclusion: Large ovaries among postmenopausal women may represent a marker of risk for endometrial cancer and may be used as an adjunct to endometrial thickness in ruling endometrial malignancy.

Key words: Ovarian volume, endometrial malignancy, postmenopausal bleeding

Post menopausal bleeding warrants immediate investigation as it is often associated with malignancy until proven otherwise. Several studies have proven that thickened endometrial lining especially in menopausal women may indicate the presence of pathology. Bleeding after menopause may be brought about by increased production of androgens, the main hormonal product of postmenopausal ovary.1

The question of why some menopausal women are at risk for endometrial malignancy despite being menopausal has challenged many clinicians. Normally, with the loss of hormonal stimulation at menopause, the ovaries undergo gradual decline in volume and become smaller. The cut-off for ovarian volume in postmenopausal women is estimated to be less than 5.8ml.2 Large ovaries with increased volume may represent a marker of higher androgen levels indicating a greater availability of substrate for estrogen synthesis, which contributes to the neoplastic development of the endometrium. Clinical studies have reported association between ovarian stromal hyperplasia and the diagnosis of endometrial cancer. Although studies have reported such association, the use of ovarian volume as a screening tool has not been fully established.

In this study, the ovarian volume was measured in women with postmenopausal bleeding, in order to determine its association with premalignant and malignant conditions of the endometrium. The objectives of this prospective case control study were the following:

1. To determine the ovarian volume in women with postmenopausal bleeding suspected of having endometrial malignancy.
2. To correlate ovarian volume measurements with endometrial tissue diagnosis such as benign, premalignant and malignant conditions in women with postmenopausal bleeding.

3. To determine whether increased ovarian volume in women with postmenopausal bleeding was associated with premalignant and malignant conditions of the endometrium.

MATERIALS AND METHODS

Included in the study were menopausal women for at least a year or more, who underwent transvaginal sonography for postmenopausal bleeding at the Comprehensive Women’s Care Unit of Cardinal Santos Medical Center from July 1, 2008 to February 28, 2009. Only those with subsequent dilatation and curettage were included in the study. Exclusion criteria consisted of those with sonographic evidence of endometrial or endocervical polyps and submucous myoma, those on hormonal replacement therapy and chemotherapeutic agents for breast carcinoma and those with non-visualized ovaries. All patients were interviewed and patient’s personal data, menstrual history, obstetrical history and medical history were recorded on the standard OB-GYN ultrasound form.

All the patients were instructed to empty their bladder prior to transvaginal scanning using the Voluson 730 Expert ultrasound machine with a 7.5mHz probe. With informed consent, transvaginal ultrasound was performed by the fellow under the supervision of the consultant on duty, with careful measurements of the uterus, endometrium and the ovaries. The uterus was visualized in the longitudinal plane and the endometrial stripe measured at its maximum anterior and posterior margins of the basal layers delineated by the echogenic interface between the endometrium and the inner myometrium. Both ovaries were measured at their largest dimensions. The standard maximal three diameters to calculate ovarian volume were obtained from 2D images. The length and height were measured in centimeters and the probe rotated 90 degrees to measure the width in centimeters. 2D ovarian volume was calculated using the prolate ellipsoid formula: Length x Width x Height in centimeters multiplied by 0.523. Only the large ovarian volume measurements were included in the statistical analysis.

The histopathological results of the endometrial curettage were obtained and correlated with the ovarian volume measurements. The patients were divided into two groups. Group I included those with benign endometrial conditions and served as the control group. Group II included those with premalignant and malignant endometrial conditions and served as the case group. Ovarian volume measurements of the two groups were compared using the t-test and significance determined by P value < 0.05. Linear regression analysis was performed to determine the correlation of increased ovarian volume measurements in patients with premalignant and malignant endometrial conditions. The sensitivity, specificity, positive and negative predictive values of 5.8ml cut-off value for ovarian volume in menopausal women, in determining the occurrence of endometrial malignancy were obtained.

RESULTS

Sixty three women with postmenopausal bleeding were recruited in the study. Only 34 had subsequent dilatation and curettage and were included in the study. Table 1 showed the demographic characteristics of the study population. The age range of women was 47 to 87 years with a mean age of 58.18 (+/-SD 8.85). The mean menopausal years was 7.12 years (+/- SD 7.21). The gravidity range had a minimum of 0 and maximum of 9 with an average of 4.03 +/- 2.23 while parity ranged from 0 to 8 with a mean of 3.56 +/- 1.84 (equivalently 4). The BMI ranged from 20 to 35 with mean of 26.17 (+/- SD 3.71). Using t-test, there was no significant difference in the demographic characteristics between group I with benign endometrial lesions and group II with premalignant and malignant lesions, except for age at P value of 0.031. Patients in group II were older with mean age of 58.60 +/- 11.575 while group I had mean age of 57.84 +/- 6.256 as shown in table 2.

Table 1. Demographic characteristics of the total patient population.

<table>
<thead>
<tr>
<th>N = 34</th>
<th>Mean +/- Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58.18 +/- 8.851</td>
</tr>
<tr>
<td>No. of Menopausal Years</td>
<td>7.12 +/- 7.210</td>
</tr>
<tr>
<td>Gravidity</td>
<td>4.03 +/- 2.236</td>
</tr>
<tr>
<td>Parity</td>
<td>3.56 +/- 1.845</td>
</tr>
<tr>
<td>BMI</td>
<td>26.18 +/- 3.713</td>
</tr>
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</table>
Table 2. Demographic characteristics of groups I and II.

<table>
<thead>
<tr>
<th></th>
<th>Group I (N = 19)</th>
<th>Mean +/- Std. Deviation</th>
<th>Group II (N = 19)</th>
<th>Mean +/- Std. Deviation</th>
<th>P value</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.84 +/- 6.256</td>
<td>58.60 +/- 11.575</td>
<td></td>
<td></td>
<td>0.031</td>
<td>S</td>
</tr>
<tr>
<td>No. of Menopausal Years</td>
<td>6.42 +/- 5.541</td>
<td>8.00 +/- 9.032</td>
<td></td>
<td></td>
<td>0.066</td>
<td>NS</td>
</tr>
<tr>
<td>Gravidity</td>
<td>4.00 +/- 2.357</td>
<td>4.07 +/- 2.154</td>
<td></td>
<td></td>
<td>0.821</td>
<td>NS</td>
</tr>
<tr>
<td>Parity</td>
<td>3.42 +/- 1.895</td>
<td>3.73 +/- 1.831</td>
<td></td>
<td></td>
<td>0.956</td>
<td>NS</td>
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<tr>
<td>BMI</td>
<td>25.84 +/- 4.206</td>
<td>26.60 +/- 3.065</td>
<td></td>
<td></td>
<td>0.191</td>
<td>NS</td>
</tr>
</tbody>
</table>

The presence of risk factors such as hypertension and diabetes mellitus was greater in Group II. Ten out of 15 (67%) patients with premalignant and malignant lesions had hypertension and/or diabetes, while only 9 of 19 patients (47%) in Group I were noted to have such risk factors.

Of the 34 patients included in the study, 19 patients in group I had benign endometrial lesions. Table 3 shows the histopathologic diagnosis of these patients. Ten patients had endometrial polyps, 5 had cystic atrophy of the endometrium while 4 had endometrial hyperplasia without atypia.

The histopathologic diagnoses of 15 patients in Group II with premalignant and malignant endometrial conditions are shown in Table 4. Thirteen had endometrioid adenocarcinoma while 2 patients had simple hyperplasia with focal atypia.

The mean endometrial stripe thickness for group I was 1.16cm (+/- SD 0.88) and 1.58cm (+/- SD 0.53) for group II. However, t-test showed no significant difference in the endometrial stripe thickness between the two groups at P value of 0.411. (Table 5)

The range of ovarian volume measurements in Group I was 0.58ml to 5.50ml with a mean of 2.04ml (+/- SD 1.12). The range of ovarian volume measurements in Group II was 3.50ml to 9.50ml with a mean of 5.71ml (+/- SD 1.91). (Table 5)

The ovarian volume measurements in Group II were bigger than those in Group I. The P value of 0.023 from t-test confirmed that there was a significant difference in the means of ovarian volume between the group with benign endometrial lesions and the group with premalignant and malignant endometrial lesions.

Table 3. Histopathologic diagnosis of patients with benign lesions (Group I).

<table>
<thead>
<tr>
<th>Histopathologic Diagnosis</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial Polyps</td>
<td>10</td>
</tr>
<tr>
<td>Cystic Atrophy of the Endometrium</td>
<td>5</td>
</tr>
<tr>
<td>Endometrial Hyperplasia Without Atypia</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 4. Histopathologic diagnosis of patients with benign lesions (Group II).

<table>
<thead>
<tr>
<th>Histopathologic Diagnosis</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial Adenocarcinoma</td>
<td>13</td>
</tr>
<tr>
<td>Simple Hyperplasia with Focal Atypia</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 5. Endometrial stripe thickness and ovarian volume of groups I and II.

<table>
<thead>
<tr>
<th></th>
<th>Group I (Benign)</th>
<th>Mean +/- Std. Deviation</th>
<th>Group II (Premalignant/Malignant)</th>
<th>Mean +/- Std. Deviation</th>
<th>P value</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial Stripe (cm)</td>
<td>1.16cm +/- 0.88</td>
<td></td>
<td>1.58cm +/- 0.53</td>
<td></td>
<td>0.411</td>
<td>NS</td>
</tr>
<tr>
<td>Ovarian Volume (ml)</td>
<td>2.04ml +/- 1.10</td>
<td></td>
<td>5.71ml +/- 1.91</td>
<td></td>
<td>0.023</td>
<td>S</td>
</tr>
</tbody>
</table>
All 19 patients in Group I with benign findings had ovarian volume measurements < 5.8ml. In Group II, with premalignant and malignant conditions, 9 had ovarian volume measurements < 5.8ml while 6 had ovarian volume measurements more than 5.8ml. Linear regression analysis showed significant association between increased ovarian volume and the presence of premalignant and malignant endometrial conditions (P = 0.000). (Table 6).

Table 6. Ovarian volume cut-off of 5.8ml in patients with benign and premalignant / malignant endometrial lesions.

<table>
<thead>
<tr>
<th>Ovarian Volume Cut-off</th>
<th>Group I Benign</th>
<th>Group II Premalignant / Malignant</th>
<th>Asymp. Sig.</th>
<th>Exact Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5.8</td>
<td>19</td>
<td>9</td>
<td>.000 (a)</td>
<td>.000</td>
</tr>
<tr>
<td>&gt; 5.8</td>
<td>0</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a = Based on Z approximation
P value = 0.000
Sensitivity = 100%
Specificity = 67.87%
Positive Predictive Value = 40%
Negative Predictive Value = 100%

Based on this study, using the mean ovarian cut-off of 5.8ml for postmenopausal women, a value less than 5.8ml reassured that 100 percent of the patients did not have malignant endometrial condition (NPV=100%) and had a specificity of 68% in correctly identifying those who did not have endometrial malignancy on initial screening. On the other hand, an ovarian volume greater than 5.8ml, had 100% sensitivity in picking up endometrial carcinoma. However, it had a positive predictive value of only 40% in confirming a patient with endometrial malignancy.

DISCUSSION

Women with postmenopausal bleeding must always be investigated as 10 percent of patients will have endometrial carcinoma. Transvaginal ultrasonography has been very useful in detecting endometrial pathology in women with postmenopausal bleeding. Ample evidence in literature supports reliability of sonographic evaluation of endometrial thickness and volume in the assessment of endometrial pathology. However, sonographic evaluation of ovarian volume in association with endometrial malignancy has yet to be established.

Recent data suggest that postmenopausal women with larger ovaries are at increased risk for endometrial carcinoma, hence ovarian volume measurements in association with endometrial pathology have been investigated. Several investigators have set different cut-off measurements of ovarian volume for menopause. Aboulgar, et al. determined the postmenopausal ovarian volume to be 3.4 ± 1.7cm. Goswany calculated it at 3.58 ± 1.40cm. Aviram, et al. stated an ovarian volume of 3.4 ± 2.2cm. Callen set it at 5.8 ± 3.6cm. This was the cut-off value used in this study.

Shemen, et al. investigated the association of ovarian volume with cancer among postmenopausal women. In his study, postmenopausal women aged 55 to 59 without cancer had a mean ovarian volume of 1.25cm³ which declined further to 1.0cm³ between 65 and 69 years. However, those with endometrial cancer had bigger volume with mean ovarian volume greater or equal to 3.0cm³. They concluded that large ovaries among postmenopausal women may represent a marker of risk for hormonally related tumor like endometrial cancer.

The enlarged ovarian volume among postmenopausal women could be explained by stromal hyperplasia. Stromal hyperplasia is most commonly seen in postmenopausal patients and may be associated with raised androgen levels and also with endometrial adenocarcinoma. Postmenopausal estrogens originate from the peripheral conversion of androgens which are produced by the adrenal glands and the ovaries.

VH Jongen, et al. studied the relationship between the presence of endometrioid cancer, degree of ovarian hyperplasia and ovarian steroid production in postmenopausal women. Results showed higher degree of ovarian stromal hyperplasia in the presence of endometrioid endometrial cancer (P=0.0001). Likewise, increasing degree of ovarian stromal hyperplasia was related to higher ovarian levels of both testosterone and androstenedione (P<0.05 and P<0.005, respectively) but not to estrone and estradiol.

An investigation was done by Lukanova, et al. on circulating levels of sex steroid hormones and risk of endometrial cancer in postmenopausal women. Among 124 postmenopausal women with invasive endometrial cancer, highest levels were estradiol (4.13) and estrone (3.67), followed by androstenedione (2.15) and testosterone (1.74). The effects of elevated androstenedione and testosterone
levels on the diseased risk seem to be mediated mainly through their conversion to estrogens which are considered to contribute to the neoplastic development of the endometrium.\(^8\)

In a very recent study, Fogle, et al. investigated whether the postmenopausal ovary is hormonally active and contributes to the circulating pool of androgens. They analyzed serum levels of testosterone, androstenedione, dehydroepiandrosterone, estrone and estradiol preoperatively, intraoperatively and postoperatively among postmenopausal women undergoing total abdominal hysterectomy with bilateral salpingooophorectomy. They concluded that postmenopausal ovary remains hormonally active, secreting significant amounts of androgens and estrogens and persists in women as long as 10 years beyond menopause. This phenomenon may be marked in menopausal women with increased ovarian volume.\(^9\)

While adrenal glands produce dehydroepiandrosterone (DHEA) and its sulphated form DHEA-S, which are converted to the more potent androgens such as testosterone and dihydrotestosterone (DHT) through peripheral conversion, the ovaries synthesize more androstenedione, testosterone and dihydrotestosterone (DHT) and negligible amounts of DHEA and DHEA-S. In order for postmenopausal ovary to continue to produce androgens, it must maintain the ability to express the enzyme necessary for androgen biosynthesis. Initial studies demonstrated by Northern analysis showed that only ovaries from postmenopausal women with endometrial hyperplasia or cancer expressed all the enzymes necessary for androgen synthesis.\(^10\)

The primary objective of this study was to determine the ovarian volume in women with postmenopausal bleeding and to investigate its association with endometrial malignancy. Results showed that smaller ovarian volumes were associated with benign endometrial conditions and bigger ovarian volumes were seen in those with premalignant and malignant conditions. All 19 patients in group I with benign histopathologic diagnosis and ovarian volume of less than 5.8ml which showed a negative predictive value of 100% but a specificity of only 68% in finding a normal or benign endometrial condition among those negative for malignancy. Higher ovarian volumes were seen in those with premalignant and malignant conditions. Of the 15 patients in group II, 6 had ovarian volume > 5.8ml and 9 had ovarian volume < 5.8ml. The cut-off value of 5.8ml had a 100% sensitivity of picking up or identifying malignant endometrial condition but only had a positive predictive value of 40% in confirming a patient with endometrial malignancy. The cut-off was highly sensitive in picking up malignant endometrial conditions and can truly identify those with benign endometrial conditions however, it yielded low specificity and positive predictive value. This could probably be explained by the cut off ovarian volume used at 5.8ml, too high for Asians. African, American and Caucasian women had larger mean ovarian volumes than Asians. Adeed, et al. investigated the normal ovarian volume among menopausal Malaysian and Chinese women. Ovarian volume among menopausal Malaysian women was 2.85 +/- SD 2.98cm\(^3\) and 3.26 +/- SD 5.09cm\(^3\) among menopausal Chinese women.\(^11\) The smaller ovaries among Asians were also consistent with their data showing that Asians have lower testosterone levels.\(^1\)

Hence, if cut-off value was lowered to 3.5ml, the ovarian volume as a screening parameter was also significant in determining benign and malignant endometrial conditions at P value of 0.000. Cut-off value of 3.5ml showed high sensitivity and specificity of 93% and 95%, respectively, with a high positive predictive value of 93% and a negative predictive value of 94.7%. (Table 7). Lowering the cut-off to 3.5ml significantly improved the specificity and positive predictive value. (Figure 1)

The results showed considerable overlap in the endometrial thickness between patients with benign and those with malignant conditions. There was no significant difference in the endometrial stripe thickness between the two groups. However, in the presence of a thickened endometrium, coupled with an increased ovarian volume, the probability of having a malignant condition is increased.

**Figure 1.** Comparison of sensitivity, specificity, positive predictive value and negative predictive value of mean ovarian volume cut-off of 5.8ml vs 3.5ml.
Table 7. Ovarian volume cut-off of 3.5ml in patients with benign and premalignant / malignant endometrial lesions.

<table>
<thead>
<tr>
<th>Ovarian Volume Cut-off (ml)</th>
<th>Group I Benign</th>
<th>Group II Premalignant / Malignant</th>
<th>Asymp. Sig. (2-tailed)</th>
<th>Exact Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.5</td>
<td>18</td>
<td>1</td>
<td>.000 (a)</td>
<td>.000</td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>1</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a = Based on Z approximation
P value = 0.000
Positive Predictive Value = 93%
Sensitivity = 93%
Negative Predictive Value = 94.7%
Specificity = 95%

CONCLUSION

In conclusion, large ovaries among postmenopausal women may represent a marker of risk for endometrial cancer. The risk is higher in patients with ovarian volume greater than 5.8ml than in those with ovarian volume less than 5.8ml. Lowering the ovarian volume cut-off value to 3.5ml is more appropriate for Asians since ovarian volume measurements in this group tend to be smaller. There is direct association between increased ovarian volume and premalignant and malignant endometrial conditions. Menopausal women with decreased ovarian volume, even if symptomatic, are most likely associated with benign conditions. On the other hand, menopausal women with increased ovarian volume, even if asymptomatic, should be closely monitored as these women may still be at risk for endometrial carcinoma. This study showed that ovarian volume measurements can be used as an adjunct to endometrial thickness in ruling out endometrial carcinoma.

REFERENCES

Birth Weight Percentiles from a Hospital-based Computerized Perinatal Database in the Philippines

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**Background:** It has been the practice of clinicians to compare birth weights with a standard nomogram applicable to a certain population in order to identify those infants who are at high risk for neonatal mortality and morbidity by defining which neonates are small or large for gestational age. However, this standard was formulated based on birth weights of a particular population in a Western country and therefore, may not be applicable to a third world country such as the Philippines.

**Methods:** Birth weights of neonates who were delivered as singleton live births at the Philippine General Hospital from January 2006 to December 2008 were determined based on a perinatal database.

**Results:** The tenth and ninetieth percentiles of birth weights of neonates in the Philippine General Hospital were generally similar to the western nomogram. However, more conclusive evidence could be derived from a population-based study rather than a hospital-based study such as this.

**Key words:** nomogram, gestational age, neonates

Birth weight is one of the indicators of good perinatal outcome. In the Philippine General Hospital, identification of infants at risk for perinatal morbidity and mortality is done with the use of a Western population-based nomogram for birth weight percentiles. Maternal weight, height, parity, ethnic group, smoking, presence of maternal co-morbidities such as diabetes mellitus, hypertension, infections, heart and kidney disease are all factors that affect the birth weight of a fetus. Birthweights that fall below the tenth percentile are labeled as small for gestational age and are associated with a higher incidence of perinatal morbidity and mortality. Fetal demise, birth asphyxia, meconium aspiration, and neonatal hypoglycemia and hypothermia are all increased, as is the prevalence of abnormal neurological development in the neonate. Consequently, birth weights that fall above the ninetieth percentile are labeled as large for gestational age, which may be attributable to maternal constitution, multiparity, increased maternal age, male fetus, and maternal race and ethnicity. By identifying neonates whose birth weights belong in the small and large for gestational age groups, clinicians are able to focus their attention on infants who are need of more intensive care than others of the same age of gestation.

In several Western countries such as the United States, Canada and the United Kingdom, birth weights are classified based on nomograms developed based on national data. In 1993, Wilcox and associates did a retrospective analysis of a computerized obstetric database from three large maternity units that had about 16000 deliveries a year. They concluded that birthweight standards require precise dating of pregnancy and should be analyzed while taking into consideration factors that affect birth weight in order for the standard to be able to describe the population from which it was derived.

A similar analysis of birth weight was undertaken by Amini and colleagues using a computerized database that collected data from deliveries in 1975 to 1992. From this large database, they were able to create a nomogram that could help the clinician identify retardation and acceleration of intrauterine fetal growth, allowing them to opportunity to improve neonatal outcomes.
The Philippine General Hospital remains as one of the major referral centers providing tertiary care to pregnant women. The Colorado Chart for Birth-weights is currently the nomogram being used to identify infants belonging in the high risk extremes. However, this nomogram was based on a Western population and has not been updated or revised since it was developed five decades ago.

Each year, all deliveries in the hospital are encoded in a computerized perinatal database being maintained by the hospital’s Obstetrics and Gynecology department. Each patient record includes data such as maternal age, medical conditions, age of gestation at the time of admission, and neonatal outcome. These data could be easily accessible and retrieved with the use of the Epi Info epidemiological software that was used in creating the computerized database.

**Objectives of the Study**

**General Objective**

To develop a nomogram of birth weight percentiles of neonates delivered in the Philippine General Hospital from January 2006 to December 2008 based on a computerized perinatal database.

**Specific Objectives**

1. To identify patients with singleton pregnancies admitted for delivery at the Philippine General Hospital from January 2006 to December 2008 from a computerized perinatal database.

2. To exclude patients admitted for delivery at the Philippine General Hospital from January 2006 to December 2008 who had risk factors for having small or large for gestational age neonates and who delivered stillbirths.

3. To classify subjects according to age of gestation at time of admission.

4. To determine the tenth and ninetieth percentiles of birth weights of neonates born in each completed week of gestation.

**MATERIALS AND METHODS**

This is a retrospective analysis of the computerized perinatal database of patients admitted at the Department of Obstetrics and Gynecology of the Philippine General Hospital from January 2006 to December 2009.

**Patient Population**

The patient population in this study included women who delivered singleton live births at the Philippine General Hospital between January 2006 and December 2008.

**Methodology**

Data from patients who delivered singleton live births at the Philippine General Hospital between January 2006 and December 2008 were retrieved using the Epi Info computer software. These data included maternal age, co-morbidities, age of gestation, mode of delivery and anesthesia used, as well as the neonatal outcome. These records were reviewed, and patients who had risk factors for giving birth to small or large for gestational age babies were excluded. The remaining patients who delivered between 24 to 42 completed weeks were then analyzed. Birth weights of live births born at each age of gestation were then retrieved along with the actual pediatric aging by Ballard Maturational Scoring. Those patients whose age of gestation had a difference of more than 2 weeks from the neonate’s actual Ballard score were also excluded. The tenth and ninetieth percentiles for each completed week of gestation were then computed and then compared with the standard birth weight nomogram.

**RESULTS**

A total of 8745 patients were included in this retrospective analysis, all of whom delivered live births at the Philippine General Hospital between January 2006 and December 2008. These patients delivered during the 24th to 42nd week of gestation. Table 1 shows the frequency distribution of patients included in the study based on the age of gestation at the time of delivery. Out of the total number of patients, 74.88% delivered during their 37th to 40th week of gestation. The remaining 25% was spread out between the remaining weeks of gestation. At less than 31 weeks and more than 41 weeks, the number of patients per gestational age was less than 1% of the total population.

Table 2 shows the computed tenth and ninetieth percentile of birth weights according to age of
gestation at time of delivery. These were then compared with the standard birth percentiles used by the Department of Obstetrics and Gynecology at the Philippine General Hospital (Table 3). No significant difference was noted between birth percentiles of neonates delivered at the Philippine General Hospital and the standard.

### Table 1. Frequency distribution of subjects according to age of gestation at time of delivery.

<table>
<thead>
<tr>
<th>Age of Gestation (weeks)</th>
<th>Frequency (n)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>9</td>
<td>0.10</td>
</tr>
<tr>
<td>25</td>
<td>12</td>
<td>0.14</td>
</tr>
<tr>
<td>26</td>
<td>19</td>
<td>0.22</td>
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<td>27</td>
<td>14</td>
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<td>28</td>
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<td>31</td>
<td>36</td>
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<td>32</td>
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<td>38</td>
<td>2189</td>
<td>25.03</td>
</tr>
<tr>
<td>39</td>
<td>1480</td>
<td>16.92</td>
</tr>
<tr>
<td>40</td>
<td>1658</td>
<td>18.96</td>
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<td>41</td>
<td>558</td>
<td>6.38</td>
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<tr>
<td>42</td>
<td>75</td>
<td>0.83</td>
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</table>

### Table 2. Birth weight percentiles for age of gestation.

<table>
<thead>
<tr>
<th>Age of Gestation (in completed weeks)</th>
<th>Frequency (n)</th>
<th>10th percentile</th>
<th>90th percentile</th>
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<tr>
<td>24</td>
<td>9</td>
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<td>700</td>
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<td>25</td>
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<td>660</td>
<td>900</td>
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<tr>
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<td>14</td>
<td>800</td>
<td>1075</td>
</tr>
<tr>
<td>28</td>
<td>18</td>
<td>945</td>
<td>1630</td>
</tr>
<tr>
<td>29</td>
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<tr>
<td>42</td>
<td>75</td>
<td>2380</td>
<td>3740</td>
</tr>
</tbody>
</table>

### DISCUSSION

In today's age of advanced technology, creating databases of large scale is no longer a daunting task. At the Philippine General Hospital, 5,000 to 6,000 patients are admitted for delivery annually. Many of these patients have high risk and complicated pregnancies. They come from indigent and low-income communities who seek antenatal obstetric care at the Philippine General Hospital. A smaller number are referrals from local health centers and other government and private institutions. After delivery, a pediatrician then provides initial care and resuscitation to the neonate, and eventually weighed and aged using physical and neurologic characteristics as specified by the Ballard Maturational Score. The neonate weight is then classified as appropriate, small or large for gestational age. Those whose weights fall below the 10th percentile are classified as small for gestational age while those whose weights are above the 90th percentile are classified as large for gestational age. Such a classification is made in order to identify those neonates who are at high risk for complications and who may be in need of closer monitoring of growth and development especially in the first year of life.

The standard used at the Philippine General Hospital for birth weight percentiles called the Colorado Chart was based on the birth weights of infants born in the United States in the 1960's. This standard is used to compare antenatal fetal weight measured clinically or sonologically to determine the presence of intrauterine growth restriction or fetal macrosomia so that appropriate management could be given to improve neonatal outcome. It is also used to compare birth weights based on pediatric aging to identify small and large for gestational age neonates. The question is whether this standard should still be applied almost 50 years after it was developed and whether an updated version should be developed.

In general, this study showed that no significant difference was seen between the birth weight percentiles of neonates delivered in 2006 to 2008 and the standard, especially in the tenth percentile. The ninetieth percentiles of the extremes in age of gestation however, did not always correlate with the standard. This could be due to the very small number of subjects who had preterm or post term pregnancies which comprised merely 25 percent.
CONCLUSION

This study endeavored to compute for birth weight percentiles of neonates delivered in the Philippine General Hospital from January 2006 to December 2008 in order to compare current neonatal outcomes with the standard set in the United States almost 50 years ago. Based on the results of this study, neonatal outcomes in the last three years are still comparable to the Western standard.

However, this study only included three years worth of data collected in a hospital-based perinatal database. The results of this study may or may not be similar if the study was population-based with data gathered from all over the country for a longer period of time. Also, the parturients in this study were not classified according to body habitus, the presence or absence of substance use or abuse, nutrition, social status and other factors that could also affect birth weight. In addition, of the 8745 subjects included in the study, almost 75 percent were term pregnancies and only the remaining 25 percent were preterm or post term.

RECOMMENDATIONS

For almost half a century now, the Philippines has been using a birth weight nomogram that was based on live births in a Western population. It will require a great amount of effort to create a nationwide database that will enable us to create a Philippine standard of birth weight percentiles that will be representative of the entire country. However, with the easy accessibility of computerized technology and the internet, such a large scale study would not be impossible.

It is our recommendation that in order to develop a Philippine nomogram of birth weight percentiles that would be more appropriate to the present time and the population for which it is being used, a retrospective or prospective study of a nationwide scale to be conducted for several years may be undertaken.

REFERENCES

Factors Affecting the Choice for the Use or Non-use of Analgesia and the Choice of the Method of Analgesia During Labor and Delivery Among Obstetricians at a Tertiary Government Institution

JEAN ANNE B. TORAL, MD, FPOGS; MICHELANGELO L. ALVAREZ, MD AND GLENN D. MARINAS, MD

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

Objective: To determine the factors affecting the choice for the use or non-use and the choice for the method of analgesia for labor and delivery among obstetricians at the Philippine General Hospital.

Methods: A cross-sectional survey was done. A self-administered questionnaire was designed based on the literature reviewed, 5 key informant interviews and 3 focus group discussions. STATA software was used for item analysis.

Results: The survey had 57 respondents out of a possible total of 83, representing 69% of the target population. Mean age of the group was 35.5 years. Males accounted for 23% and females, 77%. The mean number of years in active practice was computed at 12 years. The questionnaire took an average of 3.5 minutes to accomplish. The inability to cover the entire population was due to 1) difficulty locating respondents; or 2) lost questionnaires. There was a total of 5 lost questionnaires. Item analysis using STATA yielded a valid questionnaire with good reliability for six domains (Cronbach’s $\alpha > 0.6621$). One domain (G) was removed in its entirety due to low reliability (Cronbach’s $\alpha = 0.1510$).

Conclusion: In general, the obstetricians are knowledgeable about the topic of pain management during labor (Domain A: Knowledge of the Obstetrician). From the obstetricians’ point of view, the strongest agreement is seen in the previous experience of the patient and financial status as determinants of patient’s choice for labor analgesia (Domain B). Most obstetricians are aware of both pharmacologic and non-pharmacologic methods of labor analgesia (Domain C: Awareness of Different Methods). Many obstetricians also recommend intravenous and intramuscular use of opioids as well as epidural anesthesia. More than two-thirds also believe that verbal assurance helps the patient in labor a lot (Domain D: Practice of Analgesia). On the part of the obstetrician, the choice of analgesia is determined by many clinical factors including gravidity, presence of comorbid conditions, the stage of labor and the safety of the method (Domain E: Clinical Factors). Lastly, considering both the obstetrician and the patient, there are also numerous non-clinical factors determining the choice for analgesia including patient finances, skill and ability of the anesthesiologist, predicted ease of delivery, and proximity of the obstetrician to the birthing place (Domain C: Non-clinical Factors).

Key words: labor and delivery analgesia, obstetrician

* Presented in the XXIst Asian and Oceanic Congress of Obstetrics and Gynecology (AOCOG) March 27, 2009 as one of the ten finalists with oral presentation in the Young Gynecologist Award.
The practice of relieving pain in labor has been a controversial one throughout recorded history, as it is today. Analgesia is defined as the state of no pain. While labor pain is experienced uniquely by each woman in labor, her experience of this pain is defined also by the society and culture she is part of. A woman's attitude towards labor pain is derived from the influence of several factors. Economic status, religious beliefs, knowledge, fears, and previous experiences all interplay in the establishment of a woman's insight regarding this life event.

From the point of view of the practitioner, opinions also vary widely. At one extreme, practitioners feel the labor is a part of natural childbirth and the experience provides powerful lessons to the parturient. On the other end is the view that childbirth is no different from pain caused by any other illness or injury, therefore, should be relieved in order for the woman not to suffer.

Practitioners may include obstetricians, family physicians, and general practitioners among the registered physicians. Nurses, midwives, and traditional birth attendants also get a share of management of labor and delivery.

Even among obstetricians, there seems to be a variation in the attitude and in the practice towards labor analgesia. This is despite the general belief that maternal request is enough reason to administer labor analgesia.

The American College of Obstetricians and Gynecology (ACOG) came up with a practice bulletin on obstetric analgesia and anesthesia in 2002. This information was designed to aid practitioners in making decisions about appropriate obstetric care. It was not meant to dictate an exclusive course of treatment. It further added that variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

From the point of view of the anesthesiologist, who specializes in algology, or pain management, there is no circumstance where its is considered acceptable for a person to experience untreated severe pain amenable to safe intervention, while under a physician's care. This was the statement made by the American Society of Anesthesiologists (ASA) on pain relief during labor in 1999.

Subsequently, the ASA had come up with practice guidelines for obstetric anesthesia. The third item on this practice guideline specifically deals with anesthesia care for labor and vaginal delivery. Specific methods including epidural local anesthetic, epidural anesthesia combined with opioids, continuous epidural infusion, spinal, and combined spinal-epidural techniques are mentioned. Of course, other pharmacologic methods like intravenous sedation and non-pharmacologic methods like Lamaze also exist.

In the Philippines, no such practice bulletin exists. Rather, the concepts and the practice of obstetric anesthesia are influenced by several beliefs and perceptions.

Labor pain is believed to hasten delivery and that epidural anesthesia is expensive and even prolongs labor and increases the cesarean section rate. This belief must have been based from three previous observational studies and one randomized controlled trial published in the 1990's headed by Thorp showing an increased incidence of cesarean delivery in women who receive epidural labor analgesia compared with women who receive intravenous opioids. The meta-analysis, however, points to a prolonged labor with epidural analgesia but not with increased rates of instrumental vaginal delivery or cesarean section.

It is also well-recognized among the ranks of obstetricians and anesthesiologists that the skills of the health provider are very important. That the patient has a choice on the matter of labor analgesia has also emerged.

A lot of clinical factors are also being considered by obstetricians in their decision regarding labor analgesia. There are variables which help obstetricians predict which parturients are more likely to have severe pain during labor and delivery. Nulliparity or the first experience to labor and the need for labor induction or augmentation are most predictive.

On the part of the obstetrician, the choice may also depend on non-clinical issues including his/her level of knowledge, the setting of his/her practice including institutional policies if there are any, and the resources and materials available for labor analgesia.

At the Philippine General Hospital alone in 2003, there were approximately 3,150 spontaneous vaginal deliveries attended in the Charity Service. Of these,
only 1100 or 35% were given some form of analgesia during labor. In the private admissions, 86% to 90% of patients (n=693) get analgesia in various forms.9

The Philippine General Hospital is a good representative center capable of delivering all forms of labor analgesia. What can account, then, for the variety? Is it the obstetrician’s choice? Is it what the patient condition calls for? Is the patient given a choice? What makes one choose one from over the other?

Guided by the principles of simplicity, safety, and preservation of fetal homeostasis, a complex of factors determine the eventual choice of the obstetrician and the patient in addressing labor analgesia. The conceptual framework of this study is seen in Figure 1.

1. Labor results in severe pain for many women. Thus, the obstetrician should always address this problem.
2. Labor analgesia is safe for the mother and the fetus.
3. Patients have a choice whether or not to avail of labor analgesia. This choice is determined by a variety of non-clinical factors (e.g. knowledge, attitude, socio-cultural, economic, availability and accessibility, etc.)
4. The obstetrician can influence the choice of the patient.
5. The obstetrician’s choice is affected by several clinical and non-clinical factors (e.g. knowledge, attitude, practice, patient’s medical status, availability and accessibility, etc.)
6. There are several ways of addressing pain during labor and delivery.

General Objectives

To determine the factors affecting the choice for the use or non-use and the choice for the method of analgesia for labor and delivery among obstetricians at the Philippine General Hospital

Specific Objectives

1. To determine the knowledge of the obstetricians regarding labor analgesia
2. To determine the attitude of the obstetricians towards labor analgesia.
3. To determine the factors affecting the choice of patients for labor analgesia as perceived by the physician.
4. To determine the clinical and non-clinical factors affecting the choice of obstetricians for the use of labor analgesia.
5. To determine the awareness of the obstetricians of the various methods of labor analgesia.
6. To determine which among the various methods of labor analgesia are being practiced by the obstetricians.
MATERIALS AND METHODS

Type of Study and Target Population

This is a cross-sectional survey done among the active faculty members, senior residents, and post-residency fellows in training of the Department of Obstetrics and Gynecology of the Philippine General Hospital.

Active faculty members included all those with existing academic and/or clinical appointments from the U.P. College of Medicine and/or the Philippine General Hospital listed under the Department. Faculty members with cross-appointments from other departments of the College who practice obstetrics were also included. The senior residents of the Department are the residents on their third and fourth year of training. The post-residency fellows are limited to those who had their residency training in the same Department and are presently in their subspecialty training programs.

At present, there are 53 active faculty members and cross-appointees in the department. There are 28 third and fourth year residents. There is one chief resident. There are 18 post-residency fellows who had their residency training in the same Department.

The choice of the Department of Obstetrics and Gynecology of the Philippine General Hospital as the setting for this study is based on the following: 1) it caters to both charity and private admissions, 2) the facilities and manpower for labor analgesia are complete, thus, obstetricians and patients have all the choices at hand, and 3) it is a POGS-accredited tertiary training institution.

Methodology

The survey design utilized both the qualitative and the quantitative techniques of questionnaire development. The qualitative phase made use of key informant interviews and focus group discussions. The interviewees and the participants in the focus groups came from the target population.

An interview guide (Appendix A) was used for both the key informant interviews and the focus group discussions. It was designed and pre-tested among the investigators.

From the output of the interviews and the discussions, a questionnaire was designed and divided into domains. This was then pre-tested on a limited number of participants (n=3) before finally giving out the questionnaire to the rest of the target population.

The quantitative phase of the questionnaire involved the item analysis of the responses to the questionnaire using the STATA software.

The Qualitative Phase: Key Informant Interviews

Five key informant interviews were conducted. Verbal informed consents were taken from each. Each represented either the charity or the private section of the Department in terms of practice. They are as follows:

1. Dr. Lilibeth Sia Su - Associate Professor of the Department and senior attending obstetrician-gynecologist who practices solely at the Philippine General Hospital. She has been in active practice for the past 10 years. She is also the Vice Chair for Services of the Department. She is one of the top obstetricians in the Department in terms of number of private admissions. She provided the prevailing concepts, attitudes, and beliefs among the faculty members regarding labor analgesia at the Philippine General Hospital.

2. Dr. Ma. Concepcion Cruz - Associate Professor of the Department of Anesthesiology and part of the Obstetric Anesthesia Team of the Philippine General Hospital. She has been in active practice for more than 10 years. She provided the concepts regarding labor analgesia and the prevailing beliefs regarding the practice of labor analgesia at the Philippine General Hospital from the point of view of an anesthesiologist.

3. Dr. Marianne Blythe Tecarro - present Chief Resident of the Department of Obstetrics and Gynecology, Philippine General Hospital. She provided the information on the prevailing concepts, attitudes, beliefs, and practices regarding labor analgesia among the resident physician trainees handling charity patients at the PGH.

4. Dr. Claire Bugayong - recent graduate of the Obstetric Anesthesia Fellowship Program at the Philippine General Hospital. The prevailing concepts, attitudes, and practices regarding labor analgesia from the anesthesiology point of view as seen among charity admissions in PGH was taken from her.
5. **Dr. Ernesto Uichanco** - Associate Professor of the Department, senior attending obstetrician gynecologist and perinatologist at the Philippine General Hospital and present member of the Philippine Board of Obstetrics and Gynecology (PBOG). He provided his personal beliefs and practice regarding labor analgesia. Being a part of the PBOG accrediting hospitals for training, he was also asked regarding issues on institutional policies and guidelines.

### The Qualitative Phase: Focus Group Discussions

Three focus group discussions were conducted. They were as follows:

1. The first group was composed of senior residents of the Department (third year and fourth year residents). They have been handling their own cases at the Charity Service for at least two and half years.

2. The second group was composed of junior consultants of the Department who have been in practice of the profession for less than 5 years. They have been attending to their private patients at the Philippine General Hospital. These consultants have trained also within the same time period or had overlaps in their training (1995-2001).

3. The third group was composed of attending anesthesiologists and senior Anesthesiology residents in training who have been handling obstetric analgesia cases from the private and the charity services, respectively.

### Domains of the Questionnaire

From the output of the key informant interviews and the focus group discussions and relating them to the main conceptual framework, the questionnaire had the following domains:

1. General concepts on labor pain, attitudes and practice of obstetricians

2. Factors affecting the patients’ decision to request for labor analgesia

3. Awareness of the different methods of labor analgesia

4. Practice of the different methods of labor analgesia

5. Clinical factors affecting the choice of the obstetrician

6. Non-clinical factors affecting the choice of the obstetrician

7. Final choice for labor analgesia

### Pre-testing of the Questionnaire

Three members of the target population were asked to answer the preliminary questionnaire: two attending obstetricians who are also Clinical Associate Professors of the Department and a fourth year resident. They were timed as to how long it would take them to answer the questionnaire. After answering the questionnaire, feedback regarding the items was elicited. The questionnaire developed for pre-testing is seen in Appendix D.

### The Quantitative Phase: Item Analysis Using the STATA Software

The choices on the final questionnaire were given codes: Strongly agree - 1; Agree - 2; Disagree - 3; Strongly disagree - 4. The completed questionnaire results were encoded using the Microsoft Excel program, and further analyzed using STATA software for descriptive statistics, inter-item correlation, item-total correlation, and Cronbach's alpha.

### RESULTS AND DISCUSSION

The survey had 57 respondents out of a possible total of 83, representing 69% of the target population. There were 19 senior residents (33.5%), 15 postgraduate clinical fellows (26.5%) and 23 active consultants (40%). Mean age of the group was 35.5 years, with a range of 28 to 60 years. Males accounted for 23% (n=13) and females, 77% (n=44). Eleven respondents (19.3%) failed to indicate the year of their graduation from residency. The number of years in active practice was deduced from the year of graduation from residency. From the collected data, the mean number of years in active practice was computed at 12 years, with a range of 3 to 31 years.
The questionnaire took 3 to 4 minutes to accomplish. The inability to cover the entire population was due to 1) difficulty locating respondents; or 2) lost questionnaires (failed to return). There was a total of 5 lost questionnaires.

Table 1 shows the distribution of responses in Domain A. Questions 1-3 dealt with the knowledge of obstetricians at the UP-PGH. More than 50% the respondents strongly agree with these questions, showing that they are knowledgeable about the topic. The attitudes were brought up with questions 4, 7, 8, 9 and 10. Likewise, a majority agree to these, which show that respondents thought that pain during labor should be alleviated, and that all patients have the right to labor analgesia. Questions 5, 6 and 11 indicate that the obstetricians at the UP-PGH actively address labor pain and would do whatever they can to manage this problem.

Domain B (Table 2) deals with patient’s choice for labor analgesia, from the point of view of the obstetrician. Majority of the respondents agree that level of education (q1), family influence (q2), husband’s choice (q3), previous experiences (q4) and financial status (q5) influence this choice. Strong agreement to these influences were seen only for previous labor experience and financial status. Other influences include fear of complications, doctor’s recommendation, patient’s attitude/perception to pain, and other people’s accounts.

At the UP-PGH, most obstetricians agree that they are aware of different methods of labor analgesia (Table 3). Domain C enumerates these methods which include Lamaze, intravenous or intramuscular opioids, intrathecal and epidural methods, hypnosis, acupuncture, and inhalational agents.

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**Table 1. Domain A.**

<table>
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<tr>
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<td>54.4</td>
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<td>54.4</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
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**Table 2. Domain B.**

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<td>66.7</td>
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<td>75.4</td>
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<td>5.3</td>
<td>5.2</td>
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<tr>
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**Table 3. Domain C.**

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Domain D deals with the practice of different modalities in labor analgesia. Generally, the respondents recommend intravenous/intramuscular/intrathecal opioids (q3) and epidural (q5 and q6) modes of labor analgesia (Table 4). More than two-thirds also give positive verbal assurance to their patients during labor (q1). Half of the respondents would recommend Lamaze, while the other half would not (q2). Hypnosis (q7), acupuncture (q8) and use of inhalational agents (q9) are generally not practiced.

Most respondents agree that gravidity/parity, presence of co-morbid conditions, stage of labor, safety of method, and additional post-delivery procedures are clinical factors (Domain E) that would influence the type of labor analgesia that would be employed (Table 5).

The non-clinical factors (Domain F) that influence the method of labor analgesia include financial capability of the patient, skill and availability of the anesthesiologist, rapport with the anesthesiologist, ease of delivery and repair, and the proximity of the obstetrician to the place of delivery. Generally, all of the respondents agree with these factors (Table 6).

Table 7 shows the responses to Domain G, which attempts to summarize the questionnaire to 3 general points. Majority of respondents indicated that they have the prerogative to manage the labor pain of a patient in the way they deem right (q1) and that the patient’s choice is secondary (q3). They also agree that the anesthesiologist’s preference has a bearing on their management (q2).

Appendix E shows the inter-item, item-total correlation, and the Cronbach’s alpha for the seven domains. Following is the summary of the results.

### Table 4. Domain D.

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<td>Strongly Agree</td>
<td>28.6</td>
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<tr>
<td>Agree</td>
<td>69.6</td>
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<tr>
<td>Disagree</td>
<td>1.8</td>
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### Table 5. Domain E.

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### Table 6. Domain F.

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### Table 7. Domain G.

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<td>Strongly Disagree</td>
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June, 2010  Philippine Journal of Obstetrics & Gynecology Volume 34 (No. 2) 73
**Domain A**

When all of the items for Domain A were included, the Cronbach's alpha was 0.7289, which indicated good reliability. The removal of each item did not improve alpha, except for question number 11. The removal of this item increased alpha to 0.7346. The proponents of the study decided to retain this question though, as question A11 emphasizes the obstetrician's prerogative in the institution of labor analgesia, and is one of the objectives of the study (attitude of obstetrician).

**Domain B**

Cronbach's alpha for this domain was 0.8352, showing good reliability. The removal of any item does not improve this number.

**Domain C**

Analysis showed an alpha of 0.6621. Item analysis showed an improved alpha when the fifth question was removed. Question C5 was not removed because the continuous epidural is one of the most important methods of analgesia in labor and delivery. It is actually the gold standard as of present time.

**Domain D**

Cronbach's alpha for this domain was 0.7687. Excluding the first question from the analysis improved this number to 0.7969. This question will be retained, however, because of strong opinions regarding positive assurance as an effective method for labor analgesia.

**Domain E**

This domain had a Cronbach's alpha of 0.7874. When question one was removed, alpha improved to 0.8302. The proponents of the study decided not to exclude this question because gravidity and parity do determine how fast labor will progress and therefore the method of analgesia to be given.

**Domain F**

The Cronbach's alpha for this domain was 0.8268, which means that it was reliable. The removal of any item from the domain did not improve this value.

**Domain G**

This domain did not show any indication of reliability. Alpha for this domain was 0.1510. Removing any item from this domain did not improve alpha to an acceptable number (0.6). The proponents therefore decided to remove the entire domain from the final questionnaire.

The questionnaire was generally well-constructed as seen with the good reliability testing on item analysis using Cronbach's alpha. There were some questions which may have slightly improved the reliability of the respective domains but these were retained. Basis for retention were taken from the proceedings during the key informant interviews and focus group discussion.

The last domain (G) attempted to integrate the content of the entire questionnaire into three general points. However, this domain yielded low reliability and therefore is not necessary, and its deletion will have no effect on the outcome of the questionnaire. In fact, a question of similar content had already been stated in Domain A (A11 for G1 and G3). Question G2 is obviously out of line and has nothing to do with the objectives of the questionnaire. It was perhaps the subliminal intent of the proponents, being anesthesiologists, to determine if obstetricians indeed valued their opinion.

The final questionnaire (Appendix G) therefore contains the following domains:

1. General concepts on labor pain, attitudes, and practice of obstetricians
2. Factor affecting the patients' decision to request for labor analgesia
3. Awareness of the different methods of labor analgesia
4. Practice of the different methods of labor analgesia
5. Clinical factors affecting the choice of the obstetrician
6. Non-clinical factors affecting the choice of the obstetrician

**RECOMMENDATIONS**

This validated questionnaire may be used in various ways. First, it can be administered on a regular basis at the Philippine General Hospital to...
determine the trend of the obstetricians’ knowledge, attitudes, and practice regarding labor analgesia. There will be new senior residents, clinical fellows, and consultants, and it will be noteworthy to find out how these parameters evolve. Secondly, this questionnaire may be administered to any obstetrician practicing in an institution similar to PGH - a tertiary hospital in an urban setting catering to charity and pay patients alike.

A lot of hypotheses may be generated from this questionnaire, and may inspire new questionnaires or researches in the field of labor analgesia. It will be interesting to note that there is a paucity of male obstetricians in the target population. Is it possible for the “female” factor to be a determinant in the management of labor pain?

What do the patients on their end perceive about the management dealt to them by their obstetricians? Has the latter’s method of labor analgesia actually assured them of a pleasant experience during childbirth?

It is also recommended that results of this questionnaire be made known to policy-making bodies in the Department of Obstetrics and Gynecology, as well as the PGH, in order that the allocation of resources be evaluated and hopefully diverted to promotion of labor analgesia for obstetric patients.

Appendix A
The Interview Guide

1. What are your responsibilities when attending to a patient in labor?
2. What do you know about pain in labor?
3. Have you seen this occurring in your patient?
4. How do your patients feel about this pain during labor?
5. Do your patients verbalize this pain? In what way?
6. Do they want the pain relieved?
   If yes, how do they communicate this to you?
   If no, why not?
7. What is your initial reaction to a patient verbalizing her pain?
8. If the patient wants her pain relieved, what measures do you take?
   Does your patient readily agree to these measures?
9. If the patient does not want her pain relieved, do you try to convince her otherwise?
10. What factors do you think affect the patient’s decision to agree to a particular measure? (as perceived by the physician)
11. Is there a basis for your decision on what method to use?
    If yes, what do you base your decision on?
    If no, why have you decided to use a particular technique?
12. What methods do you particularly advocate? Why?
13. Are you aware of other methods? Do you use them?
    If yes, what are these? How often and when do you have them used?
14. Have you seen complications from the methods you have used?
15. Have you seen complications from the methods you have not used?
16. What do you do when complications arise?
17. What clinical factors in your patients do you consider when you recommend a particular measure? (e.g. age, gravidity/parity, age of gestation, other co-morbid conditions, etc.)
18. Are there non-clinical factors in the patient that also affect your decision? (e.g. socio-cultural, economic, religion, etc.)
19. Where do you attend to labor and delivery?
   Do you have an assistant/s? Do you need more assists?
20. What are your requirements for an adequate workplace for labor and delivery? Does your center or workplace fulfill these requirements?

REFERENCES

Rectus Abdominis Endometriosis Without Previous Surgery: A Case Report

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Endometriosis is a benign condition in which endometrial glands and stroma are present outside the uterine cavity. The most common sites are the ovaries. Abdominal wall implantation, although uncommon, typically occurs in areas of previous surgical scars, usually involving the subcutaneous tissue. Endometriosis arising in the rectus abdominis muscle is rare. A case of extrapelvic endometriosis, spontaneously arising within the rectus abdominis muscle, in the absence of a previous surgical scar, is presented here.

Key words: endometriosis, abdominal wall, rectus abdominis, spontaneous

Endometriosis is a common gynecologic condition in which endometrial glands and stroma are present outside the uterine cavity. In some instances, the presence of hemosiderin-laden macrophages may be the only tell-tale signs. This condition affects up to 10% of reproductive-aged women, with the prevalence rate of as much as 35% among infertile women. The ovaries are the most common sites involved, followed by the pelvic peritoneum, the cul de sac of Douglas, and the uterosacral, round and broad ligaments. Extrapelvic implantation of endometrial tissues have been reported in areas such as the gastrointestinal (2%-4% of all cases). The abdominal wall is an uncommon site and the cases so described usually occur in areas of old surgical scars, with the incidence pegged at 1%-2% following hysterotomy and 0.03% - 0.4% after a cesarean section, the reason for the discrepancy being that the early decidua has more pleuripotential capabilities which result in cellular replication. Rarely, endometriosis may occur spontaneously in the abdominal wall without previous history of pelvic surgery or endometrial manipulation. The cases described by Ramsanahe, Hashim and Munoz all occurred around the area of the umbilicus. Abdominal wall endometriosis usually occurs in the subcutaneous layer, if not in the area of previous surgical scars, around the area of the umbilicus. Involvement of the rectus abdominis muscle is rare. In a 2005 report by Coeman, et al., only 11 cases have been described in medical literature. In their report, two more cases were reported but these were with previous pelvic surgeries. A Pubmed search for rectus abdominis endometriosis without previous surgery yielded only one study by Ideyi SC, et al. in 2003.

This is a case of a 43 year old diagnosed with abdominal wall endometriosis. In this hospital, this is the first reported case of extragenital endometriosis involving the rectus abdominis muscle without previous history of surgery. This case is presented because of its rarity, in order to increase clinicians' awareness to the possibility of the condition arising spontaneously without a surgical scar and in order to propose a hypothesis for its pathogenesis.

THE CASE

A 43 year old nullipara was referred for evaluation of a tender suprapubic mass. She is single

* First Place, POGS Cebu Residents' Interesting Case Contest, May 29, 2009; Cebu Institute of Medicine, Cebu City.
and denies any history of coitus. She claims to have regular 28-day menstrual cycles, associated with dysmenorrhea. There was no history of previous surgery.

Five years prior to admission, she noted right inguinal pain occurring on the first 3 days of her menstrual period. Consultation with a gynecologist was done and after an unremarkable transrectal sonogram, she was told she had pelvic endometriosis and was prescribed with continuous combined oral contraceptive pills which afforded no relief. One year prior to admission, a 2cm x 2cm soft tissue mass was noted on the suprapubic area, which was tender upon palpation especially during the first 3 days of her menstrual cycle. She noted an increase in severity of pain, persisting 5 days after the last day of her menstrual period. She consulted another physician who referred her to a surgeon. An MRI was done, which revealed a soft tissue mass measuring 2.4cm x 3.3cm x 2.5cm at the origin of the right rectus abdominis muscle with no osseous involvement nor evidence of aneurysm. (Figure 1) On physical examination, a 4cm x 4cm soft, fluctuant, tender mass was palpable about 1cm above the symphysis pubis, a little to the right of the midline. The skin overlying the mass was normal without evidence of discolorations. There were no other pertinent physical examination findings. In spite of the fact that there was absence of a previous surgery, the symptom of cyclic pain raised the possibility of an abdominal wall endometria.

An excisional biopsy was performed. Intraoperatively, the mass noted to be within the rectus abdominis muscle near its origin from the symphysis pubis. It was described as a cystic structure with chocolate-brown material within, adherent to the surrounding muscle and tendon. (Figure 2) Gross examination of the mass revealed a soft to firm, tan to brown, irregular mass measuring 35cm x 20cm x 12mm. Cut surface was tan to brown and partly hemorrhagic. Also noted was a cystic cavity measuring 6mm in greatest diameter. (Figure 3) Microscopic examination revealed sections of fibromuscular tissue exhibiting foci of endometrial glands and stroma, the former lined by pseudostratified columnar cells and surrounded by dense cellular stroma. A few cystic ducts were also seen. The surrounding areas showed focal aggregates of round cells and hemosiderin-laden macrophages. (Figure 4) Histopathologic diagnosis was endometriosis.

Postoperative recovery was uneventful and she was discharged with instructions to return for GnRH agonist therapy.

**DISCUSSION**

Endometriosis refers to ectopic endometrial glands and stroma. These implants are usually located in the pelvis but can occur almost anywhere
Figure 2. Intraoperative findings showing the cystic mass on the right rectus abdominis muscle adherent to the surrounding muscle and tendon.

Figure 3-1. Gross appearance of the excised mass which was partly hemorrhagic.

Figure 3-2. The irregular chocolate-filled cystic structure.
extrapelvic endometriosis was 34-40 years in two studies, whereas pelvic endometriosis is commonly diagnosed between 25-30 years of age. This patient, at initial presentation, was 42 years old.

Different theories have been proposed to account for the origin and pathophysiology of endometriosis. Although not one of these theories can adequately explain its etiology, the most widely accepted theory is that endometriosis results from retrograde menstruation. This theory assumes transportation of endometrial tissue from the uterus in a retrograde fashion into the peritoneal cavity. The coelomic metaplasia theory hypothesizes that the coelomic cavity contains uncommitted progenitor cells or cells capable of differentiating into endometrial tissue. The most recently proposed cellular immunity theory suggests that alterations in cell-mediated and humoral immunity allow ectopic endometrial cells to proliferate. On the other hand, the direct implantation theory is the basis for explaining its occurrence in the abdominal wall, particularly along surgical scars or tracts resulting from invasive abdomino-perineal procedures, considering the possibility of iatrogenic transfer of endometrial cells into surgical or procedural wounds. Abdominal wall endometriosis is present in approximately 0.8% of all women who had cesarean deliveries. However, this cannot be the theory behind the causation of the condition in this particular patient as there is no history of any surgical operation or

Figure 4-1. Mircosscopic Appearance A. Endometrial glands (pointed by the black arrows) and stroma (pointed by the white arrow) B. High power view of an endometrial gland lined by pseudostratified columnar cells.

Figure 4-2. Mircosscopic finding of round cells and hemosiderin-laden macrophages.

in the body. Extrapelvic endometriosis has been reported in areas such as the urinary system, the gastrointestinal tract, pulmonary structures, skin, central nervous system and abdominal wall. Unlike pelvic endometriosis, it is diagnosed in an older cohort of women. The median age at diagnosis of
procedure. Primary cutaneous endometriosis is rare, with a prevalence of 0.5 - 1.0%, with no history of abdominal surgery. Transfer of endometrial cells to extrapelvic sites not associated with surgical violation of the uterus is believed to result from hematogenous or lymphatic spread of endometrial tissue, which may explain the rare occurrence of abdominal wall endometrioma without any surgical intervention, as presented by this patient. Although not proven with imaging studies such as a contrast-enhanced magnetic resonance angiography, in this case, the most logical hematogenous pathway to explain how endometrial tissues could reach the rectus abdominis muscle is as follows: a possible venous stasis at the level of the common iliac vein could cause retrograde venous blood flow such that venous drainage from the uterus which may contain functional endometrial cells and stroma empty into the uterine vein, then into the internal iliac vein, then instead of draining through the common iliac vein, venous blood backflows into the external iliac vein, then backflows into the inferior epigastric branch which tranverse the rectus abdominis muscle.

Abdominal wall endometriosis is generally found within the skin or subcutaneous tissues of the abdominal wall. Rectus abdominis endometrioma, wherein the endometriotic focus is within the body of the uterus, is rare and sparsely reported in medical literature with only 11 new cases since it was first described in 1993 by Coley. All these cases were with previous surgeries, except for one 28 year old woman, described by SC Ideyi, et al.

The value of imaging studies when diagnosing abdominal wall endometrioma varies. A definitive preoperative diagnosis cannot be made with ultrasound or CT scan. In a study by TN Huff, et al. magnetic resonance imaging proved to be the most specific modality for diagnosis because of its ability to detect hemorrhagic nodules containing degenerated blood products, including methemoglobin. Likewise, V Coeman, et al. stated that MRI is highly sensitive in detecting very small masses and offers excellent differentiation of endometriomas from neighboring tissue. The multitude of signal patterns seen in endometriomas is due, in part, to the different stages of blood products found within these implants. A high proportion of glandular tissue versus encysted blood provides a moderate to high contrast enhancement on CT and MRI. In this patient, the MRI was able to distinguish the cystic mass from the surrounding muscle fibers but the definitive diagnosis of endometriosis was only possible with histopathologic correlation.

The treatment of endometriotic foci in the abdominal wall is usually surgical, by excision of the mass, or it can be expectant, depending on the severity of the symptoms. Complete excision of the lesions offers the best opportunity for relief of pain. In one study of 250 women, surgical excision resulted in a 70% cure rate for pelvic pain and a recurrence rate of less than 5% after 5 years. The approach of wide excision and drainage has been recommended as an alternative to wedge excision because of less adhesion formation and a recurrence rate (23%) similar to cyst stripping and ablation. Medical treatments for endometriosis have focused on the hormonal alteration of the menstrual cycle in an attempt to produce a pseudo-pregnancy, pseudomenopause, or chronic anovulatory state. The pain associated with endometriosis is usually treated initially with oral contraceptive agents or non-steroidal anti-inflammatory drugs, because these agents have fewer side effects and are less expensive than other treatment options. Gonadotropin-Releasing Hormone (GnRH) agonists, as well as other agents such as danazol or progestational agents, which are usually reserved for use if the first-line agents fail to provide an acceptable degree of relief. For this patient, no relief was noted with the use of non-steroidal anti-inflammatory agents nor with oral contraceptive pills. Large-scale clinical trials have compared the efficacy of GnRH agonists with that of danazol and reported that GnRH agonist is as effective as danazol in: 1) reducing the growth of endometriotic implants, 2) relieving symptoms during the initial 6-month - 12-month follow-up periods after cessation of therapy. The decision to use a GnRH agonist instead of danazol postoperatively in this patient was made after a thorough discussion with the patient regarding the benefits and side effects of both drugs. Since medical therapy does not eradicate the disease and surgical therapy is associated with a reasonably high rate of recurrence of disease and symptoms, it seems logical to consider combined medical and surgical therapy in an attempt to maximize the benefits of both, thus the plan of management in this patient.

**SUMMARY AND CONCLUSION**

Abdominal wall endometriosis, particularly those occurring in the rectus abdominis muscle is an uncommon disorder. Its occurrence in the absence of
a prior abdomino-pelvic surgical procedure makes it even rarer. Knowledge of this disease has progressed little because of its rarity. The most plausible theory to explain its pathogenesis is the hematogenous theory. A good history and physical examination, a high index of suspicion, plus an adequate understanding of the disease are some of the most powerful tools a clinician needs in his arsenal. Since it is often diagnosed only upon histologic examination postoperatively, it should be considered in the differential diagnosis of abdominal wall masses. Combined medical and surgical treatments may offer the best options to maximize symptom relief.

REFERENCES

Non-HPV Associated Adenosquamous Cervical Carcinoma in a 54-Year Old Virgin*

NIÑA MARLA L. ABELLERA, MD; RAFAEL S. TOMACRUZ, MD, FPOGS; NEPHTALI M. GORGONIO, MD, FPOGS AND MA. PATRICIA L. LUNA-SUN, MD, FPOGS

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A 54-year old, single, nulligravid, without history of sexual contact, was admitted due to postmenopausal bleeding. Transrectal ultrasound revealed myoma uteri and thickened endometrium. She was thus scheduled to undergo endometrial curettage. However, prior to the performance of the endometrial sampling procedure, there was profuse vaginal bleeding with note of a possible prolapsed submucous myoma. She thus underwent emergency exploratory laparotomy with total hysterectomy and bilateral salpingooophorectomy.

Intraoperatively, necrotic masses were noted within the endocervical canal. Frozen section of the uterus and these masses revealed malignancy. Intraoperative referral to a gynecologic oncologist was done and bilateral pelvic lymphadenectomy and surgical staging were performed. Final histopathologic report revealed Cervical Adenosquamous Carcinoma. She subsequently underwent external beam radiotherapy and vaginal brachytherapy.

With the knowledge that almost all cases of cervical cancer is due to the Human Papilloma Virus (HPV), that this virus is almost exclusively transmitted by sexual contact, and the fact that she never engaged in sexual practices, there was doubt as to the source of the cancer. To help resolve this issue, an HPV DNA Polymerase Chain Reaction assay was performed on paraffin block samples and these all turned out negative for HPV. She may possess one of the rarest forms of cervical cancer - one that is not associated with the Human Papilloma Virus.

Key words: cervical carcinoma, virgin

* Second Place, 2010 POGS Interesting Case Contest.
are adenocarcinomas. The remainder includes the other rare types, such as adenosquamous, mucinous, and small cell and neuroendocrine types.5

The 0.3 percent of cases of cervical cancer not associated with HPV is usually due to metastatic disease or the primary rare types, such as adenosquamous, mucinous, small cell carcinoma, neuroendocrine type and even cervical lymphoma and sarcoma. Women without sexual contact who develop cervical cancer are thus suspected of possessing the non-HPV associated types. We are thus presenting a 54-year old virgin who had adenosquamous carcinoma of the cervix that was later determined not to be associated with HPV by polymerase chain reaction.

THE CASE

AL, a 54-year old, single, nulligravid, without history of sexual contact, was admitted at our institution for the first time on September 24, 2008 due to postmenopausal bleeding.

Her condition started nine months prior to admission (PTA) when she had intermittent vaginal bleeding, occurring every 30-40 days, lasting 4-10 days, amounting to 1 minimally soaked pad per day. There were no associated signs or symptoms. She consulted her gynecologist and was advised to undergo a transrectal ultrasound. This showed an anteverted uterus measuring 4.45cm x 4.67cm x 6.8cm, with 2 myomatous masses: M1 – submucous, anterofundal measuring 2.51cm x 2.08cm and M2 – intramural, fundal measuring 2.14cm x 1.29cm; cervix measured 2.75cm x 3.79cm; endometrium measured 1.11cm; right ovary measured 1.73cm x 0.93cm while the left ovary was not visualized. Based on these findings, her gynecologist advised dilatation and curettage (D & C). She did not consent to the procedure and was subsequently lost to follow up.

Three days PTA, with the persistence of the postmenopausal bleeding and passage of yellowish, non-foul smelling vaginal discharge, she consulted her attending physician who again advised D & C. She finally consented to the procedure and was subsequently admitted.

Review of her past medical history revealed that she underwent an appendectomy in 1978. Family history was unremarkable. She is a single nulligravid woman who denies history of sexual contact. Her menarche occurred at the age of 10, with subsequent menses occurring every 30 days, lasting 3-4 days, amounting to 3-4 moderately-soaked pads per day, with no dysmenorrhea. She has been postmenopausal for 3 years and is not on hormone replacement therapy. She has never had a Pap smear done.

On physical examination, she was conscious, coherent, and not in any cardiorespiratory distress. She had stable vital signs, with pink palpebral conjunctivae and anicteric sclera. No cervical lymphadenopathy was noted. Breast, lung and heart findings were essentially normal. She had a soft, flabby, non-tender abdomen with an infraumbilical incision scar and no palpable masses. On pelvic examination, she had normal external genitalia with an intact hymen. Speculum and internal examinations were deferred upon patient's request. Her attending physician decided to do these procedures at the operating room under anesthesia.

After administration of anesthesia and while preparing the patient for the D&C, she bled profusely. The profuse bleeding prevented an adequate visualization of her vagina and cervix. An internal examination revealed the presence of a firm mass within the vaginal canal. Impression at this time was a prolapsed submucous myoma. Because her vital signs became unstable due to the vaginal bleeding, the attending physician decided to perform an emergency exploratory laparotomy with total hysterectomy and bilateral salpingooophorectomy (THBSO). She was stabilized with crystalloids and blood products were ordered for intra-operative use.

On laparotomy, there was no free fluid in the abdomen. The uterus was not enlarged, uterine serosa was smooth and both adnexae were grossly normal (Figure 1). We proceeded to perform THBSO. Upon removal of the specimen, the cervix was not identified. Friable, hemorrhagic tissue admixed with blood clots spilled into the pelvic cavity from the vagina (Figure 2). The vagina itself had a smooth mucosal surface with no nodulations or masses attached to its walls. Gross examination of the ectocervix showed no masses nor lesions. The uterine corpus measured 3cm x 2.8cm and on cut section revealed a smooth and thin endometrium. The endocervical canal was smooth with no gross lesions. There was no identifiable point of attachment of the said masses. The attending physician suspected a possible malignancy so the uterus and the friable masses were sent to Pathology for frozen section analysis. A referral to a gynecologic oncologist was likewise made.
Figure 1. Uterus measured 3cm x 2.8cm. On cut section, the endometrium was smooth and thin and measured 0.1cm.

Figure 2. Friable necrotic mass within the cervical canal.

The frozen section revealed a malignant tumor consistent with squamous cell carcinoma, the cervix being the most likely organ of origin. The gynecologic oncologist contemplated on performing parametrectomy and vaginectomy but decided against doing so due to the unstable hemodynamic status of the patient. Inspection and palpation of the abdominal peritoneum and organs and bilateral lymphadenectomy of the iliac areas were performed. The liver, spleen, stomach, subdiaphragmatic area, intestines and parietal peritoneal surfaces were smooth and grossly normal. No residual tumor was noted.

Estimated blood loss for the operation was 800mL. She was transfused 2 units of packed RBC. Subsequent postoperative course was unremarkable and she was discharged improved on the fourth postoperative day.

Final histopathological report showed (Figures 3 & 4): Adenosquamous Carcinoma (Introital Mass) arising from the cervix; Atrophic endometrium with focus of simple hyperplasia; Leiomyoma, subserous; No significant pathologic changes, bilateral ovaries and fallopian tubes; 5 right pelvic lymph nodes and 3 left pelvic lymph nodes negative for tumor.

Figure 3. Adenosquamous carcinoma (Low power view: tumor cells growing in solid nests and sheets).

Figure 4. Adenosquamous carcinoma (High power view: Cells have basophilic, vacuolated or clear cytoplasm).

The final diagnosis for the patient was: Adenosquamous carcinoma, cervix Stage IB2, S/P Exploratory laparotomy, Total abdominal hysterectomy, Bilateral salpingo-oophorectomy, Bilateral pelvic lymphadenectomy.
Since only a simple hysterectomy was performed in a woman with cervical carcinoma, complete radiotherapy, consisting of Pelvic External Beam Radiotherapy (5,040 cGy) and High-Dose Rate Brachytherapy (2,800 cGy) was instituted. She tolerated the treatment well and is presently following up with her gynecologic oncologist. At present, she has no evidence of tumor recurrence and a vaginal cytologic smear done in August 2009 showed radiation changes with no malignant cells.

The presence of cervical carcinoma in a woman with no sexual contact brought out issues regarding its etiology, knowing that almost all cases of cervical cancer is associated with the human papilloma virus (a sexually transmitted virus). Thus, paraffin block samples of the tumor were sent to India for HPV DNA determination. Polymerase Chain Reaction (PCR) assay analysis was negative for HPV DNA.

**DISCUSSION**

During the time of Hippocrates in 400 BC, cervical cancer was thought to be incurable. Because of progress in the art and science of medicine, from the invention of the colposcope by Hans Hinselmann in 1925, to the development of cervical cytologic screening by Papanicolau and Trout in 1941, much has evolved in the knowledge and management of cervical carcinoma. A study by Harald zur Hausen and Gisam published in 1976 theorized a link between the Human Papilloma Virus and the development of cervical carcinoma. Continuing research by zur Hausen in the early 1980s confirmed this link, thus earning him the Nobel Prize for Medicine in 2008. Prior to 1999, all stages of cervical cancer were generally managed with radiotherapy. However, with definite evidence of the benefit of adding chemotherapy in a concurrent setting, chemoradiation is now considered the gold standard in the management of this disease. These developments have dramatically contributed to the present diagnostic, therapeutic, and, more importantly, the preventive approaches to cervical carcinoma.

The American Cancer Society provides the following risk factors for cervical cancer: human papilloma virus infection, smoking, HIV infection, Chlamydia infection, dietary factors, hormonal contraception, multiple pregnancies, exposure to the hormonal drug diethylstilbestrol (DES), and a family history of cervical cancer. There is a possible genetic risk associated with HLA-B7.

The most important risk factor in the development of cervical cancer is the presence of human papillomavirus, or HPV. More than 150 types of HPV are known to exist. Of these, 30-40 affect the genital tract and 15 are classified as high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 & 82), 3 as probable high risk (26, 53 & 66) and 12 as low risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 & CP6108). The high-risk or oncogenic types have the greatest potential in causing cervical carcinoma.

HPV triggers alterations in the cells of the cervix that can lead to the development of cervical intraepithelial neoplasia (CIN). If undiagnosed and not properly managed and monitored, this precursor lesion can continue to develop into invasive cervical cancer. Women who have had many sexual partners, or who have had partners with multiple sexual relations have a greater risk of developing cervical cancer. The medically-accepted paradigm is that only women infected with HPV have the potential to develop CIN and cervical cancer. HPV is thus viewed as a sexually transmitted disease. So does virginity “protect” women from the development of this disease? Are virgins “exempted” from acquiring cervical cancer?

Human Papillomavirus infection has been implicated in virtually all cases of cervical cancer. According to Prof. Walboomers, HPV is the necessary cause of this disease in 99.7 percent of cases. Based on case-control studies performed worldwide (the Philippines included), HPV types 16 and 18 account for approximately 71 percent of these cases, while HPV types 31 and 45 account for an additional 9%. Based on these information, one can infer that there is a very minute chance (0.3%) that this malignancy will not be associated with HPV. It has been inferred that rare types of cervical cancer and metastatic disease may account for this group of patients. A thorough literature search at PUBMED and OVID for articles pertaining to non-HPV associated cervical cancer in virgins was made but no article or case report was found. An unpublished, anecdotal report in the 1990s from a consultant of the Section of Gynecologic Oncology at the UP-PGH revealed two women without prior sexual contact who developed cervical carcinoma. One was a case of cervical sarcoma, while the other was cervical lymphoma.

Our patient, being a single, nulligravid woman who denies having any form of sexual relations, may
thus be presumed to belong to the minority of women who have non-HPV associated cervical cancer. What could be the clinical impact of this situation? Should virgins be exempt from cervical cytologic screening in their lifetime? Should they be exempt from the universal recommendation of HPV vaccination?

HPV infection is generally sexually transmitted, but vaginal penetration is not necessary for infection to occur. Skin to skin genital contact may be sufficient to transmit the virus from one partner to the next. After entering the epithelium via surface abrasions, the virus infects the cells in the basal layers. There is no spread to deeper tissues or stroma nor is there systemic spread via the bloodstream. HPV infection is entirely intraepithelial and no viremia is produced. This explains the relatively asymptomatic nature of women with HPV infection.

Viral replication is a slow process and is critically dependent upon the differentiation of host cells. It does not dictate its development within its host or cause apoptosis, or programmed cell death. Instead, it uses the natural life cycle of the host cell in its differentiation and proliferation to new virions. Viral antigens and infectious viruses are produced only when cells begin to differentiate into squamous cells in the mid and upper layers of the epithelium and become keratinized as they approach the epithelial surface. This process may take a very long time to occur and not all women infected with HPV will eventually manifest with CIN or cervical cancer. Like any virus, this can just be a self-limiting infection and no clinical disease will ever be manifested. However, virus-infected cells may lie dormant for months and years, and may begin to differentiate and proliferate with decreasing immunity of the host or individual.

To determine whether the patient possesses HPV, Polymerase Chain Reaction (PCR) assay for HPV DNA was performed. Detection of HPV DNA using this PCR assay has been well established and has been utilized in clinical trials for primary cervical cancer screening and in the improvement of conventional cervical cytology. This method has a specificity of 98%-100% and a high sensitivity, with a lower limit of detection being 1250 particles per 1mg of tissue or 10-20 HPV particles in a smear containing around 10,000 cells. We were actually intrigued how a self-confessed postmenopausal virgin could develop cervical cancer. To resolve this issue, several paraffin blocks of the cervix and friable tumor from our patient were tested to determine if HPV indeed was present. The assay was negative for HPV DNA. She may indeed be part of the “super-minority” of women with non-HPV associated cervical cancer.

Malcolm Griffiths theorized that it is erroneous to assume that only women with the risk factors for cervical carcinoma have a high likelihood of developing this malignancy and that only this subset of women would benefit from screening procedures. He cited several studies concluding that the probability of developing cervical malignancy is the same among all women, regardless of their sexual activity or apparent lack of it. It is a fact that no one should be considered immune to cervical cancer. But due to the fact that 99.7 percent of cervical malignancies are associated with HPV infection, it is safe to assume that women with high risk factors are more likely to develop cervical cancer than those women, particularly nuns and virgins, who have not been exposed to the virus.

Because of the impact cervical cancer poses worldwide, attempts have been made to reduce its incidence by preventive measures. Awareness of the pathogenesis of HPV infection and cervical cancer and the risk factors associated with them are important considerations. According to the US National Cancer Institute’s 2005 Health Information National Trends survey, only 40 percent of American women have heard of HPV and only 20 percent know of its link to cervical cancer.

The widespread introduction of the Papanicolaou test for cervical cancer screening has resulted in a dramatic reduction in the incidence and mortality of cervical cancer worldwide. This screening procedure was in fact known to be the greatest advancement in cancer control in the 20th century. Abnormal cervical cytology results may suggest the presence of the precursor of cervical carcinoma (CIN), allowing clinical treatment to prevent its progression to invasive disease. The American Cancer Society (ACS) and the American Society of Colposcopy and Cervical Pathology (ASCCP) recommend that cervical cancer screening should begin three years after the onset of vaginal intercourse and/or no later than 21 years of age. In this country, where social norms are more on the conservative side, women with no sexual contact are advised to have their first Pap smear between the ages of 30 to 35. This was based on several factors: 1. The median age of women developing cervical cancer in the Philippines is around 45 years of age; 2. The pathogenesis from HPV infection to cervical
cancer usually takes 10-15 years; 3. The difficulty in convincing this group of non-sexually active women to have a cervical cytologic screening test. Considering the age of this patient, should she have been advised to have a Pap smear even if she denies any history of sexual relations? Based on the aforementioned recommendations and premises, she should have had this screening test during her reproductive years.

While the Pap test is considered an effective screening tool, confirmation of malignancy relies on a histologic sample from a cervical biopsy procedure. This is often done through colposcopy, a magnified visual inspection of the cervical transformation zone using a dilute acetic acid solution and Lugol’s iodine to highlight abnormal cells on the surface of the cervix. Excision procedures, such as Loop Electrosurgical Excision Procedure (LEEP) or cervical conization, can also be performed to document the extent of the cervical neoplasia and act as a therapeutic procedure in some cases of CIN. Confirmation of cervical malignancy will then enable the gynecologic oncologist to tailor his/her treatment according to the appropriate stage of the patient’s disease.

In this patient’s case, there was no benefit of a tissue diagnosis prior to the operative procedure. It is possible that the attending physician did not consider cervical carcinoma as a differential diagnosis because the patient had no sexual contact. A pelvic examination was not performed on the patient and the findings on ultrasound were used as the basis for management. Unfortunately, this practice of depending solely on the sonographic report is a relatively common practice in our setting. The importance of performing thorough physical and pelvic examinations can never be overemphasized. Diagnostic procedures should merely serve as adjuncts to confirm a clinical impression.

When this patient experienced vaginal bleeding at the operating table prior to the D & C, the decision to perform an emergency exploratory laparotomy and THBSO was a judgment call on the part of the attending physician. She could not visualize the lower genital tract due to the profuse hemorrhage. Her assessment of the vaginal mass was a prolapsed submucous myoma. Again, the ultrasound finding of a submucous myoma could have swayed her in believing that this myoma prolapsed out and was causing the bleeding. Careful inspection of the “vaginal mass” could have alerted the attending physician to the nature of the said mass. In retrospect, we could see that the masses within the vagina were friable and necrotic – characteristics favoring a malignant process.

Inadequate evaluation of the patient led to inaccurate diagnosis of the cause of her postmenopausal bleeding. The surgical procedure thus performed was not appropriate for a patient with a cervical malignancy. Though a radical parametrectomy and upper vaginectomy were contemplated in an attempt to “correct” the surgery, this was not feasible considering the unstable nature of the patient’s condition. Thorough abdominal examination and pelvic lymphadenectomy, though, were performed.

Of course it is easy to make these comments in retrospect. The attending physician was acting on the best interests of the patient when she made the decision to perform the laparotomy, knowing that her unstable hemodynamic status secondary to massive hemorrhage could be best managed by removing the source of the bleeding. The situation was remedied, though, by suspecting intra-operatively that the masses spilling into the pelvic cavity after cervical amputation were malignant in nature. A frozen section analysis was ordered and a gynecologic oncologist was called in. Though the surgical inadequacy could have been alleviated with a radical parametrectomy, it was more prudent to perform other staging procedures that would not have further compromised our patient. In the end, she survived the operation without any morbidities, was discharged well, underwent adjuvant radiotherapy, and is presently in remission from the malignancy.

Squamous cell carcinoma is the most common histologic type of cervical cancer (80-85%) followed by adenocarcinoma (15%). The uncommon histologic types include adenosquamous carcinoma, small cell carcinoma, and neuroendocrine carcinoma. The patient had the adenosquamous cell carcinoma. The glandular component most likely originated from the endocervical mucosa while the squamous component originated from the ectocervical mucosa. In a study by Matthews, et al. in May 2004 on the possible presence of HPV in rare types of cervical cancer, it was concluded that even the uncommon histologic types of cervical carcinoma are associated with HPV, and that most of these are similar to those found to cause the common types of cervical cancer.

Cervical carcinoma is a clinically staged disease. If we determined her to be a Stage IB2 prior to any
definitive procedure, she could have been managed by any of the following: 1) concurrent chemotherapy using Cisplatin given weekly for 6 courses with pelvic external beam radiation therapy (EBRT) and brachytherapy (chemoradiation); 2) neoadjuvant chemotherapy (three rapidly delivered courses of platinum-based chemotherapy) followed by radical hysterectomy and bilateral lymphadenectomy with or without bilateral salpingo-oophorectomy with or without adjuvant postoperative radiation or chemoradiation; 3) pelvic EBRT concurrent with chemotherapy followed by RHBSO with selective lymphadenectomy; 4) primary radical hysterectomy and bilateral pelvic lymphadenectomy, which usually needs to be followed with adjuvant chemoradiation. 18

The surgical procedure was inadequate since only a simple hysterectomy was performed on our patient. To rectify this situation, she was given adjuvant radiotherapy in the form of external beam radiotherapy and brachytherapy. Concurrent chemotherapy with single-agent Cisplatin was advised but patient refused.

Prognosis depends on the stage of the cancer. With treatment, the 5-year survival rate for all stages is approximately 72%. In patients with Stage I cancer, the 5-year survival rate reaches 80-90%. According to the International Federation of Gynecology and Obstetrics (FIGO), survival improves when concurrent chemotherapy with Cisplatin-based regimen is given with radiotherapy.

CONCLUSION

Presented is a 54-year old woman with non-HPV-associated adenosquamous cervical carcinoma. Though she was inadequately managed from a surgical point of view, she subsequently had pelvic radiotherapy to alleviate this management inadequacy. She is presently on regular follow up and is in remission from her disease.

It is now well known that cervical carcinoma is almost exclusively associated with HPV. But we have discovered that our patient’s cancer is non-HPV associated. How can we explain this occurrence? How did the 0.3 percent of women with cervical carcinoma without the HPV association develop the disease? Considering the risk factors listed by the American Cancer Society, we can rule out HIV and Chlamydial infection, hormonal contraception, smoking, exposure to diethylstilbestrol and sexual behavior as probable causes or predisposing factors in our patient. However, we can only surmise that there could be a genetic factor involved. It is possible that our patient could have developed the disease due to a genetic predisposition. However, this may be very difficult to prove at this time. Though the rarer types of cervical cancer still predominantly possess HPV-based on the study of Matthews, these types are probably the ones that are non-HPV associated. Moreover, a non-HPV associated cervical cancer should alert the physician on the possibility of metastatic disease from another primary, usually within the genital tract.

The clinical implication of non-HPV associated cervical cancer is that all women, regardless of sexual behavior, are candidates for primary and secondary preventive measures. The recommendations provided by the American Cancer Society (ACS) and the American Society of Colposcopy and Cervical Pathology (ASCCP) for all women (including those who are not or have never been sexually active) are clear: cervical cancer screening should begin three years after the onset of vaginal intercourse and/or no later than 21 years of age. Though the age requirement for performance of the first Pap test could be “relaxed” because of the conservative nature of Filipino women and societal norms, this should nonetheless be performed when she is at least in her thirties. HPV vaccination may protect a virgin from HPV-associated disease and a Papanicolaou smear may detect neoplasia arising from non-HPV associated conditions in this subset of women. In both scenarios, all women can be protected from a very dreaded disease that has affected women and their families in the prime of their lives.

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