Carbetocin Versus Oxytocin for the Prevention of Postpartum Hemorrhage Following Elective Cesarean Section: Rizal Medical Center Experience*

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Postpartum hemorrhage is a preventable event in abdominal and vaginal deliveries. Conventional incremental dosing or continuous infusion of oxytocin has been employed for these. Carbetocin, as an analogue is associated with longer half-life and has clinical benefits.

Objective: The objective was to compare the effectiveness of carbetocin and oxytocin when administered after elective uncomplicated cesarean section (CS) for the prevention of postpartum hemorrhage.

Design: Randomized single blind controlled trial of patients admitted at Rizal Medical Center from June to October 2012.

Participants and Methods: A total of 70 patients were randomized to carbetocin (n=35) and oxytocin (n=35) for the prevention of postpartum hemorrhage and analyzed by intention-to-treat. Baseline demographic and obstetric profile, indications for CS, estimated blood loss, hematocrit, hemoglobin, need for uterine massage, additional uterotonic, uterine tone and involution were compared immediate post-operative and 24 hours after.

Results: Baseline profiles were similar between the two groups. Post-operatively, hemoglobin and hematocrit levels in the carbetocin group were statistically significant and were associated with lesser need for additional uterotonic agents, uterine massage and a well contracted uterus immediate post-operative and 24 hours thereafter. The estimated blood loss was significantly lower in the carbetocin group however, the two groups did not significantly differ in terms of blood transfusion requirements and post-op blood pressure.

Conclusion: Carbetocin as a uterotonic agent is an acceptable alternative for the prevention of postpartum bleeding in elective cesarean section. A cost-benefit analysis is mandated.

Key words: carbetocin, oxytocin, postpartum hemorrhage, uterine tone, uterine involution, randomized trial

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In several trials, carbetocin was associated with a decrease in postpartum hemorrhage. It reduced the use of additional uterotonics and uterine massage and therefore reduced the incidence of blood transfusion.

The present study aimed to evaluate the role of carbetocin vs oxytocin in reducing blood loss and postpartum hemorrhage.

**Research Question**

Is carbetocin effective as compared to oxytocin in the management of postpartum hemorrhage following elective cesarean section?

**General Objective**

The general objective of the study was to compare the effectiveness of carbetocin and oxytocin when administered after elective uncomplicated cesarean section in preventing postpartum hemorrhage of patients admitted at Rizal Medical Center from June to October 2012.

**Specific Objectives**

1. To compare the demographic and baseline characteristics of the 2 groups who will undergo elective CS.
2. To compare the preoperative and postoperative hemoglobin and hematocrit levels between carbetocin and oxytocin groups who will undergo elective cesarean section at Rizal Medical Center from June to October 2012.
3. To compare whether there is a need for giving additional uterotonics between patients given carbetocin and oxytocin.
4. To compare the need of doing uterine massage after administration of drug between the 2 groups
5. To compare the difference in uterine tone and early involution between the 2 groups
6. To compare the need of giving blood products postoperatively between the 2 groups
7. To compare the systolic and diastolic blood pressure preoperatively, after administration of the drug and postoperatively.

**Rationale**

The best preventive strategy is to administer a uterotonic drug soon after delivery of the neonate to decrease the risk of postpartum hemorrhage.

**MATERIALS AND METHODS**

**Study Design, Setting and Duration**

This is a randomized controlled trial comparing the use of carbetocin and oxytocin for the prevention of postpartum hemorrhage following elective cesarean section. Single blinding was done wherein the surgeon and the patients were blinded and only the principal investigator knew as to what drug was administered after delivery of the neonate. Giving of additional uterotonics depended on the discretion of the surgeon.

Subjects were seen either at the outpatient department or at the emergency room of Rizal Medical Center. The trial was completed in five months.

**Study Participants**

**Inclusion Criteria:**

1. With informed consent
2. At least 18 years old
3. Term uncomplicated pregnancy (>37 weeks) undergoing elective cesarean section
4. At least one risk factor for postpartum hemorrhage (repeat cesarean section, multiple pregnancy, >gravida 3 and with malpresentation)

**Exclusion Criteria:**

1. Hypersensitivity to oxytocin and carbetocin
2. <37 weeks AOG
3. Placenta previa
4. Abruptio placenta
5. Women undergoing cesarean section with general anesthesia
6. Significant disease (heart disease, thyroid disease, preeclampsia, diabetes mellitus, pulmonary disease, liver and renal disease)
7. Classical uterine incision
8. Fetal distress

Women with placenta previa or abruptio placenta were excluded because they were at a higher risk for hemorrhage. Women undergoing cesarean section with general anesthesia were also excluded, because carbetocin is licensed for use with regional anesthesia only.
Sample Size Estimation

The number of samples to be collected was computed using 95% level of confidence and 80% power of the study. With an estimated difference in the intraoperative blood loss of 41ml from the study of Boucher, et al., at least 35 subjects per group were needed.

Investigator and Patient Blinding

To avoid potential confounders, an independent research physician was tasked to perform the randomization procedure. Another physician who assessed outcomes was unaware of the group assignments of these patients. Similarly, patients were not aware of the meaning of the treatment codes assigned.

Data Collection

The study population was divided into 2 groups. They were examined by the senior OB resident on duty. The findings, maternal risk factors and clinical assessment prior to cesarean section were recorded. Study group A received single intravenous injection of 100 microgram carbetocin while study group B received 8 hours infusion of oxytocin 20 units after delivery of neonate. Informed consent was obtained.

Preoperative and postoperative hemoglobin levels were extracted at entry and 24 hours postpartum and sent to the laboratory. Records on the preoperative and postoperative hemoglobin levels were kept. Data were collected regarding the use of additional uterotonics and uterine massage between the 2 groups depending upon the discretion of the surgeon. Vital signs particularly blood pressure were recorded pre-operatively, after intervention, post-operatively and at the recovery room. The additional uterotonics included additional oxytocin dosage to the drip or giving methylergometrine maleate IM/IV, also a uterotonic agent. Assessment of uterine tone between the 2 groups was made by the surgeon by palpation of the uterus whether it is 1) boggy - soft, atonic uterus, 2) firm - when gentle pressure depressed the uterus slightly or transiently, 3) well contracted uterus -hard, non-depressible uterus. Likewise, assessment of uterine involution was made 1) below the umbilicus, 2) at the level of the umbilicus and 3) above the umbilicus. Both tone and involution were evaluated before delivery of the neonate, after intervention, immediate post-operatively and 24 hours post-operatively. Blood transfusion was given to the 2 groups depending on the 24-hour post-operative hemoglobin, hematocrit level and clinical assessment of the surgeon.

Primary Outcome

The comparison of hemoglobin and hematocrit levels between the 2 groups.

Secondary Outcome

Proportion of patients requiring additional uterotonics, uterine massage, tone, involution and blood transfusion between the 2 groups.

Statistical Analysis

The analysis was done using MEDCALC version 3.0. Descriptive statistics included mean and standard deviation for continuous variables. Discrete data were summarized as percentages. Testing for sample homogeneity at baseline was done using chi-square test and independent T-test. Comparison of outcomes was done using paired Test, independent T test for continuous data and chi-square for categorical data. All P-values <0.05 were considered significant.

RESULTS

A total of 70 patients were randomized to carbetocin (n=35) and oxytocin (n=35) for the prevention of post-partum hemorrhage. At baseline, there was no significant difference between carbetocin and oxytocin in terms of mean age (mean 30 versus 31, P=.55, respectively); gravidity (P=.73); parity (P=.39) and gestational weeks (P=.15). The primary indications for cesarean section in this study included a repeat CS, followed by malpresentation (footling breech) (P=.66). The number of repeat cesarean sections did not statistically differ between the two groups (P=.26).

Hemoglobin and Hematocrit Levels

A significant reduction in the post-operative hemoglobin levels from the baseline preoperative level was noted in the carbetocin group (mean 118 to 108, P<.001). Likewise, the levels were also
significantly low post-operative in the oxytocin group (mean 116 to 96, P<.001).

Post-operatively, levels in the carbetocin group were statistically higher (mean 108.6 versus 96.03, P=.001)

A significant reduction in the post-operative hematocrit levels from the baseline preoperative level was noted in the carbetocin group (mean 0.36 to 0.33, P=.001). Likewise, the levels were also significantly low post-operative in the oxytocin group (mean 0.36 to 0.31, P=.018).

Post-operatively, levels in the carbetocin group were statistically higher (mean 0.33 versus 0.31, P=.001)

**Blood Pressure**

Systolic and diastolic BP were not significantly different immediate post intervention between the two groups, immediate post-operative and while recovering (between group P=.37 and P=.40, respectively) (Figures 3 & 4).

### Table 1. Baseline profile of pregnancies randomized to carbetocin versus oxytocin to prevent post-partum hemorrhage, Rizal Medical Center, June to October 2012.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Carbetocin N (%)</th>
<th>Oxytocin N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>30 (5.7)</td>
<td>31 (6.3)</td>
<td>.55*</td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11 (31)</td>
<td>15 (43)</td>
<td>.73**</td>
</tr>
<tr>
<td>3</td>
<td>12 (35)</td>
<td>11 (31)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6 (17)</td>
<td>6 (17)</td>
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</tr>
<tr>
<td>≥5</td>
<td>6 (17)</td>
<td>3 (9)</td>
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<tr>
<td>Parity</td>
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<td></td>
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<td>1</td>
<td>13 (37)</td>
<td>18 (52)</td>
<td>.39**</td>
</tr>
<tr>
<td>2</td>
<td>16 (45)</td>
<td>10 (28)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 (9)</td>
<td>6 (17)</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>3 (9)</td>
<td>1 (3)</td>
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<tr>
<td>Gestational Weeks</td>
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<td></td>
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</tr>
<tr>
<td>37-38</td>
<td>18 (51.5)</td>
<td>20 (57.2)</td>
<td>.15**</td>
</tr>
<tr>
<td>39-40</td>
<td>16 (45.7)</td>
<td>11 (31.5)</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>1 (2.8)</td>
<td>4 (11.3)</td>
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<td>Indication for Cesarean Section</td>
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<td>28 (80)</td>
<td>29 (83)</td>
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<td>Malpresentation (breech)</td>
<td>4 (11)</td>
<td>6 (17)</td>
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</tr>
<tr>
<td>Footling breech</td>
<td>3 (9)</td>
<td>0</td>
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<tr>
<td>Repeat Cesarean Section</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First time</td>
<td>15 (43)</td>
<td>16 (46)</td>
<td>.26**</td>
</tr>
<tr>
<td>Twice</td>
<td>11 (31)</td>
<td>16 (46)</td>
<td></td>
</tr>
<tr>
<td>Thrice</td>
<td>7 (20)</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td>Four times</td>
<td>2 (6)</td>
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<tr>
<td>Duration of Cesarean Section</td>
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<td>1.11 (0.40)</td>
<td>1.17 (0.38)</td>
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<tr>
<td>Mean Preoperative SBP (SD)</td>
<td>117.5 (6.8)</td>
<td>118.3 (8.3)</td>
<td>.68*</td>
</tr>
<tr>
<td>Mean Preoperative DBP (SD)</td>
<td>69.4 (7.7)</td>
<td>73.2 (8.5)</td>
<td>.06*</td>
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<td>Resident's Year Level Doing the Operation</td>
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<td>8 (23)</td>
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<td>3rd Year</td>
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<td></td>
</tr>
<tr>
<td>4th Year</td>
<td>13 (37)</td>
<td>12 (31)</td>
<td></td>
</tr>
</tbody>
</table>

*No significant difference by independent T-test, ** by chi-square test
Need For Additional Uterotonics

A statistically lower proportion of women in the carbetocin group required additional uterotonic agents post-operatively (5.7% versus 34.3%, P=.003). (Table-2).

Uterine massage was less required in the same group (5.7% versus 48.6%, P=.001).

The estimated blood loss was significantly lower in the carbetocin group (mean 585mL versus 702.8mL, P=.026)

The two groups did not significantly differ in terms of blood transfusion requirements. (P=.17).

Figure 1. Preoperative and post-operative hemoglobin levels in pregnancies given carbetocin versus oxytocin, Rizal Medical Center, June to October 2012.

Figure 2. Preoperative and post-operative hematocrit levels in pregnancies given carbetocin versus oxytocin, Rizal Medical Center, June to October 2012.

Figure 3. Trend in systolic BP levels in pregnancies given carbetocin versus oxytocin, Rizal Medical Center, June to October 2012.

Figure 4. Trend in diastolic BP levels in pregnancies given carbetocin versus oxytocin, Rizal Medical Center, June to October 2012.
**Uterine Tone and Involution**

The effects of the two drugs on uterine tone (Table 3) and uterine involution (Table 4) are presented. A statistically significant higher proportion of uteri in the carbetocin group were well contracted after the delivery of the neonate (23% versus 0, P=.001); immediately after the intervention was given (77% versus 8%, P=.001); immediate post-operative (60% versus 26%, P=.001) and 24 hours after post-operative (77% versus 8%, P=.001).

A statistically significant higher proportion of uteri in the carbetocin group were below the umbilicus immediately after the intervention (66% versus 29%, P=.007); and immediate post-operative (97% versus 57%, P=.001). No significant difference

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Carbetocin</th>
<th>Oxytocin</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Need for Additional Uterotonics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (5.7)</td>
<td>12 (34.3)</td>
<td>.003**</td>
</tr>
<tr>
<td>No</td>
<td>33 (94.3)</td>
<td>23 (65.7)</td>
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<tr>
<td>Uterine Massage</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
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<td>17 (48.6)</td>
<td>.001**</td>
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<td>18 (51.4)</td>
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<tr>
<td>Estimated Blood Loss (mL)</td>
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<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>585.7 (190)</td>
<td>702.8 (237)</td>
<td>.026*</td>
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<td>Blood Transfusion</td>
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<td>7 (20)</td>
<td>.17</td>
</tr>
<tr>
<td>No</td>
<td>33 (94.3)</td>
<td>28 (80)</td>
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</table>

*Significant difference by independent T-test **Chi-square test

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<tr>
<th>Uterine Tone</th>
<th>Carbetocin</th>
<th>Oxytocin</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>After Delivery of Neonate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boggy</td>
<td>7 (20)</td>
<td>25 (71)</td>
<td>.001**</td>
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<tr>
<td>Firm</td>
<td>20 (57)</td>
<td>10 (29)</td>
<td></td>
</tr>
<tr>
<td>Well contracted</td>
<td>8 (23)</td>
<td>0</td>
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</tr>
<tr>
<td>After Intervention</td>
<td></td>
<td></td>
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<tr>
<td>Boggy</td>
<td>0</td>
<td>16 (46)</td>
<td>.001**</td>
</tr>
<tr>
<td>Firm</td>
<td>8 (23)</td>
<td>16 (46)</td>
<td></td>
</tr>
<tr>
<td>Well contracted</td>
<td>27 (77)</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td>Immediate Post-operative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boggy</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>.014**</td>
</tr>
<tr>
<td>Firm</td>
<td>13 (37)</td>
<td>25 (71)</td>
<td></td>
</tr>
<tr>
<td>Well contracted</td>
<td>21 (60)</td>
<td>9 (26)</td>
<td></td>
</tr>
<tr>
<td>24 Hours Post-Operative</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Boggy</td>
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<td>16 (46)</td>
<td>.001*</td>
</tr>
<tr>
<td>Firm</td>
<td>8 (23)</td>
<td>16 (46)</td>
<td></td>
</tr>
<tr>
<td>Well contracted</td>
<td>27 (77)</td>
<td>3 (8)</td>
<td></td>
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</table>

Significant difference by independent **Chi-Square Test
immediately after the neonate was delivered (P=.053) and at 24 hours post-operative. (P=.18)

DISCUSSION

In search of a more effective uterotonic agent, the present clinical trial of carbetocin versus standard oxytocin aimed to compare the two drugs in relation to vital maternal outcomes after an elective abdominal delivery.

The trial has shown that standard doses of carbetocin prevented significant decreases in hematocrit and hemoglobin post-operative by having minimal blood loss. Carbetocin also decreased the need for additional uterotonics, uterine massage and the avoidance of blood transfusion. Furthermore, carbetocin was associated with good uterine involution and tone immediate post-delivery when compared to oxytocin.

The clinical trial result supports the composite findings in a meta-analysis involving 11 studies. Among women who underwent elective CS, carbetocin resulted in a statistically significant reduction in the need for therapeutic uterotonics compared to oxytocin, but there was no difference in the incidence of postpartum hemorrhage. This review revealed that compared to oxytocin, carbetocin was also associated with a reduced need for uterine massage following both cesarean delivery (RR 0.54; 95% CI 0.37 to 0.79; two trials, 739 women) and vaginal delivery (RR 0.70; 95% CI 0.51 to 0.94; one trial, 160 women). Six trials of these meta-analysis compared carbetocin to oxytocin in which four studies in turn examining its ability to prevent postpartum hemorrhage among those undergoing elective cesarean section.

The position of the fundus relative to the position of the umbilicus is an indicator of the state of uterine involution. Immediate uterine involution was observed as early post-delivery of the neonate, however comparative proportions were insignificant. It is to be reiterated that the rate of uterine involution differs across parity and gravidity. The study of Dimitrov, et al. showed that the uterine involution in primiparous and premature vaginal deliveries starts from lower values of the symphysis pubis-uterine fundus than in the multiparous and in cases of term delivery. The rate of uterine involution in primiparous increases gradually in the earliest day after delivery (from 0.95 to 1.6 cm per day), while in multiparous this increase starts after the 4th day. When cesarean section is performed and in cases of preterm delivery, the rates of uterine involution are delayed and uneven. Uterine involution described in this trial is immediate, after the administration of carbetocin and oxytocin, which are adjunctive to the normal

<table>
<thead>
<tr>
<th>Time Points</th>
<th>Carbetocin</th>
<th>Oxytocin</th>
<th>P-value</th>
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</thead>
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<tr>
<td><strong>After Delivery of Neonate</strong></td>
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</tr>
<tr>
<td>Below umbilicus</td>
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<td>.053</td>
</tr>
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<td>At the level of umbilicus</td>
<td>31 (89)</td>
<td>27 (77)</td>
<td></td>
</tr>
<tr>
<td>Above umbilicus</td>
<td>2 (6)</td>
<td>8 (23)</td>
<td></td>
</tr>
<tr>
<td><strong>After Intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below umbilicus</td>
<td>23 (66)</td>
<td>10 (29)</td>
<td>.007**</td>
</tr>
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<td>Above umbilicus</td>
<td>1 (3)</td>
<td>3 (8)</td>
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<td><strong>Immediate Post-operative</strong></td>
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<tr>
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<td>34 (97)</td>
<td>20 (57)</td>
<td>.001**</td>
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<td>15 (43)</td>
<td></td>
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<tr>
<td><strong>24 Hours Post-Operative</strong></td>
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<td>Below umbilicus</td>
<td>34 (97)</td>
<td>31 (89)</td>
<td>.18</td>
</tr>
<tr>
<td>At the level of umbilicus</td>
<td>1 (3)</td>
<td>4 (11)</td>
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</tr>
<tr>
<td>Above umbilicus</td>
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<td>0</td>
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</tr>
</tbody>
</table>

Significant difference by independent **chi-square test
physiologic return of the normal tonus and decrease of the uterine fundic height immediately after surgery. The authors were assured that these differences in parity and gravidity have been controlled adequately by the sufficient and fair randomization of subjects.

A study by Borruto, et al. reported that the fundus was below the umbilicus in more patients who received carbetocin at 0, 2, 6, and 24 h on the ward (P < 0.05). The latter study concluded that a single 100mcg IV injection of carbetocin was as effective as a continuous 2-h infusion of oxytocin in controlling intraoperative blood loss after placental delivery. Mean blood loss after carbetocin administration was 30ml less than after oxytocin delivery. The percentage of patients with blood loss ≤500ml was greater with carbetocin.11

The use of carbetocin has not been adequately endorsed in this institution due to many published reports on its adverse effects and its relatively high cost. However, the study of Rath, et al. showed that the risk of headache, tremor, hypotension, flushing, nausea, abdominal pain, pruritus and feeling of warmth was similar in women who received carbetocin or oxytocin.11 The findings from two recent double-blind randomized trials12,13 and one retrospective study suggest that carbetocin may also represent a good alternative to conventional uterotonic agents for prevention of postpartum hemorrhage even after vaginal deliveries.

The clinical advantage of carbetocin over oxytocin has been compared. Clinicians prefer to employ carbetocin because of its longer half-life which is approximately 4-10 times longer than that reported for oxytocin. It combines the safety and tolerability profile of oxytocin with the sustained uterotonic activity of injectable ergot alkaloids. Furthermore, carbetocin can be administered as a single dose injection either intravenously or intramuscularly rather than as an infusion over several hours as is the case with oxytocin.

Another clinical advantage of carbetocin in the prevention of post-partum bleeding is that it has a long duration of action compared with intravenous oxytocin alone and a better cardiovascular side effect profile compared with syntometrine.14,15 In addition to being an effective treatment for the prevention of postpartum hemorrhage following cesarean delivery, carbetocin may also become the drug of choice for postpartum hemorrhage prevention after vaginal delivery in high-risk women and those who suffer from hypertensive disorders in pregnancy. Preeclampsia is still a contraindication to the administration of carbetocin, and further studies will be required to assess the cardiovascular effects of carbetocin before it can be advocated for routine use in preeclamptic patients.15 In addition, carbetocin was able to reduce pain perception during postoperative days improving quality of life of women. De Bonis, et al. showed that mean scores of postoperative pain in the day of surgery in carbetocin group was significantly lower than in oxytocin group and remained significant three days after cesarean section. In the day of surgery and a day after surgery, women of the carbetocin group who needed analgesic drugs were significantly lower than women of the oxytocin group.16

The present study was limited as it failed to monitor uterine involution post 24 hours. This technical difficulty was due to the rapid turnover and practices of clinicians to discharge their patients as early as the 2nd post-operative day. Another limitation was the author’s failure to report the incidence of adverse effects carbetocin. The authors surmised that carbetocin is a synthetic analogue of oxytocin, hence pharmacodynamics may be similar. However, the authors found a study that contradicts other studies in terms of the safety and tolerability of carbetocin. The study by Ortiz-Gomez17 showed that carbetocin was accompanied by an increased incidence of side effects without any improvement in the prevention of obstetric hemorrhage. Significant differences in uterine contraction in vaginal bleeding and the incidence of side effects, particularly headache and tremor, were more pronounced in the carbetocin group. The authors also had no pharmaco-economic evaluation of the two drugs for cost-benefit analysis.

In summary, carbetocin is associated with reduction in estimated blood loss, resulting to a significantly minimum drop in hematocrit and hemoglobin levels. It also resulted to good uterine tone and involution as early as post delivery of the neonate and prevented the additional administration of uterotonic agents.

**CONCLUSION**

Post-operatively, hemoglobin and hematocrit levels in the carbetocin group were statistically higher (mean 108.6 versus 96.03, P=.001 and mean 0.33 versus 0.31, P=.001, respectively). Oxytocin group required additional uterotonic agents post-operatively (5.7% versus 34.3%, P=.003).
A statistically significant higher proportion of uteri in the carbetocin group were well contracted after the delivery of the neonate (23% versus 0, P=.001); immediately after the intervention was given (77% versus 8%, P=.001); immediate post-operative (60% versus 26%, P=.001) and 24 hours post-operative (77% versus 8%, P=.001).

Carbetocin enhanced early postpartum uterine involution. A statistically significant higher proportion of uteri in the carbetocin group were below the umbilicus immediately after the intervention (66% versus 29%, P=.007); and immediate post-operative (97% versus 57%, P=.001). No significant difference in terms of the degree of uterine involution immediately after the neonate was delivered (P=.053) and at 24 hours post-operative (P=.18).

The estimated blood loss was significantly lower in the carbetocin group (mean 585mL versus 702.8mL, P=.026) however, the two groups did not significantly differ in terms of blood transfusion requirements (P=.17) as well as post-operative systolic and diastolic blood pressures (P=.37, P=.40).

Uterine massage was less required in the carbetocin group (5.7% versus 48.6%, P=.001).

RECOMMENDATIONS

Carbetocin is a good alternative to prevent postpartum hemorrhage, however its cost prohibits clinicians from prescribing it. Similarly, even if there is a general safety profile for patients with high cardiovascular risk, extreme caution is practiced in its use during hypertension-complicated pregnancies. The authors recommend that incidence of adverse effects be reported, and uterine involution beyond the 24 hour mark be monitored.

REFERENCES

Sonographic Findings Predictive of Early Pregnancy Loss: A Retrospective Review*

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The objective of this study was to determine if abnormal sonographic findings among live embryos are predictive of early pregnancy loss.

Methods: This was a retrospective cohort analytic study involving 419 pregnant women with viable first trimester pregnancy transvaginal sonographic examination. Sonographic characteristics of the choriondecidual appearance, gestational sac position, yolk sac size, fetal heart rate, subchorionic hemorrhage and laterality of the corpus luteum were noted. The clinical outcome of pregnancy was considered abnormal if a spontaneous first trimester pregnancy loss of less than 12 weeks’ gestation occurred following the sonogram. Univariate and multivariate logistic regression analyses were performed to estimate odds ratios for the independent predictor variables in the study. Sensitivity, specificity and accuracy were computed.

Results: Irregular choriondecidual appearance, low gestational sac, macro yolk sac, presence of subchorionic hemorrhage and laterality of corpus luteum formation were not significantly associated with early pregnancy loss. Fetal bradycardia ≤100bpm was significantly associated with early pregnancy loss, OR 26.672, 95%CI 9.721-73.179. The sensitivity and specificity of fetal bradycardia as predictors of early pregnancy loss were 41.4% and 96.7% respectively. It had a 48% positive predictive value, 95.7% negative predictive value and 92.8% accuracy.

Conclusion: Sonographic finding of fetal bradycardia ≤100bpm is a predictor of early pregnancy loss. It may be recommended that a woman with a viable early first trimester gestation with fetal bradycardia should have a repeat sonogram later in the first trimester to re-assess fetal viability.

Key words: sonographic findings, fetal bradycardia, early pregnancy loss

Approximately 15% of clinically evident pregnancies and 60% of chemically evident pregnancies end in spontaneous abortions. Eighty percent of spontaneous abortion occurs prior to 12 weeks of gestation. In 1980, Miller, et al. in evaluating post-implantation pregnancy wastage, reported that 43% of pregnancies end in failure. However, only one-fifth of these cases are clinically recognized as spontaneous abortions. In most instances, the etiology of first trimester pregnancy wastage is unknown. In general, significant embryologic malformations that result in demise can be the result of genetic or chromosomal, environmental or combined factors.

In many settings, transvaginal ultrasound is used routinely for early pregnancy confirmation. However, the fact remains that no single test is available in differentiating a pregnancy that is likely to continue or not. Perhaps, ultrasonography is the best single diagnostic test. The availability of a high resolution transvaginal ultrasound imaging has made it possible to visualize embryonic development from a very early stage in pregnancy. No single ultrasound measurement of the different anatomical features in the first trimester has been shown to have a high predictive value for determining early pregnancy outcome. Ultrasound parameters combined with maternal serum hormone levels, maternal age, smoking habits, obstetric history and the occurrence of vaginal bleeding have all been combined in multivariate analyses, with mixed results.

At present, transvaginal ultrasound is the imaging examination of choice to evaluate the anatomy and physiology of the human fetal parts from as early as the third week post implantation onwards. In particular, transvaginal sonography, with its ability to provide accurate in-vivo images of the early gestational sac, has also provided pivotal
clues to the epidemiology and pathophysiology of early pregnancy failure. In comparison to a transabdominal approach, vaginal transducers provide superior resolution with respect to examining the appearance and contents of the gestational sac as well as the ovaries and adnexa. Various sonographic features have been discussed with respect to accuracy in predicting pregnancy outcome. They include small sac size relative to the embryo, embryonic bradycardia, distorted sac shape, enlarged or abnormal yolk sac and subchorionic hemorrhage.

Transvaginal sonography has revolutionized clinical practice by providing definite evidence of fetal viability in early pregnancy as early as six weeks. In patients with normal pregnancies, when embryo viability is confirmed, the rate of pregnancy loss is low at a reported incidence of 3.2%. One study showed that if a gestational sac was visible, the embryonic loss rate was 11.5%; with a yolk sac it was 8.5%; with an embryo less than 5 mm in length, it was 7.2%; and with an embryonic length of 6-10 mm, it was 3.3%. Achiron, et al. in 1991 found embryonic heart rate to be a promising parameter in predicting embryonic outcome after ultrasound proven viability. Several authors have reported spontaneous abortions after describing embryos with heart rates less than 85 beats per minute. An unusually slow heart rate or fetal bradycardia is a cause of concern. As many as 18% of women with vaginal bleeding during the first half of pregnancy have ultrasonographic evidence for a subchorionic hemorrhage as the etiology for their bleeding. The clinical significance of this type of hemorrhage is controversial, with some investigators reporting an increased incidence of spontaneous abortion, and others concluding that this condition does not adversely affect pregnancy outcome. A yolk sac diameter more than two standard deviations (2 SD) from the mean predicted abnormal pregnancy outcome with a sensitivity of 91.4%, specificity of 66% and a positive predictive value of 88.8%.

Such abnormal sonographic findings on the embryo can be used to identify the subgroup of pregnancies that are at higher risk of early pregnancy loss and thus require closer follow-up.

Objectives

General Objective

This study aimed to determine if sonographic findings among live embryos of irregular choriondecidual appearance, low gestational sac position, macro yolk sac, fetal bradycardia and presence of subchorionic hemorrhage as well as laterality of the corpus luteum are predictive of early pregnancy loss.

Specific Objectives

1. To determine the incidence of sonographic findings of irregular choriondecidual appearance, low gestational sac position, macro yolk sac, fetal bradycardia, and presence of subchorionic hemorrhage among live embryos.
2. To identify the incidence of laterality of the corpus luteum in first trimester pregnancy scans.
3. To determine the association of irregular choriondecidual appearance, low gestational sac position, macro yolk sac, fetal bradycardia, and presence of subchorionic hemorrhage as well as laterality of the corpus luteum with early pregnancy loss.
4. To compute for the sensitivity and specificity of significant sonographic feature/s among irregular choriondecidual appearance, low gestational sac position, macro yolk sac, fetal bradycardia, presence of subchorionic hemorrhage and laterality of corpus luteum as predictor/s of early pregnancy loss.
5. To identify confounding maternal characteristics associated with early pregnancy loss among women with first trimester ultrasound evaluation.

Definition of Terms

Irregular choriondecidual appearance refers to the sonographic appearance of the echoes that surround an early intrauterine gestational sac which includes irregular or distorted sac shape; a thin (<2mm), weakly echogenic, or irregular chorioicidal reaction; and absence of the double decidual sac sign when the mean sac diameter (MSD) exceeds 10 mm.

Low gestational sac position refers to an abnormally low position of the gestational sac within the endometrial cavity.

Macro yolk sac has a diameter of >6 mm which is an abnormal feature.
Fetal bradycardia  fetal heart rate less than or equal to 100 bpm.13

Subchorionic hemorrhage an anechoic area on ultrasound that has a falciform shape, and is usually observed behind or below the gestational sac, separating the chorion from the inner wall of the uterus.14

Abortion is the expulsion of the product of conception or termination of pregnancy before 20 weeks gestational age or at less than 500 grams birthweight.15

Early pregnancy loss spontaneous early abortion or spontaneous first trimester fetal loss (<12 weeks age of gestation).13

Advanced Maternal Age maternal age of 35 years or above.16

MATERIALS AND METHODS

This was a retrospective cohort analytic study of pregnant women at risk of having spontaneous early abortion.

Subjects included all women (total enumeration) with first trimester pregnancy 5 to 9 weeks' gestation who underwent transvaginal sonographic examination between January 2010 to February 2011 at the Women's Health Care Unit of St. Luke's Medical Center. All scans were done by board-certified obstetrician-gynecologist sonologists. Only the first scan that showed detectable fetal cardiac activity was included. Exclusion criteria included the following: ectopic pregnancy, multiple pregnancies, missed abortion, fibroids or any other uterine disorder.

Gestational age was confirmed by last menstrual period, if known, and by the crown-rump length measurement on the study scan for between 5 to 9 weeks' gestation, determining the crown-rump length measurement is considered the most accurate method of dating.

A real time B-mode scan was initially performed to define the uterine position, size and morphology. Sonographic characteristics or descriptions of the choriodecidual appearance (regular or irregular)14, gestational sac position (normal or low)14, yolk sac size (<6mm or ≥6mm, macro yolk sac)14, fetal heart rate (>100bpm or ≤100bpm, bradycardia)13, subchorionic hemorrhage (absent or present)14 and laterality of the corpus luteum (right or left) were noted.

Maternal clinical characteristics were likewise retrieved from their ultrasound records and this included maternal age (<35 years or ≥35 years) and history of previous abortion/s (with or without history of previous abortion/s).

The clinical outcome of pregnancy was determined by means of follow up ultrasound examination, interview with the referring physicians, telephone calls to physicians' offices and review of delivery and/or pathology records. Normal clinical outcome or successful pregnancy outcome was determined by normal second- or third trimester sonograms, or if clinical records confirm normal pregnancy progression. The clinical outcome was considered abnormal if a spontaneous early abortion or first trimester pregnancy loss of less than 12 weeks' gestation occurred following the sonogram.

This study was limited by the use of several ultrasound machines and by the different sonologists who interpreted the ultrasound findings. Interobserver bias was not eliminated in this study.

Data management and encoding were facilitated using Microsoft Excel and SPSS 17.0 for Windows programs. The descriptive statistics were determined by means of the SPSS frequency, descriptives and crosstabs procedures. For the comparison between means, t tests were performed. Computations and analysis were carried out using Chi-square and Fisher's tests to determine association among categorical variables. With the same software, univariate and multivariate logistic regression analyses were performed to estimate odds ratios for the independent predictor variables in the study. This included the estimation of the 95% confidence intervals of the event risks. A P value of < .05 was considered statistically significant. For fetal heart rate, a Receiver Operating Characteristic (ROC) curve was processed. A cut off value was explored in association with early pregnancy loss. The point in the curve where both sensitivity and specificity have highest values nearest to the area under the curve of 1.0 was considered as a diagnostic cut off point from this study.

RESULTS

There were a total of 419 subjects included in this study over the 14-month study period. The maternal ages ranged from 16 to 42 years with a mean...
maternal age of 30.87 ± 5.006 years. All subjects were scanned between 5 to 9 weeks age of gestation and the mean age of gestation at time of first trimester scan was 7.06 ± 1.297 weeks' gestation. The fetal heart rate recorded ranged from 38 to 197 bpm with a mean fetal heart rate of 143.44 ± 26.761 bpm.

Table 1 shows the sonographic characteristics of the first trimester scans of the subjects included in this study. The incidence of irregular choriodecidual appearance and low gestational sac position was only 0.2% each for there was only one of 419 cases each recorded for the said sonographic characteristics. Likewise, the incidence of finding a macro yolk sac or a yolk sac ≥6 mm in diameter was only 0.7% as there were only three recorded cases. The most common abnormal sonographic finding among the subjects scanned was presence of subchorionic hemorrhage with an incidence of 82.1% (344/419 cases). Fetal bradycardia or finding of fetal heart rate <100 bpm was found only in 25 subjects giving an incidence of 6.0%. As to the laterality of the corpus luteum, right-sided corpus luteum formation was more than twice as common as a left-sided corpus luteum formation with an incidence of 69.9% and 30.1%, respectively. Moreover, the table also shows the maternal clinical characteristics obtained from the ultrasound records. Among the 419 women included in this study, about one-fifth (21.7%) of the subjects were more than or equal to 35 years of age and 15.5% had a history of previous abortion/s.

Table 2 shows the distribution of pregnancy outcomes. Of the 419 subjects, 29 women (6.9%) had an early pregnancy loss or a spontaneous first trimester pregnancy loss.

Table 3 shows the univariate analysis of the association of the sonographic and maternal clinical characteristics according to pregnancy outcome. Since there were too few cases of irregular choriodecidual appearance, low gestational sac position and macro yolk sac or yolk sac size ≥6 mm in diameter, Chi square test may be invalid or not reliable. Even if the finding of subchorionic hemorrhage was the most common sonographic abnormality among the subjects, only 8.0% of these cases had an early pregnancy loss. Results showed that there was no association of presence of subchorionic hemorrhage with early pregnancy loss that was statistically significant (P=0.685). Likewise, laterality of the corpus luteum did not show an association with early pregnancy loss that was statistically significant (P=0.780). Only the finding of fetal bradycardia or fetal heart rate ≤100 bpm was found to be associated with early pregnancy loss that was statistically significant at P<0.001. Among the 25 cases with fetal bradycardia 48% (12/25 of cases) had early pregnancy loss. Fetal bradycardia rendered these women about 20 times at increased risk of
having an early pregnancy loss, OR 20.471, 95%CI 8.124-51.517.

As to maternal clinical characteristics, history of previous abortion/s was not associated with early pregnancy loss (P=0.425). It was maternal age ≥35 years which was associated with early pregnancy loss and this association was statistically significant at P=0.002. Among the 91 women aged ≥35 years, 13 or 14.2% had early pregnancy loss. Advanced maternal age, age ≥35 years, rendered these women about three times at increased risk of having early pregnancy loss, OR 3.303, 95%CI 1.524-7.156.

Table 4 shows that in a multivariate analysis of both sonographic and maternal clinical characteristics according to pregnancy outcome, fetal bradycardia and advanced maternal age were still the same variables that were significantly associated with early pregnancy loss. Fetal bradycardia, fetal heart rate ≤100 bpm, rendered a woman to about 26 times at increased risk of early pregnancy loss, OR 26.672, 95%CI 9.721-73.179. Advanced maternal age of ≥35 years rendered a woman to about 5 times at increased risk of early pregnancy loss, OR 4.666, 95%CI 1.891-11.513.

Table 3. Sonographic and maternal clinical characteristics according to pregnancy outcome, univariate analysis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pregnancy Outcome</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early Pregnancy Loss*</td>
<td>Successful Pregnancy **</td>
</tr>
<tr>
<td>Sonographic Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choriodecidual appearance†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>(28/418) 6.7%</td>
<td>(390/418) 93.3%</td>
</tr>
<tr>
<td>Irregular</td>
<td>(1/1) 100%</td>
<td>–</td>
</tr>
<tr>
<td>Gestational sac position†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>(28/418) 6.7%</td>
<td>(390/41) 93.3%</td>
</tr>
<tr>
<td>Low</td>
<td>(1/1) 100%</td>
<td>–</td>
</tr>
<tr>
<td>Yolk sac size†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6mm</td>
<td>(27/416) 6.5%</td>
<td>(389/416) 93.5%</td>
</tr>
<tr>
<td>≥6mm (macro yolk sac)</td>
<td>(2/3) 66.7%</td>
<td>(1/3) 33.3%</td>
</tr>
<tr>
<td>Fetal heart rate‡</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;100 bpm</td>
<td>(17/394) 4.3%</td>
<td>(377/394) 95.7%</td>
</tr>
<tr>
<td>≤100 bpm (bradycardia)</td>
<td>(12/25) 48.0%</td>
<td>(13/25) 52.0%</td>
</tr>
<tr>
<td>Subchorionic hemorrhage</td>
<td></td>
<td>0.685</td>
</tr>
<tr>
<td>Absent</td>
<td>(23/344) 6.7%</td>
<td>(321/344) 93.3%</td>
</tr>
<tr>
<td>Present</td>
<td>(6/75) 8.0%</td>
<td>(69/75) 92.0%</td>
</tr>
<tr>
<td>Laterality of the corpus luteum</td>
<td></td>
<td>0.780</td>
</tr>
<tr>
<td>Right</td>
<td>(19/293) 6.5%</td>
<td>(274/293) 93.5%</td>
</tr>
<tr>
<td>Left</td>
<td>(9/126) 7.1%</td>
<td>(117/126) 92.9%</td>
</tr>
<tr>
<td>Maternal Clinical Characteristics</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Age‡</td>
<td></td>
<td>0.425</td>
</tr>
<tr>
<td>&lt;35 years</td>
<td>(16/328) 4.9%</td>
<td>(312/328) 95.1%</td>
</tr>
<tr>
<td>≥35 years</td>
<td>(13/91) 14.3%</td>
<td>(78/91) 85.7%</td>
</tr>
<tr>
<td>History of previous abortion/s‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>(23/354) 6.5%</td>
<td>(331/354) 93.5%</td>
</tr>
<tr>
<td>Yes</td>
<td>(6/65) 9.2%</td>
<td>(59/65) 90.8%</td>
</tr>
</tbody>
</table>

* Early Pregnancy Loss - 1st trimester pregnancy loss, < 12 weeks age of gestation  
**Successful Pregnancy - normal pregnancy progression to > 12 weeks age of gestation  
† In cases where ≥ the events were too few, Chi square test may be invalid or not reliable
Table 4. Sonographic and maternal clinical characteristics according to pregnancy outcome, multivariate analysis (Qualitative).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sig.</th>
<th>Exp (B)</th>
<th>95% CI for Exp (B)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal heart rate ≤100 bpm</td>
<td>0.000</td>
<td>26.672</td>
<td>9.721</td>
<td>73.179</td>
<td></td>
</tr>
<tr>
<td>Maternal age ≥35 years</td>
<td>0.001</td>
<td>4.666</td>
<td>1.891</td>
<td>11.513</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.000</td>
<td>0.026</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5 shows that by quantitative analysis, in terms of actual maternal age, the odds of early pregnancy loss are increased by more than 62% for every 5-year increase in maternal age holding fetal heart rate constant. Likewise, the odds of early pregnancy loss decrease by more than 22% for every 10 beats per minute increase in fetal heart rate holding maternal age constant.

Table 6 shows the outcomes of pregnancies with fetal bradycardia. There were 25 cases of fetal bradycardia and 12 of them (48.0%) terminated in early pregnancy loss. The sensitivity and specificity of fetal bradycardia, fetal heart rate ≤100 bpm, as a predictor of early pregnancy loss was 41.4% and 96.7%, respectively. A sonographic detection of fetal bradycardia of ≤100 bpm had a 48% positive predictive value and a 95.7% negative predictive value. The accuracy of fetal bradycardia as a predictor of pregnancy loss was 92.8%.

In the Receiver Operating Characteristic (ROC) curve, the true positive rate (sensitivity) was plotted in function of the false positive rate (1-specificity) for different cut-off points of the fetal heart rate as a parameter. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. In this study population, fetal bradycardia cut-off of 98bpm was the cut-off that would give the highest possible sensitivity and specificity combined. There were 19 cases of fetal bradycardia, fetal heart rate ≤98bpm, and 9 of them (47.3%) terminated in early pregnancy loss. It has a low sensitivity at 31% but has a higher specificity at 97.4%. The accuracy of fetal
bradycardia ≤98bpm was likewise 92.8%. A sonographic detection of fetal bradycardia of ≤98bpm had a 47.4% positive predictive value and a 95% negative predictive value, similar to that of fetal bradycardia at ≤100 bpm.

DISCUSSION

Transvaginal ultrasound has become an invaluable tool in the evaluation of the embryo as a patient in early pregnancy. Several researches have come up with multiple parameters that will predict unfavorable pregnancy outcome including those cases where normal cardiac activity has already been sonographically demonstrated.

Harris, et al. in 2006, did a prospective study in a series of patients with a sonographic finding of a chorionic "bump," which was an irregular, convex bulge from the choriodecidual surface into the first-trimester gestational sac. The pregnancy outcomes of these cases with irregular choriodecidual appearance were compared with the general population and infertility first-trimester control groups. The finding of an irregular choriodecidual appearance in the first trimester sonogram was associated with a guarded prognosis for the early pregnancy with a livebirth rate of <50%. In this study, there was only one case of irregular choriodecidual appearance which eventually resulted in early pregnancy loss. The incidence was only 0.2% with a 100% poor outcome. Using univariate analysis, the difference would have been statistically significant, however, due to the low incidence, the chi-square test may be invalid.

Low gestational sac within the endometrial cavity also predicts poor pregnancy outcome since this means that the sac is beginning to detach from its normal implantation site and serially goes down on its way to expulsion. In this study, there was likewise only one case of low gestational sac which also resulted in early pregnancy loss. The incidence was only 0.2% with a 100% poor outcome. Using univariate analysis, the difference would have been statistically significant however as with the irregular choriodecidual appearance due to the low incidence, the chi-square test may be invalid.

A yolk sac size of more than 6mm in diameter is considered a macro yolk sac and is a predictive of poor outcome. A yolk sac more than 2 standard deviations from the mean predicted abnormal pregnancy outcome with a sensitivity of 91%, specificity of 66% and a positive predictive value of 88.8%. In this study, 66.7% of those with abnormal yolk sac resulted in early pregnancy loss with a sensitivity of only 6.9%, specificity of 99.7% and positive predictive value of 66.7%. However, since there were only 3 cases with this abnormal sonographic finding, a univariate analysis may not be valid to formulate conclusive association.

Subchorionic hemorrhage maybe due to partial detachment of the trophoblast from the uterine wall or abruption of the edge of the chorion frondosum-decidua basalis complex. As many as 18% of women with vaginal bleeding during the first half of pregnancy have sonographic evidence of a subchorionic hemorrhage as the etiology for their bleeding. The clinical significance of this type of hemorrhage is controversial, with some investigators reporting an increased incidence of spontaneous abortion. In this study, the incidence of a sonographic finding of subchorionic hemorrhage was 17.9%. With only 8.0% of cases resulting in early pregnancy loss, its association with poor outcome was not statistically significant (P=0.685). This study showed similar results as with the study of Lulu, et al. in 1996, reporting that subchorionic hematoma in early pregnancy may not be all that significant, since the presence of hematoma does not necessarily imply poor outcome. It has been said that subchorionic bleed likely represents an incidental finding, therefore, and when small and asymptomatic, may be of no clinical significance.

Devajaran, et al. conducted a retrospective study to observe the relationship between the laterality of ovulation and the viability of pregnancy. It has been reported that a predominant right sided ovulation exists in human being as has been reported in the past and that there was no statistically significant difference between the laterality of corpus luteum and viability of pregnancy. Similar to the results of this study, right-sided corpus luteum formation was more than twice as common as a left-sided corpus luteum formation, 69.9% vs 30.1%. On univariate analysis, laterality of corpus luteum formation was not significantly associated with early pregnancy loss (P=0.780).

As to reviews on embryonic heart rate, Achiron, et al. constructed normograms for the embryonic heart rate in 603 embryos at 5.5 to 11 weeks' gestation to determine whether deviation from the normal heat rate can predict fetal loss after ultrasound proven viability. In their study, 15 of the 23 spontaneous abortion cases recorded embryonic heart rates outside the 95% confidence interval or crown-rump length.
In another review by Benson, et al. (1994) involving pregnancies of less than 8 weeks' gestation with an embryonic heart rate of ≤90 bpm, fetal demise occurred in all 7 embryos with heart rate < 70 bpm, 10 of 11 with heart rates of 70-79 bpm, and 15 of 19 with heart rates of 80-90 bpm. In a very large series involving 2,164 singleton pregnancies between 6 and 8 weeks' gestation, Stefos and co-workers (1998) observed subsequent embryonic demise in all embryos that presented with a heart rate of ≤85 beats/minute.

The results of this retrospective study were similar with the findings of Benson and Doubilet in 2005 where among the 25 pregnancies 5 to 9 weeks' gestation, there were 12 cases of fetal bradycardia and all of them terminated in early pregnancy losses. All had repeat sonograms showing early intrauterine embryonic or fetal demise within a week's time from the sonographic detection of heart rate ≤100 bpm. As in this retrospective study, using fetal heart rate ≤100 bpm as cut-off for fetal bradycardia, the incidence was 6.0% and early pregnancy loss occurred in 48.0% of cases with a sensitivity of 41.4% and a specificity of 96.7%. Its positive and negative predictive values were 48% and 95.7%, respectively with an accuracy of 92.8%. Furthermore, in the Receiving Operating Characteristic Curve that was processed, a fetal bradycardia cut-off of 98 bpm likewise gave a low sensitivity at 31% but a higher specificity at 97.4% with nearly similar positive and negative predictive values at 47.4% and 95%, respectively. The accuracy was the same at 92.8%.

As with the previous reports, there was significant association between fetal bradycardia and early pregnancy loss. In both univariate and multivariate analyses of the various abnormal sonographic findings in first trimester scans, fetal bradycardia at ≤100bpm, was significantly associated with early pregnancy loss, OR 26.672, 95%CI 9.721-73.179. The dynamic changes occurring in the growth of the embryo as the age of gestation progresses and the corresponding changes in heart rate should never be overlooked in interpreting this study's results. Doubilet, et al. reported that at 5 to 6 weeks' gestation, the mean embryonic heart rate is 101 bpm, which increases to 143 bpm by 8 to 9 weeks' gestation and subsequently plateaus at approximately 140 bpm. Therefore, it is not unusual for an initially detected embryonic heart rate to be somewhat slower than the fetal heart rate recorded later in pregnancy. These findings further emphasize that despite a high sensitivity and specificity of fetal bradycardia as a predictor of subsequent early pregnancy loss, the biologic variation and the dynamism of the corresponding heart rate for age of gestation should likewise be considered in the further monitoring and observation of pregnancy progression.

Moreover, this investigative study also included possible confounding clinical variables in the subjects or maternal characteristics such as the maternal age and any history of previous abortion/s. History of previous abortion/s was not significantly associated with early pregnancy loss (P=0.425). On the other hand, in both univariate and multivariate analyses taking into consideration all possible abnormal sonographic findings, advanced maternal age was significantly associated with early pregnancy loss, OR 4.666, 95%CI 1.891-11.513. It cannot be overemphasized that advanced maternal age of ≥35 years is a risk factor for aneuploidy which subsequently is a common cause of early pregnancy loss.

A quantitative analysis of the association of fetal heart rate and maternal age with early pregnancy loss was likewise made in this investigative review. In terms of actual maternal age, the odds of early pregnancy loss are increased by more than 62% for every 5-year increase in maternal age holding fetal heart rate constant. Likewise, the odds of early pregnancy loss decrease by more than 22% for every 10 beats per minute increase in fetal heart rate holding maternal age constant.

**CONCLUSION**

It is significant to establish a sonographic parameter predictive of poor outcome or impending first trimester loss so as to be guarded in the reassurance provided to patients and their further work-up and monitoring. An abnormal ultrasound despite viability would caution the treating physician to order a subsequent sonogram in 7 to 10 days.

The incidence of irregular chorionic decidual appearance and low gestational sac position was low at 0.2% each. Likewise, the incidence of finding a macro yolk sac or a yolk sac ≥6 mm in diameter was only 0.7%. The most common abnormal sonographic finding among the subjects scanned was presence of subchorionic hemorrhage with an incidence of 82.1%. Fetal bradycardia or finding of fetal heart rate ≤100 bpm was found only in 25/419 subjects giving an incidence of 6.0%. As to laterality of the corpus luteum, right-sided corpus luteum formation was more than twice as common as a left-
sided corpus luteum formation with an incidence of 69.9% and 30.1% respectively.

Irregular choriodecidual appearance, low gestational sac, macro yolk sac, presence of subchorionic hemorrhage and laterality of corpus luteum formation were not significantly associated with early pregnancy loss. Among the abnormal first trimester sonographic findings only fetal bradycardia fetal heart rate ≤ 100 bpm, was significantly associated with early pregnancy loss, OR 26.672, 95%CI 9.721-73.179. The sensitivity and specificity of fetal bradycardia as a predictor of early pregnancy loss were 41.4% and 96.7% respectively. Fetal bradycardia of ≤ 100 bpm had a 48% positive predictive value, 95.7% negative predictive value and 92.8% accuracy.

Among the possible confounding maternal characteristics studied among the subjects that may affect first trimester outcome, history of previous abortion/s was not significantly associated with early pregnancy loss (P=0.425) while advanced maternal age was with OR 4.666, 95%CI 1.891-11.513.

**RECOMMENDATIONS**

Based on the gathered data, it may be recommended that a woman with a viable early first trimester gestation with abnormal sonographic findings should have a repeat sonogram later in the first trimester to re-assess fetal viability. As to sonographic features that may be prognostic factors of adverse outcomes, the investigators recommend a long-term study beyond the first trimester and adverse perinatal outcomes such as preterm labor, growth restriction and oligohydramnios be likewise evaluated. Moreover, results of this study would need further validation in a prospective review enrolling more patients from a multi-center study. It is hoped that in a multi-center study, a possible risk scoring index for first trimester patients coming in for an ultrasound will be formulated.

**REFERENCES**

13. Douillet PM, Benson CB. Outcome of first trimester pregnancies with slow embryonic heart rate at 6-7 weeks gestation and normal heart rate by 8 weeks at US. Radiology 2005; 236(2): 643-6.
Rapid Fetal Fibronectin Alone and in Combination with Cervical Length in Predicting Preterm Delivery Among Symptomatic Pregnant Women in a Philippine Tertiary Hospital: A Retrospective Cohort Study from 2009 to 2012*

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Department of Obstetrics and Gynecology, The Medical City

Background: The objective of this study was to determine the likelihood of delivery given a positive or negative rapid fetal fibronectin test result in symptomatic pregnant women in a Philippine tertiary hospital. Another objective was to determine if the likelihood of delivery is increased when fetal fibronectin is combined with cervical length assessment.

Methods: Medical records from 2009 to 2012 of patients between 24 weeks and 34 weeks and 6 days gestation with symptoms of preterm labor were retrieved and selected for this study. Rapid bedside fetal fibronectin results and cervical length measurements obtained via ultrasonography were gathered along with the interval duration from fibronectin testing, cervical length measurement and delivery.

Results: Thirty-one patients had fetal fibronectin samples and outcome data. The admission-to-delivery interval was 33.6 days shorter in the group with positive fetal fibronectin results than in the group with negative fetal fibronectin results. (20.2 ± 15.48 compared with 53.8 ± 26.95; P<0.05). The positive predictive values for delivery within 7, 14 and 21 days were 33.3%, 50% and 50%, respectively while the negative predictive values were 96%, 92% and 92%, respectively.

The positive likelihood ratios for delivery within 7, 14 and 21 days were 4.7, 5.2 and 5.2, respectively. The negative likelihood ratios for delivery within 7, 14 and 21 days were 0.4, 0.56 and 0.56, respectively.

The sensitivity combining a positive fetal fibronectin and short cervical length (<25 mm) in determining delivery before 34 weeks of gestation was 50%.

Conclusion: Several studies conclude that fetal fibronectin has a high negative predictive value suggesting that a negative result renders a patient unlikely to deliver within 7 days. This study shows that fetal fibronectin has fair to good strength as a short-term predictor of preterm labor based on qualitative strength of likelihood ratios. Given a positive fibronectin result, the likelihood that a patient will deliver prematurely within 7 days is 4.7 times. Given a negative result, the likelihood that a patient will not deliver is 2.5x than delivery will occur within 7 days.

Key words: Fetal fibronectin, cervical length, preterm labor

The worldwide estimates for preterm birth according to the World Health Organization (WHO) is 9.6%. In Asia, it is approximately 9.6%. In the US, preterm birth rate is 12.8% as of 2006.1

Preterm delivery rate has averaged 11.15% in the last 15 years according to the Philippine Obstetrical and Gynecological Society (POGS). At the Philippine General Hospital, the average preterm delivery rate in the last 5 years is 21.52%.3

In The Medical City the preterm delivery rate from 2007 to 2011 was 8.8%. In 2011 alone, the preterm delivery rate was 9.15%.2 These data are comparable with preterm delivery rates reported.

According to the Philippine Department of Health, as of 2006, 7.4% of infant mortality is attributed to preterm delivery. Eight percent of deliveries in 2008, have birth weight less than 2500grams as a complication of preterm delivery.3,4

* Finalist, POGS-Residents’ Research Paper Contest last October 24, 2012.
The diagnosis of preterm labor is made based on the following criteria: uterine contractions of 4 in 30 minutes, cervical dilatation of at least 3cm, and cervical effacement of 80% or greater. Studies have been made on cervical length measurement and fetal fibronectin as predictors of preterm delivery. These studies determined whether patients went into spontaneous labor and subsequently delivered within days or weeks of testing.

Review of Related Literature

Definition and Advantages of Fetal Fibronectin

Fetal fibronectin was first described by Lockwood in 1991. Fibronectins are adhesive glycoproteins with multiple isoforms found in extracellular matrix and plasma. It is uniquely found in the basement membrane, near the choriodeditial interface, and produced by fetal membranes. It provides adherence for the chorion to the decidua.

Fetal fibronectin is normally found in cervicovaginal fluid in the first 20 weeks of gestation as the gestation sac implants and attaches to the endometrium. After 20 weeks, when the implantation has been completed, the presence of fetal fibronectin in the cervix or vagina indicates mechanical or inflammatory disruption of the membrane’s attachment to the decidua. It is speculated that cervical disruption or dilatation will result in the release of fibronectin into the cervical discharge. It was also noted that fetal fibronectin was found in the amniotic fluid so that its presence in the vagina may also indicate the presence of amniotic fluid in the cervicovaginal secretions.

A negative fetal fibronectin test result suggests absence of preterm labor, thus, avoiding unnecessary hospitalization, and, the side effects of tocolytics and steroids. In contrast, a positive test may indicate the presence of preterm labor. Tocolytics may then be administered thereby delaying delivery to allow time for administration of steroids to enhance fetal lung maturity or transfer of a patient to a tertiary hospital with a neonatal intensive care unit. Pregnancies may be brought closer to term thereby avoiding the adverse effects of prematurity. Studies by Peaceman, et al. and Tekesin, et al. have shown that a negative fibronectin test is of more use than a positive fibronectin test.

The Food and Drug Administration in the United States has approved the use two fetal fibronectin assays for assessing preterm labor: the manual enzyme immunoassay and the rapid assay. The rapid assay is a semi-quantitative membrane immunoassay that uses monoclonal anti-fetal fibronectin antibody (FDC-6) coupled to a blue microsphere and an immobilized polyclonal goat anti-fibronectin antibody. The control lines on the device are interpreted with the TLiQ analyzer. Our study used the rapid assay fibronectin test which proves to have equivalent performance to the enzyme immunoassay which has an 8-24 hour turn-around time.

Fibronectin samples are collected by placing a sterile polyester tip swab in the posterior cul-de-sac for ten seconds. The swab is then placed in a fibronectin extraction buffer kit that uses a monoclonal anti-fibronectin antibody (FDC-6) for ten minutes. Fibronectin concentrations >50 ng/mL show as two lines on the cassette and is interpreted as positive. Results are either positive or negative. Fetal fibronectin sampling is not done in patients with sexual intercourse, vaginal examination or transvaginal ultrasound done within 24 hours.

Several studies claimed that fetal fibronectin is an accurate predictor of preterm delivery. In a study by Tekesin, et al., in 2005, fetal fibronectin was found to be effective in predicting risk of delivery with negative predictive values of 98.4%, 98.4% and 96% within 7, 14 and 21 days of testing, respectively.

A multicenter trial by Peaceman, et al., in 1997, reported that fetal fibronectin had an even higher negative predictive value at 99.5% for delivery within 7 days. The clinical value of a negative fetal fibronectin suggests that preterm delivery will not occur within 7 days.

Some studies were inconclusive about the value of fetal fibronectin. Berherella, et al., in 2008, reviewed five controlled studies and did not find any evidence to either support or refute the use of fetal fibronectin test for management of women with symptoms of preterm labor. The recommendation was to conduct further research.

There have also been studies that disprove the accuracy of fetal fibronectin in determining preterm delivery. Sanchez-Ramos, et al., published a meta-analysis in 2009, involving 32 studies, which concluded that fibronectin has limited accuracy in predicting preterm birth within 7 days of sampling.
in their randomized control trial that the use of fetal fibronectin does not affect the gestational age at delivery, frequency of use of medical interventions, length of stay in labor and delivery or rate of inpatient admissions.\textsuperscript{12}

A local prospective study by Libiran, et al., in 2011, noted that fibronectin alone has low accuracy of predicting preterm delivery (LR+ 1.7 and LR- 0.8). Combined fibronectin and cervical length has moderate accuracy in predicting preterm delivery (LR 0.14) The study concluded that a negative fibronectin test is a good indicator that preterm delivery is unlikely to occur. Cervical length predicts preterm delivery more accurately than fibronectin. Fibronectin is of value when combined with cervical length measurement.\textsuperscript{23}

Currently, the American College of Obstetrics and Gynecology recommends that fetal fibronectin should not be used routinely to screen low risk asymptomatic women, but the test may be useful to screen high-risk patients for preterm labor.\textsuperscript{1,8,13}

**Objectives of the Study**

The objective was to determine the likelihood of delivery given a positive or negative rapid fetal fibronectin test result in symptomatic pregnant women at The Medical City. The authors also aimed to determine if the likelihood of delivery is increased when fetal fibronectin is combined with cervical length assessment.

**MATERIALS AND METHODS**

**Data Collection**

This retrospective cohort study was conducted from January 2009 to January 2012 at The Medical City. Fetal fibronectin test has only been made available in the institution in 2009. Approval from the medical records section to scan through the data was obtained.

**Subject Inclusion and Exclusion Criteria**

Pregnant women between 24 weeks and 34 weeks and 6 days age of gestation with associated regular uterine contractions, cervical dilatation and cervical effacement, who had fetal fibronectin testing done, with or without cervical length measurement by ultrasonography, were included in this study.

A gestational age cut-off of 34 weeks and 6 days was used as cut-off because evidence indicates that infants delivered between 34 and 37 weeks of gestation experience morbidity and mortality at rates similar to term infants delivered between 37 and 40 weeks.\textsuperscript{18} In the charts, the regular uterine contractions were all documented by tocodynamometry, as having at least 4 contractions in 30 minutes. Cervical dilatation was from 0 to 3 centimeters and cervical effacement was at least 50%.\textsuperscript{21}

All pregnancies were singleton and had none of the following complications or risk factors for preterm delivery: preterm rupture of membranes, intrauterine infection, incompetent cervix, intrauterine growth restriction of the fetus, preeclampsia, suspected fetal asphyxia, or a major fetal anomaly.\textsuperscript{5,7,17}

**Data Documentation**

Data collected on patient's demographic information (age, gravidity, parity), fetal fibronectin
test result, digital cervical examination, gestational age at fetal fibronectin testing, gestational age at delivery, fibronectin testing-to-delivery interval and pregnancy outcome were tabulated.

The measured outcome was delivery within 7, 14 and 21 days following a positive or negative fetal fibronectin result.

Data Analysis

Fetal fibronectin test results were correlated with date and gestational age at delivery. A positive fetal fibronectin test result was considered a true positive if delivery occurred within 7, 14 or 21 days after the positive test result, and considered a false positive result if spontaneous delivery did not occur within 7, 14 or 21 days.17

A negative fetal fibronectin test result was considered true negative if delivery did not occur within 7, 14 or 21 days after the negative test result, and considered false negative if delivery occurred within 7, 14 or 21 days.17

Cervical length of less than 25mm (10th percentile) was categorized as short and that of more than 25mm was long.15

Data were expressed as means and standard deviations or number of observations with appropriate proportions. Nominal values were analyzed with the X² test. Sensitivity, specificity, positive and negative predictive values were calculated for the above outcomes. The likelihood ratio of a positive result [(sensitivity)/(1-specificity)] and the likelihood ratio of a negative result [(1-sensitivity)/specificity)] were calculated. Statistical significance was assumed for P < 0.05.17

RESULTS

A total of 31 patients met the inclusion criteria. Table 1 describes the demographic and clinical characteristics of the study population. No statistically significant differences were observed concerning maternal age, gravidity, parity, gestational age at enrollment and gestational age at delivery. As expected, a statistically significant difference in admission-to-delivery interval was found.

The mean admission-to-delivery interval was 53.8±26.95 days for those with negative results and 20.2±15.48 days for those with positive results (P<0.007). This is 33.6 days shorter in the group with positive fetal fibronectin results. The overall preterm delivery rates in our study population were 35% for less than 37 weeks of gestation and 16% for less than 34 weeks.

Fetal Fibronectin

The sensitivity, specificity and predictive values for each delivery category are shown in Table 2. The rapid fetal fibronectin assays had a sensitivity of 66.7% and specificity of 85.7% in predicting risk of delivery within 7 days, and a sensitivity of 60% and specificity of 88.5% for those who delivered within 14 and 21 days.

For spontaneous delivery before 34 weeks, fetal fibronectin had a sensitivity of 40%, specificity of 84.6%, positive predictive value of 33.3% and a negative predictive value of 88%. For spontaneous delivery before 37 weeks, fetal fibronectin had a sensitivity of 33.3%, specificity of 89.5%, positive predictive value of 66.7% and a negative predictive value of 68%.

<table>
<thead>
<tr>
<th>Table 1. Demographic and clinical characteristics at the time of presentation among patients with positive and negative fetal fibronectin test results.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>fFN (+) n=6</strong></td>
</tr>
<tr>
<td>Mean Maternal Age (y)</td>
</tr>
<tr>
<td>Mean Parity</td>
</tr>
<tr>
<td>Mean Gravidity</td>
</tr>
<tr>
<td>Gestational Age at Enrollment (wk)</td>
</tr>
<tr>
<td>Gestational Age at Delivery (wk)</td>
</tr>
<tr>
<td>Admission-to-Delivery Interval (d)</td>
</tr>
</tbody>
</table>
The positive predictive values for delivery within 7, 14 and 21 days were 33.3%, 50% and 50%, respectively. The negative predictive values for delivery within 7, 14, and 21 days were 96%, 92% and 92%, respectively.

The positive likelihood ratio was 3.17 for delivery before 37 weeks of gestation and 2.6 for delivery before 34 weeks. The positive likelihood ratios (LR+) were 4.7, 5.2 and 5.3 for delivery within 7, 14 and 21 days. (Table 2)

The negative likelihood ratio was 0.75 for delivery before 37 weeks of gestation and 0.71 for delivery before 34 weeks. The negative likelihood ratios (LR-) were 0.4, 0.45 and 0.45 for delivery within 7, 14 and 21 days. (Table 2)

Fetal Fibronectin Combined with Cervical Length

Cervical length measurement was available in 19 of the 31 patients tested for fetal fibronectin. The sensitivity, specificity and predictive values for each delivery category are shown in Table 4. The rapid fetal fibronectin combined with cervical length had a sensitivity of 50% and specificity of 82.4% in predicting risk of delivery within 7 days and a sensitivity of 50% and specificity of 86.7% for those who delivered within 14 and within 21 days.

For spontaneous delivery before 37 weeks of gestation, fetal fibronectin combined with cervical length had a sensitivity of 42.9%, specificity of 91.7%, positive predictive value of 75% and a negative predictive value of 73.3%. For spontaneous delivery before 34 weeks of gestation, fetal fibronectin combined with cervical length had a sensitivity of 50%, specificity of 86.7%, positive predictive value of 50% and a negative predictive value of 86.7%.

Positive predictive values for delivery within 7, 14 and 21 days were 25%, 50% and 50%, respectively. The negative predictive values were 93.3%, 86.7% and 86.7% for delivery within 7, 14, and 21 days, respectively.

The positive likelihood ratio was 5.17 for delivery before 37 weeks of gestation, 3.76 for delivery before 34 weeks. The positive likelihood ratios (LR+) were 2.84, 3.76 and 3.76 for delivery within 7, 14 and 21 days. (Table 4)

The negative likelihood ratio was 0.62 for delivery before 37 weeks of gestation and 0.58 for delivery before 34 weeks. The negative likelihood ratios (LR-) were 0.61, 0.58 and 0.58 for delivery within 7, 14 and 21 days.

Table 2. Efficacy of rapid fetal fibronectin for prediction of delivery within 7, 14 and 21 days and less than 37 and 34 weeks age of gestation after specimen collection.

<table>
<thead>
<tr>
<th>Timing of Delivery</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV n</th>
<th>PPV %</th>
<th>NPV n</th>
<th>NPV %</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7 days</td>
<td>66.7</td>
<td>85.7</td>
<td>2/6</td>
<td>33.3</td>
<td>24/25</td>
<td>96</td>
<td>4.7</td>
<td>0.40</td>
</tr>
<tr>
<td>≤ 14 days</td>
<td>60</td>
<td>88.5</td>
<td>3/6</td>
<td>50</td>
<td>23/25</td>
<td>92</td>
<td>5.2</td>
<td>0.45</td>
</tr>
<tr>
<td>≤ 21 days</td>
<td>60</td>
<td>88.5</td>
<td>3/6</td>
<td>50</td>
<td>23/25</td>
<td>92</td>
<td>5.2</td>
<td>0.45</td>
</tr>
<tr>
<td>&lt; 37 weeks</td>
<td>33.3</td>
<td>89.5</td>
<td>4/6</td>
<td>66.7</td>
<td>17/25</td>
<td>68</td>
<td>3.17</td>
<td>0.75</td>
</tr>
<tr>
<td>&lt; 34 weeks</td>
<td>40</td>
<td>84.6</td>
<td>2/6</td>
<td>33.3</td>
<td>22/25</td>
<td>88</td>
<td>2.6</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Table 3. Demographic and clinical characteristics at the time of presentation among patients with fetal fibronectin and cervical length results.

<table>
<thead>
<tr>
<th></th>
<th>fFN (+)/CL &lt;25 mm n=4</th>
<th>fFN (-)/CL &gt; 25 mm n=15</th>
<th>T-test P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOG at fFN</td>
<td>31.18±1.984</td>
<td>30.59±3.231</td>
<td>0.736</td>
</tr>
<tr>
<td>AOG on Delivery</td>
<td>34.25±4.335</td>
<td>37.48±2.387</td>
<td>0.059</td>
</tr>
<tr>
<td>fFN-to-Delivery Interval</td>
<td>22.5±16.543</td>
<td>49.07±26.037</td>
<td>0.072</td>
</tr>
</tbody>
</table>
DISCUSSION

Presence of Fibronectin in Patients in Preterm Labor

Risk scoring systems, biochemical markers of inflammation, fetal fibronectin and cervical length determination are tools being studied to decrease unnecessary interventions for patients with symptoms of preterm labor and to identify patients who might benefit from tocolysis, corticosteroids and transfer to a tertiary care facility.

Lockwood, et al., were the first to publish that the presence of fibronectin in patients in preterm labor was associated with preterm delivery. Fibronectin was present in 50.4% of women with preterm uterine contractions and intact membranes. In our study, fetal fibronectin was present in 19% of patients with symptoms of preterm labor.

Fetal Fibronectin

In our study, sensitivity and specificity of fetal fibronectin in predicting pre-term delivery within 7 days of rapid fetal fibronectin testing were found to be 66.7% and 85.7%, respectively. Fetal fibronectin is more specific than it is sensitive. (Table 2)

The positive likelihood ratio (LR+) for delivery within 7 days is 4.7. This is the likelihood that a patient with a positive fetal fibronectin test result will deliver within 7 days. This study shows that given a positive fibronectin result, the likelihood that the patient will deliver prematurely within 7 days is 4.7 times more than she will not. (Table 3)

The negative likelihood ratio, on the other hand, is 0.4. This study shows that given a negative fibronectin test result, the likelihood that the patient will deliver prematurely within 7 days is about 0.4 or 40%. Conversely, the likelihood that she will not deliver prematurely is 60%. So that, when the test is negative, the likelihood that she will not deliver within 7 days is 1/0.4 or 2.5 times. (Table 3)

Table 4. Efficacy of rapid fetal fibronectin alone and in combination with cervical length in predicting preterm delivery among symptomatic pregnant women. 

<table>
<thead>
<tr>
<th>Timing of Delivery</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV n</th>
<th>PPV %</th>
<th>NPV n</th>
<th>NPV %</th>
<th>LR (fFN+, short Cx)</th>
<th>LR -(fFN-, long Cx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7 days</td>
<td>50</td>
<td>82.4</td>
<td>1/4</td>
<td>25</td>
<td>14/15</td>
<td>93.3</td>
<td>2.84</td>
<td>0.61</td>
</tr>
<tr>
<td>≤ 14 days</td>
<td>50</td>
<td>86.7</td>
<td>2/4</td>
<td>50</td>
<td>13/15</td>
<td>86.7</td>
<td>3.76</td>
<td>0.58</td>
</tr>
<tr>
<td>≤ 21 days</td>
<td>50</td>
<td>86.7</td>
<td>2/4</td>
<td>50</td>
<td>13/15</td>
<td>86.7</td>
<td>3.76</td>
<td>0.58</td>
</tr>
<tr>
<td>&lt; 37 weeks</td>
<td>42.9</td>
<td>91.7</td>
<td>3/4</td>
<td>75</td>
<td>11/15</td>
<td>73.3</td>
<td>5.17</td>
<td>0.62</td>
</tr>
<tr>
<td>&lt; 34 weeks</td>
<td>50</td>
<td>86.7</td>
<td>2/4</td>
<td>50</td>
<td>13/15</td>
<td>86.7</td>
<td>3.76</td>
<td>0.58</td>
</tr>
</tbody>
</table>

In our study, the negative predictive value for delivery within 7 days was high with a value of 96%, comparable to the 99.5% obtained by Peaceman, et al. and 98.4% obtained by Tekesin, et al. In these respective studies, the authors concluded that a negative fibronectin result was highly predictive that delivery will not occur within 7 days. But, despite this high negative predictive value, it can be noted that the prevalence of preterm delivery in these trials were unusually low. The high negative predictive value of fetal fibronectin for delivery within 7 days was influenced by the low prevalence of the primary outcome in each trial. In other words, even without any testing, 97% of the participants would not have experienced the outcome.8

Positive and negative predictive values were not used to analyze results in this study since predictive values are influenced by prevalence of outcomes. The prevalence of preterm delivery in Asia is 9.6% and 9.15% in our institution. Likelihood ratios were used in determining the accuracy of fetal fibronectin as a predictor of preterm labor because likelihood ratios are not affected by prevalence. Likelihood ratios were also used in studies by Sanchez, et al. and by Honest, et al.20

Positive likelihood ratios greater than 10 and negative likelihood ratios less than 0.1 indicate that a test is clinically useful (Table 5). Likelihood ratios between 2 to 5 (+LR) and 0.2 to 0.5 (-LR) yield small increases and decreases, respectively, in the posttest probability of a disease. In our study, the likelihood ratios of a positive test result for delivery within 7, 14 and 21 days were 4.7, 5.2 and 5.2, respectively. The likelihood ratios of a negative test result for delivery within 7, 14 and 21 days were 0.4, 0.45 and 0.45, respectively. This translates to fetal fibronectin having fair to good strength in predicting delivery within 7, 14 and 21 days, based on likelihood ratios. (Table 3)

These results are in accordance with a meta-analysis done by Sanchez, et al. In their study, the
overall pooled positive and negative likelihood ratios were 4.2 (95% CI 3.53-4.99) and 0.29 (95% CI 0.22-0.38), respectively. Our results are also comparable to a meta-analysis by Honest, et al. who obtained positive and negative likelihood ratios of 4.01 and 0.78.

By using likelihood ratios, this study avoided the influence of prevalence on fetal fibronectin test accuracy.

**Fetal Fibronectin Combined with Cervical Length**

In this study, the sensitivity of a positive fetal fibronectin result combined with short cervical length (< 25 mm) in determining delivery before 34 and 37 weeks of gestation is 50%. This is comparable to a study by Goldberg, et al., wherein 60% delivered before 37 weeks of gestation and 50% delivered before 32 weeks.

The likelihood ratios of a positive fetal fibronectin and a short cervical length for delivery within 7, 14 and 21 days are 2.84, 3.76 and 3.76, respectively. The likelihood ratio of a negative fetal fibronectin and a long cervix for delivery within 7, 14 and 21 days are 0.61, 0.58 and 0.58, respectively. (Table 4)

The results for fetal fibronectin combined with cervical length obtained from this study suggest fair strength of the combination in predicting preterm delivery. (Table 5)

<table>
<thead>
<tr>
<th>Quality of Strength</th>
<th>LR +</th>
<th>LR -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>Very good</td>
<td>6</td>
<td>0.2</td>
</tr>
<tr>
<td>Fair</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Useless</td>
<td>1</td>
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LR, likelihood ratio
Source: Elavunkal and Sinert (2009)

Although fetal fibronectin and cervical length may, independently and additively, estimate risk of preterm delivery in asymptomatic women, cervical length does not seem to contribute to prediction of delivery within 14 days in symptomatic fetal fibronectin positive women, according to the study done by Franco, et al. Our results for fetal fibronectin combined with cervical length are in accordance with their findings.

**Clinical Application of Results**

To put into clinical use, we use Bayes’ theorem, which involves the odds of having or not having the disease after testing with fetal fibronectin. Using the prevalence of preterm birth in our institution and in Asia, we can compute the likelihood of delivery within 7 days, given a positive or negative fibronectin test.

The preterm birth rate in our institution is 9.15%, almost similar to the preterm birth rate of 9.6% in Asia. Our pre-test odds was 0.1 and our posttest odds was 0.47, which, when converted, was equal to a 33% probability rate. This means that the probability of preterm delivery increased from 9.15% to 33% given a positive fetal fibronectin result. Using the same theorem, when the test was negative, the probability that the patient would deliver decreased from 9.15% to 3%.

When fetal fibronectin and cervical length were combined, we found that the probability of preterm delivery decreased from 33% (with the use of fibronectin alone) to 22% (positive fetal fibronectin and short cervical length). This may be attributed to the decrease in sample size of patients who underwent cervical length determination.

A positive fetal fibronectin result indicates a 4.7 chance that a patient will deliver within 7 days. This may prompt the obstetrician to administer tocolytics to delay preterm delivery and steroids to help fetal lung maturity. The need for transfer to a tertiary hospital with a neonatal intensive care unit may be indicated. A negative fibronectin result on the other hand indicates a 2.5 chance that a patient will not deliver within 7 days therefore avoiding unnecessary admissions and the side effects of administering tocolytics and steroids.

**Limitations and Recommendations of the Study**

We recommend conducting a prospective study, to avoid confounders such as technicalities in fibronectin sampling and cervical length measurement, and to standardize the tocolytics and steroids administered to the patients. We recommend increasing the sample size and doing cervical length assessment in all tested for fibronectin to correct the limitations of our study.
CONCLUSION

This study confirms studies by Ramos-Sanchez, et al. that fetal fibronectin is of some value in predicting preterm delivery. This study shows that fetal fibronectin has fair to good strength as a short-term predictor of preterm labor based on qualitative strength of likelihood ratios. Given a positive fibronectin result, the likelihood that a patient will deliver prematurely within 7 days is 4.7 times. Given a negative result, the likelihood that a patient will not deliver is 2.5 times than delivery will occur within 7 days.

Studies have not clearly shown the value of combining fetal fibronectin and cervical length in the prediction of preterm delivery, as in our study. It is therefore recommended that more comprehensive studies with larger sample sizes be conducted, to increase the statistical power of the outcomes and to accurately assess their correlation.

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A Case of Genital Tuberculosis in a 32 Year Old Nulligravid*

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Cervical tuberculosis, though rare, should be a consideration in cases presenting as pelvic inflammatory disease or malignant looking lesions of the cervix. Symptoms may vary but a high index of suspicion should be kept in mind owing to a persistently high prevalence of tuberculosis in developing countries like the Philippines. The patient in focus is a 32 year old nulligravid with a history of endometrial tuberculosis and prior anti-Koch’s therapy, now complaining of abnormal vaginal discharge. On examination, she had a malignant looking exophytic growth on the cervix which turned out to be cervical tuberculosis. Further examination revealed involvement of the ovaries as well. With a prior history of endometrial tuberculosis, a diagnosis of genital tuberculosis was made. The diagnosis is achieved by the interplay of clinical assessment, risk factors and laboratory investigations. Prognosis of genital tuberculosis is generally good but an additional challenge arises with the emergence of multidrug resistance to standard anti-tuberculosis therapy.

Key words: genital tuberculosis

Tuberculosis remains a public health concern worldwide. In 2010, the largest number of new cases occurred in Asia, accounting for 60% of new cases globally. Tuberculosis exists in two forms: pulmonary and extrapulmonary. Genital tuberculosis is one form of extrapulmonary TB, affecting about 12% of patients with pulmonary tuberculosis and representing 15% to 20% of extrapulmonary tuberculosis. In 92% of cases, genital tuberculosis is secondary to a focus in the lungs, lymph nodes, urinary tract, bones or joints. Genital tuberculosis usually involves the upper genital tract, primarily the endometrium and fallopian tubes. To accurately assess the actual incidence of genital tuberculosis is difficult since 11% of cases are asymptomatic. Commonly involved genital organs include the fallopian tubes in almost all cases (95% to 100%), endometrium in 50% to 60%, the ovaries in 20% to 30%, the vulva and the vagina in 1% and the myometrium in 2.5% of genital tuberculosis cases. The cervix accounts for only 0.1% to 0.65% of all cases of tuberculosis and 5% to 24% of genital tract TB.

Such a case is presented due to the rarity of this condition and that it clinically mimics carcinoma of the cervix. Moreover, the issue of multidrug resistance in tuberculosis occurring worldwide is now becoming a public health burden, which makes this case worth reporting.

Clinical History

M.C. is a 32 year old single, nulligravid, caregiver, from Quezon City, who consulted due to yellowish foul-smelling discharge.

The patient is a diagnosed case of endometrial tuberculosis in May 2003 previously treated with quadruple anti-Koch’s therapy for 6 months. Initially, she experienced prolonged and profuse menses consuming 8 fully soaked pads per day lasting for 2 weeks. Histopathology result post fractional curettage revealed endometrial tuberculosis. Close contact with an index case of pulmonary tuberculosis was not established. Resolution of symptoms was noted on initiation of treatment. However, complete eradication of the tuberculous infection was not documented since no follow up consultation was done.

* 1st Place Winner, 2013 Midyear Residents' Interesting Case Paper Presentation Contest last 11 April 2013, Ballroom 2, The Oriental Hotel, Legaspi City, Albay.
One month prior to consult, she noted profuse yellowish foul-smelling vaginal discharge associated with hypogastric pain. She was treated as a case of pelvic inflammatory disease in the province. She was given Metronidazole and an unrecalled vaginal suppository without relief of symptoms. She claimed to have low-grade fever and weight loss of about 12kg in 1 month. She denied changes in bowel or bladder habits. Persistence of symptoms prompted consult at a clinic where a transvaginal ultrasound was done. Results showed a cervical mass measuring 4.7cm x 4.0cm x 3.9cm. Neoplasm versus a chronic granulomatous process was being considered. She was then referred to a tertiary institution.

(2/15) The patient reported persistence of above symptoms with missed menses. On physical examination, she was averagely built and well nourished weighing 52kg. General examination was normal with no evidence of pallor or lymphadenopathy. Systemic examination was non-contributory. On examination of the abdomen, a firm, fixed, non-tender pelvo-abdominal mass spanning the hypogastric to the umbilical area was palpated. Speculum examination showed a barrel-shaped cervix with circumosal erosions and a 3cm friable, irregularly shaped mass completely occluding the cervical os. The same findings were noted on internal examination with a slightly enlarged uterus and shallow right lateral fornix. (Figure 1) The rest of the examination findings were essentially normal. Sputum AFB and chest x-ray showed negative results.

(2/27) Due to the appearance of the cervical mass, a cervical malignancy was entertained. She was referred to the Gynecology-Oncology subspecialty for cervical mass biopsy, which revealed chronic granuloma. She was referred to the Gynecology Infectious subspecialty afterwards. An irregularly shaped, friable pink mass at the posterior cervical lip was appreciated on speculum examination. On internal examination, the cervix was ballotable with a solid polypoid non-tender mass. The uterus was not enlarged and no adnexal tenderness was appreciated but adnexal nodularities were palpated at the right adnexal area. A diagnosis of cervical tuberculosis was made. Visual acuity and liver function checked prior to initiation of treatment showed normal results. She was subsequently started on quadruple anti-Koch's therapy. A transvaginal ultrasound was requested which showed a normal-sized anteverted uterus with a myoma nodule. The endometrium was irregularly thickened with fluid interphase. Both ovaries were nodular with periovarian adhesion. Pyosalpinx was considered in the left adnexa. With these findings in mind, a diagnosis of genital tuberculosis was made.

(3/16, 28) The patient was monitored closely. No improvement was seen on follow-up. On succeeding transvaginal ultrasound, there was an increase in the size of the cervical and ovarian mass. Multidrug resistance was considered at this time. A cervical punch biopsy sent for AFB smear and culture yielded *Mycobacterium tuberculosis* susceptible to Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin. She was subsequently referred to the Tuberculosis Directly Observed Treatment Short course (DOTS) program for anti-Koch's therapy. Starting on the second month of therapy, there was gradual decrease in the size of the mass with resolution of vaginal discharge and other symptoms with onset of weight gain. (Figure 2). However, her menses failed to recur.

**DISCUSSION**

Tuberculosis (TB), one of the oldest diseases known to affect humans is an infectious disease caused by a bacterium, which primarily affect the lungs. TB is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. Transmission usually takes place through the airborne spread of droplet nuclei produced by persons with infectious pulmonary tuberculosis. While both are preventable and curable, TB remains one of the
world’s major causes of illness and death. Tuberculosis can affect any organ in the body, exist without any clinical manifestation and recur. In 1993, the World Health Organization (WHO) declared TB to be a global health emergency.

According to the World Health Organization, 8.8 million people fell ill with TB in 2010 and 1.4 million died from it. Over 95% of deaths occur in low and middle-income countries. Tuberculosis is among the top three causes of death for women aged 15 to 44. The prevalence of genital tuberculosis is directly proportional to the incidence of pulmonary tuberculosis in an area. Most recent reports from developed countries showed an incidence of genital TB as 1% but in developing world where tuberculosis is common, figures as high as 10% were noted.

In 1744, Morgagni described the first case of genital TB following a postmortem examination of a 20-year old woman who died of tuberculosis.

Figure 2. Photograph of cervix prior to treatment.

Figure 3. Irregular endometrium with fluid interphase. Bilateral nodular ovaries with periovarian adhesions. Consider pyosalpinx, left adnexa.
Figure 4. Uterus with multiple myometrial calcifications. Bilateral tubo-ovarian complex mass. Pelvic adhesions.

Figure 5. Normal sized anteverted uterus with myoma nodules and tuberculous implants. Thin endometrium with synechiae. Normal ovaries. Dilated left fallopian tube. Pelvic adhesions.
*Mycobacterium tuberculosis* accounts for 90%-95% of cases of genital TB. However, *Mycobacterium bovis* may be the causal agent in about 5%-10%, of cases especially when the organisms are acquired from the gastrointestinal tract. It should be emphasized that genital tuberculosis is not the same as pelvic tuberculosis. The latter involves the mesenteric or pelvic lymph nodes without involvement of the genital tract.

Tuberculosis of the female genital tract is almost always secondary to a focus elsewhere in the body. The primary focus may be quiescent but secondary lesions may appear in the genital tract years later and the sequelae may be devastating especially if infertility results. Primary lesion may be in the lungs (50%), lymph nodes (40%), urinary tract (5%), bones and joints (5%) or abdomen (25%). Pelvic organs are infected from a primary focus by three principal routes namely hematogenous, lymphatic and direct spread from a neighboring viscus.

Genital tuberculosis develops in 5%-13% of patients with pulmonary tuberculosis. After the tubercle bacilli has invaded the lung, in most cases the bacilli are disseminated by way of the bloodstream within hours and deposited in various organs of the body. This bacillemia may persist for 6 weeks or longer, if the disease is not recognized and treated promptly with antituberculous drugs. Tubercle bacilli also may reach the bloodstream and thus the genital tract from extrapulmonary and chronic pulmonary lesions. The fallopian tubes are believed to be the initial and most frequently affected organ involved in 90%-100% of cases of genital mycobacterial infection. Rarely the ovary, cervix and endometrium can be infected primarily from the bloodstream. Hematogenous spread of TB bacilli to the tubes results in involvement of the submucosa (endosalpingitis) at the outer ends with gradual spread medially to the endometrium. Direct spread of infection to the fallopian tubes results in exosalpingitis with tubercles on the surface. Tuberculous peritonitis is commonly seen with genital tract involvement and may also be associated with rupture of a caseous abdominal lymph node or, less frequently, with spread from an intestinal focus.

A less common mode of infection, lymphatic spread, occurs when the primary lesion is in the abdominal cavity. In some countries in which people drink raw milk (unpasteurized), infection, which spreads by way of the alimentary tract and caused by the bovine tubercle bacillus is still reported. Gavaller and coworkers reported that in one area in Hungary, 33% of cases of female genital TB were due to bovine bacillus, which was spread to the fallopian tubes by way of the lymphatics.

Direct extension to the genital tract organs from tuberculous abdominal viscera, such as the bladder, rectum, appendix and intestines, has been described. Some researchers believe that this spread is along the peritoneal surface. The ovaries may be involved by direct infection from a neighboring structure such as the bowel. However, in most instances, peritoneal involvement can also be the result of spillage of infected material from the fallopian tubes; thus, the primary process is not always clear. It also may occur when adhesions bind the bladder or intestine to the fallopian tubes and perforation of a tuberculous ulcer results in direct spread to the genital organs.

In 1%-2% of cases, genital TB may be due to direct contact with infected semen. Primary infection of the vulva, vagina and cervix may result from direct inoculation at sexual intercourse with persons having genitourinary TB and ascending spread of infection from these sites may occur. This type of disease may also occur in a woman who has TB of another organ and who excretes tubercle bacilli in her stool, urine or sputum. When these excretions come into contact with the external genitalia, TB of the vulva or vagina may result, particularly if the skin is abraded or broken. The criteria necessary for the diagnosis of primary genital tract TB are 1) the genital lesions should be the first tuberculous infection in the body and 2) and regional lymph nodes should demonstrate the same stage of TB development as do the genital organs.

It was reported that the fallopian tubes are involved in almost all cases (90% to 100%), the endometrium in 50% to 60% of cases, ovaries in 20% to 30%, cervix in 5% to 15%, vulva and vagina in 1% and myometrium in 2.5%. The ovaries may be involved by direct infection from a neighboring structure such as the bowel. However, in most instances, infection spreads from the tubes, and the process extends to the surface of the ovaries. The cervix is involved by spreading from the endometrium or as part of the hematogenous infection. Tuberculous infection of the vagina and vulva may follow injury or abrasion to these structures in the presence of tubercle bacilli from the upper genital tract, intestinal tract or the lungs.

Genital TB is a challenging disease both from diagnostic and therapeutic point of view as it has few characteristic symptoms. The majority of cases...
were between 20-45 years of age. Postmenopausal women account for 7%-11% of cases of genital TB. The clinical presentation of genital tuberculosis is extremely variable depending on the site involved. About 20% of patients with genital TB give a history of TB in their immediate family. As a rule, they were exposed to an adult with TB during childhood. According to most series, patients with genital TB will give a history of prior diagnosis or treatment of extragenital TB approximately 30% to 50% of the time. Constitutional symptoms such as weight loss, low-grade fever, fatigue or poor general health may be present. In the acute phase, the presentation may resemble classical acute pelvic inflammatory disease (PID) with pelvic pain, fever and vaginal discharge. Some patients gave a history of recurrent pelvic inflammatory disease that has not responded to the usual antibiotic therapy. Approximately 11% of patients with genital TB are asymptomatic and the majority of women are diagnosed during investigations for infertility. In most studies, infertility is the presenting complaint in 40% to 50% of patients. In a study by Qureshi, et al. the most common presenting symptom was infertility (42.5%). It was primary in 78% and secondary in 22% of cases. In a ten year clinicopathological study of Mondal and Dutta, 65% to 70% of patients with genital TB presented with infertility, pelvic or abdominal pain in 50%-55%, and menstrual disturbances in 20%-25%. The second most common complaint is lower abdominal or pelvic pain present in 25% to 50% of cases. The pain is not usually severe and may be present for several months already. The pelvic pain becomes more severe when progression of genital TB takes place and is usually aggravated by coitus, exercise and menses. The third most common symptom of genital TB is menstrual irregularity in the form of menorrhagia, menometrorrhagia, intermenstrual bleeding, oligomenorrhea, postmenopausal bleeding or amenorrhea. Abnormal vaginal bleeding occurred in 18% of individuals. Amenorrhea and vaginal discharge were present in about 5% of cases, while post-menopausal bleeding accounted for 2% of patients presenting with genital tuberculosis. In a study made by Madhu and Davinder, 15% of cases suffered with menorrhagia, 10% with oligomenorrhea, 5% with secondary amenorrhea and 66% had normal periods. Ten percent of women suffer secondary amenorrhea due to asherman. Primary amenorrhea is extremely rare. It is well known that advanced, active pulmonary TB may produce amenorrhea, particularly if it is associated with fever and weight loss. However, active pulmonary TB is rarely found concomitantly with active genital TB. Moreover, ovarian failure due to complete destruction of the ovary rarely occurs to cause amenorrhea. The most likely explanation is that given by Malkani and Nogales-Ortiz and Villar, who attributed amenorrhea to end-organ failure secondary to endometrial caseation. On the other hand, 50% to 88% of cases report undisturbed menstrual cycle.

Most cases of confirmed genital tuberculosis will have a perfectly normal clinical examination (43%), while about a quarter of cases will present with an adnexal mass (23.6%). Bimanual examination will reveal an adnexal mass or fixation of pelvic organs. Tuberculous tuboovarian masses are less tender than those due to pyogenic infection, although secondary infection may produce sharp pain and tenderness. Peritoneal involvement may give rise to ascites. Many patients appear with a symptom complex similar to that of ovarian carcinoma presenting with abdominal distention, pelvic tumor, ascites and elevated CA-125 level. Tuberculous lesions of the cervix present with postcoital bleeding, abnormal discharge and on examination, have appearances similar to cancer of the cervix. The affected cervix may be hypertrophied, ulcerated or may show friable papillary growth. Most of the cervical lesions appearing as an ulcer, red papillary erosion, or a proliferative growth resembling cervical cancer are descending infection from the upper genital tract. The diagnosis of cervical TB is usually made by histological examination of a cervical biopsy specimen. Staining for acid fast bacilli may not be very useful in making a diagnosis. Although isolation of mycobacterium is the gold standard for diagnosis, one third of cases are culture-negative, therefore presence of typical granulomata is sufficient for diagnosis if other causes of granulomatous cervicitis are excluded. The Pap smear reveals dyskaryotic cells, epithelial cell atypia, multiple giant cells, histiocytes and epithelioid cells arranged in clusters, simulating the appearance of granulomata. A punch biopsy is required for histopathological evaluation to identify the lesion and differentiate it from cancer. Histopathologic examination reveals granulomatous inflammation and sometimes marked inflammatory atypia along with frequent hyperplastic mucosal changes. Caseation may be seen.

The possibility of TB infection of the genital tract should always be considered, especially in a patient...
from an area where TB is endemic. Diagnosis is achieved most effectively through a combination of high index of suspicion, thorough clinical assessment and the use of appropriate investigations. High risk factors include a history of previous pulmonary TB infection, contact with a pulmonary TB sufferer, recent travel to or migration from high prevalence countries, residence in high prevalence areas, low socioeconomic background, drug abuse, HIV positive status and individuals of black African and Asian descent.\(^1\) Since genital tuberculosis is considered as one of the secondary manifestations of tuberculosis with its primary site in the lungs, one may expect a history of pulmonary tuberculosis or x-ray evidence of tuberculosis. However, in many instances the primary pulmonary lesion has already been arrested.\(^4\)

More than 75% of the patients with active, culture-proven genital tuberculosis have a normal chest x-ray. It is important not to use chest x-ray as exclusion for the diagnosis of genital tuberculosis.\(^7\) The gold standard remains the isolation of acid-fast bacilli in biological specimens or culture, although diagnosis based on histologically characteristic granulomata is accepted.\(^2,7\) Whenever feasible, every effort should be made to send specimens and tissue for culture, in order to confirm diagnosis and establish drug sensitivities.\(^1\) Since the endometrium is involved in the majority of cases and is readily accessible to sampling, it is often the first site at which attempts at definitive diagnosis are directed.\(^2\)

Endometrial tissue may be obtained by aspiration biopsy or by dilatation and curettage or directly at hysteroscopy.\(^1\) The histologic examination of endometrial tissues removed by biopsy or curettage, especially from the cornual area where spread from the tubes first occurs, affords a rapid method of diagnosing genital TB in at least 50% of cases.\(^2,4\) Dilatation and curettage may increase the yield on endometrial specimens merely by increasing the amount of tissue available for histologic evaluation and cultures.\(^2\) Endometrial biopsy is best performed at the end of the menstrual cycle, or within 12 hours after the onset of menstrual flow, at which time the tubercles reach their maximum growth.\(^1,2,4\) Its sensitivity suffers from sampling errors but can be very helpful if granulomata are found or, less commonly, if smears or cultures are positive.\(^5\) Histology demonstrates the typical caseous granulomatous lesions with giant epitheliod cells. This lesion is highly suggestive of TB but is not diagnostic, as it appears in fungal infections and sarcoidosis.\(^1\) One negative biopsy or one negative curettage does not exclude the diagnosis of genital TB. Serial sections are needed to be studied because the lesions are frequently patchy.

**Management**

Female genital tuberculosis is treated with the same long-term, combined drug therapy used in pulmonary and extrapulmonary tuberculosis. Surgery should be undertaken only after continuous drug treatment of 12-18 months' duration. In women of childbearing age, an attempt can be made to preserve one ovary. Successful pregnancy is unlikely, however, after complete antituberculosis treatment or tuboplastic surgery.\(^5\)

Six month regimens including four drugs in the initial phase (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol) followed by continuation phase (Rifampicin and Isoniazid) are highly effective in patients with fully sensitive organisms. Combined therapy enhances compliance and reduces the risk of secondary drug resistance. Although chemotherapy is the mainstay of treatment, surgery may be indicated where medical therapy has failed to resolve symptoms and in the presence of a persistent pelvic mass.\(^1\)

**Genital Tuberculosis and Pregnancy**

Despite effective therapeutic regimens for genital tuberculosis, sterility remains a major complication. Medical regimens have been successful at alleviating symptoms of menstrual disorders and pain. Succeeding endometrial sampling often reveals cure however, extensive damage to the fallopian tubes and the endometrium is often irreversible, and chances of successful intrauterine pregnancy are low. In one extensive literature review in 1976, only 31 cases of successful pregnancy were reported out of approximately 7000 cases of genital tuberculosis. In these patients, with fertile partner, in vitro fertilization should be considered. In Sweden, no intrauterine pregnancy was reported out of 187 cases of genital TB after therapy.\(^2\) If genital tuberculosis is not treated early in its course, irreparable damage to the tubes may occur and the risk of ectopic pregnancy in these patients is estimated to be 33% to 72%.\(^2\) Microsurgical reconstructive tubal surgery is not recommended because of the risk of reactivation of silent infection and the poor treatment outcome. A study reported one extrauterine pregnancy and no full term pregnancy in 51 salpingoplasty operations.
If patients are adequately treated before their tubes are irreversibly damaged, the chance of successful pregnancy is reasonably good with a 20% pregnancy rate reported in one study. However, an appreciable risk of ectopic pregnancy is expected if the tubes are patent but extensively affected. The overall post therapy fertility in patients with genital tuberculosis reported 155 full term pregnancies (2.2%), 125 extrauterine pregnancies and 67 abortions.\(^4\) In a ten-year clinicopathological study by Mondal and Dutta on female genital tuberculosis and its impact on fertility, 9 patients conceived of which 8 suffered spontaneous abortions after therapy. Only one patient had a successful pregnancy and the baby was born through cesarean section.\(^8\) They concluded that genital tuberculosis is an important cause of female infertility in developing countries. Successful uterine pregnancy is rare after treatment and chances of ectopic pregnancy are high.\(^8\)

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Deception: A Case of Acromegaly with Concomitant Hyperreactio Luteinalis in Pregnancy

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The incidence of hyperandrogenic state in pregnancy is low. Ovarian tumors, such as Hyperreactio luteinalis, are the most frequent cause. Other disease entities may also cause hyperandrogenic state in pregnancy such as pituitary adenoma. We describe a 29 year old, primigravid, who presents with acromegalic features for the first time during pregnancy. She delivered via an emergency low transverse cesarean section due to cephalo-pelvic disproportion. Intra-operatively, the bilateral ovaries were cystically enlarged with multiple cysts. Post-partum, diagnostics were started to investigate the probable cause of the acromegalic features. At 4 months post partum, there was resolution of the clinical features as well as normalization of the bilateral ovaries. The development of Hyperreactio luteinalis as well as incidental finding of pituitary microadenoma is the probable cause for the acromegalic features developed during pregnancy.

Key words: Growth hormone, insulin-like growth factor, acromegaly, pregnancy, hyperreactio luteinalis

Major hormonal changes emerge during pregnancy hence a variety of endocrine disorders can complicate pregnancy and vice versa. Virilization during pregnancy is uncommon. This can manifest as clitoral enlargement, increased muscle strength, acne, hirsutism, frontal hair thinning and deepening of voice. Possible causes include polycystic ovary syndrome, ovarian and adrenal tumors, pituitary adenomas and certain enzyme deficiency.

Hyperreactio luteinalis is a benign, self-limiting syndrome characterized by bilateral ovarian enlargement associated with high levels of human chorionic gonadotrophin and hyperandrogenism. It is usually associated with multiple pregnancies and trophoblastic diseases. However, about 30 cases of Hyperreactio luteinalis in normal singleton pregnancy has been reported.

Although the maternal pituitary gland is not essential for the maintenance of pregnancy, physiological changes in the pituitary gland during pregnancy complicates evaluation of pituitary neoplasms. The prevalence of pituitary microadenomas is 11%. These tumors generally are too small to cause bony erosion or to put pressure on the optic chiasm. Any morbidity is caused by excessive hormone secretion such as acromegaly.

Acromegaly is a rare condition caused by excessive growth hormone secretion usually due to a benign pituitary adenoma. Fertility is commonly impaired in patients with acromegaly due to altered gonadotropin secretion, which is caused by the destruction of gonadotroph cells or hyperprolactinemia, and hyperandrogenemia. Few data are available on pregnancy in acromegaly: fewer than 100 pregnancies have been reported, usually as isolated cases. Limited data are available about pregnancy in acromegaly. Hence, the appearance of acromegalic features for the first time during pregnancy prompted review of this problem.

* 2nd Place Winner, 2013 Midyear Residents’ Interesting Case Paper Presentation Contest last 11 April 2013, Ballroom 2, The Oriental Hotel, Legaspi City, Albay.
DISCUSSION

This is a case of R.C., 29 years old, G1P0, who came in due to watery vaginal discharge. She was diagnosed with polycystic ovarian syndrome in 2002 for which she was given oral contraceptive. There were no other history heredo-familial disease but one sister had acromegalic features during her pregnancy. She had irregular menses occurring every 1-2 months consuming 2 -3 pads per day with associated dysmenorrhea on Day 2 of menses.

features and there was further increase in her shoe size from size 9 to 11. At 24 weeks AOG, the patient started to experience easy fatigability and body weakness, and progression of coarse facial features. She also noted appearance of coarse hair pattern in her extremities. Her relatives noticed deepening of her voice and loud snoring.

At 30 weeks AOG, the patient experienced generalized body weakness. Consult was done and she was subsequently admitted. On physical examination, the patient was weak looking. Coarsening of facial features was noted described as enlargement of the nose and with frontal bossing. There was also note of clitorimegaly and bipedal edema. Upon admission, the patient was noted to be hypokalemic with potassium of 2.9 mmol/L. She was referred to Internal Medicine for further evaluation. Assessment was hypokalemia and t/c acromegaly during pregnancy. Correction of hypokalemia was done and she was advised work-up post-partum for the acromegaly. She was subsequently discharged after correction of hypokalemia.

Regular pre-natal check-up followed with intake of multivitamins and ferrous sulphate. She was also regularly seen at the Internal Medicine with biweekly determination of potassium. She was maintained on kalium durule.

Admission

The patient came in due to watery vaginal discharge. This was accompanied by hypogastric pain radiating to the lumbosacral area. Physical examination revealed same findings with the previous admission (coarsening of facial features described as enlargement of the nose and with frontal bossing.) Pelvic exam still showed clitorimegaly. Speculum exam revealed pooling of clear amniotic fluid. On internal examination, cervix was 4cm dilated, 50% effaced, negative BOW, cephalic, station -3. On the 6th hour of labor, cervix was fully dilated at station 0. There however was no further descent after 2 hours. She was therefore referred for an emergency low transverse cesarean section with an indication of failure in descent secondary to cephalopelvic disproportion. She delivered to a live term baby girl, birth weight 3232g, Birth Length 48cm, APGAR score 9/9, Maturity index 40 weeks, Appropriate gestational age. Incidental finding was enlarged multicystic ovaries measuring 6cm x 6cm each.

Figure 1. Comparative picture of R.C. before and during pregnancy.
Postoperatively, elevation in blood pressure was managed with Amlodipine. The rest of the hospital days were unremarkable. She and her baby were subsequently discharged on her 4th hospital day.

Two weeks post-partum, there was note of gradual resolution of the acromegalic features. On her 16 weeks post-partum, laboratory test revealed high normal result of growth hormone. Imaging studies revealed bilateral polycystic ovaries (on transvaginal ultrasound) and pituitary microadenoma measuring 2mm (on MRI).

**DISCUSSION**

We are presented with a 29 year old, G1P1 (1001), with history of polycystic ovarian syndrome, who developed acromegalic features and gestational hypertension during her pregnancy. Family history revealed she had one sister who developed same acromegalic features during her pregnancy with resolution of the problem post-partum. Incidental finding of bilateral cystic ovarian masses was noted during her cesarean delivery. Post-partum, resolution of the acromegalic features, high normal result of growth hormone, bilateral polycystic ovaries and pituitary microadenoma on imaging studies, prompted the service to consider the following differential diagnosis: Placental aromatase deficiency, luteoma of pregnancy, Hyperreactio luteinalis, Pituitary adenoma particularly prolactinoma and growth hormone-secreting pituitary adenoma.

Placental aromatase deficiency is an autosomal recessive disorder. Placental aromatase is needed for the final aromatization of androgens to estrogen and protect the fetus against the action of fetal androgens. Patients with this condition usually manifest with marked maternal virilization during the second half of pregnancy. The female babies born to these women will have ambiguous genitalia. Hence, the normal genitalia of the patient’s baby excludes placental aromatase deficiency.

Luteoma of pregnancy represents an exaggerated luteinization reaction of the normal ovary to the altered hormonal levels of pregnancy. It is typically seen in multigravida. This condition may result in maternal virilization. This can also manifest as clitoral enlargement, increase muscle strength, acne, hirsutism, frontal hair thinning and deepening of...
the voice. Pregnancy of luteoma is considered because it can cause maternal virilisation and the symptom regress post-partum. This tumor is usually solid and unilateral. Typical sonographic characteristics include a solid, complex-appearing unilateral mass with cystic features that correspond to areas of hemorrhage. They usually regress after delivery, but may recur in subsequent pregnancies. However, this was ruled out because the ovaries seen intraoperatively were cystic and bilateral.

Pituitary adenoma is a benign tumor of the pituitary gland. It may secrete hormones or it can be clinically inactive. The endocrinologic morbidity that is associated with these tumors is dependent on the specific underproduction or overproduction of hormones associated with the tumor. Prolactinomas and growth hormone secreting pituitary microadenoma are considered in this case because these can cause acromegalic features.

Prolactinoma is a benign tumor of the pituitary gland that produces hypersecretion of prolactin. Prolactinomas may symptomatically enlarge during pregnancy and may cause the acromegalic features. Although the patient has pituitary adenoma, menstrual irregularities and development of maternal virilization, this was ruled out because serum prolactin level was normal.

Growth hormone (GH) secreting pituitary adenoma usually causes acromegalic features in patients, since this tumor is responsible for 98% of acromegaly. During pregnancy, the pituitary gland increases its size by approximately 135%. One of the hormones that can be affected is the growth hormone. During the 1st trimester, the growth hormone is primarily pituitary in origin. However, as early as 8 weeks, placental growth hormone can be detected. At around 17 weeks, the placenta is the principal source of growth hormone during pregnancy. Thereafter, the placenta contributes in the circulating GH. Thus, maternal pituitary gland is not essential for the maintenance of pregnancy.

The increase in the size of the pituitary gland during pregnancy may cause existing pituitary adenoma enlargement due to the somatotrope hyperplasia secondary to the stimulatory effects of the peripheral hormone such as estrogen. This tumor growth may cause hypersecretion of growth hormone which in turn increases insulin growth factor 1 (IGF-1) which is the primary mediator for the growth promoting effects of growth hormone.

Acromegaly is a rare condition due to excessive GH secretion, usually by a benign pituitary adenoma. Fertility is commonly impaired in patients with pituitary tumors due to hormonal hypersecretion when the tumor is functional; or from the mass effect causing destruction of gonadotropin-secreting cells or compression of both normal gonadotrope cells and pituitary stalk, producing hyperprolactinemia and anovulation. Therefore there are very limited data available about pregnancy with acromegaly, although it appears that pregnancy is usually carried to term.

Acromegaly may not manifest with clear diagnostic features. Its usual presentations include: Acral enlargement (86%), Maxillofacial changes (74%), Excessive sweating (48%), Arthralgias (46%), Headache (40%), Hypogonadal symptoms (38%), Visual deficit (38%), Fatigue (26%), Weight gain (18%) and Galactorrhea (9%). A serum IGF-I level is a good tool to assess integrated GH secretion and is excellent for diagnosis, monitoring and especially screening. A random IGF-I value (a marker of integrated GH secretion) should be measured for diagnosis and monitoring after a therapeutic intervention. Serum GH assays are not standardized and should not be used interchangeably. Multiple samples, random GH, and GH after glucose administration have considerable variability and are useful, but they must be used in the clinical context. A GH value <1 ng/mL after an oral glucose tolerance test (OGTT) (75g of glucose orally followed by GH measurements every 30 minutes for 120 minutes) is considered normal. The latest clinical practice guideline for the diagnosis and treatment of acromegaly suggests that the serum GH nadir after glucose administration to be lowered to 0.4 ng/mL to increase sensitivity of testing. Once a biochemical diagnosis of acromegaly has been made, a magnetic resonance imaging (MRI) scan of the pituitary gland should be performed because a pituitary GH-secreting adenoma is the cause in most cases. The particular protocol was followed in this patient.

This case presented with acromegalic features both clinically and biochemically (high normal GH) and cranial MRI with contrast and dynamic study revealing pituitary microadenoma. We hypothesized that probably prior to the pregnancy, the pituitary microadenoma which did not secrete excess growth hormone hence the patient was asymptomatic. According to literature, menstrual irregularity is one of the earliest signs of acromegaly in women which
is seen in the patient's menstrual history. Normally the pituitary gland enlarges to 135% with 45% increment in the first trimester during pregnancy. The increase in the volume to as much as 120% is due to hyperplasia of mature lactotrophs. Theoretically, the stimulatory effect of peripheral hormone surges (such as estrogens) during pregnancy could cause adenoma enlargement due to tumor growth or hemorrhage, or tumor infarction in patients with growth-hormone secreting adenomas.7 Probable enlargement of the 0.2cm microadenoma in the patient during pregnancy caused the hypersecretion of growth hormone hence occurrence of the symptoms.

The bilateral ovarian cysts seen intraoperatively, may have been an independent condition in this case or may have probably augmented the symptomatology. Hyperreactio luteinalis probably secondary to the polycystic ovaries present during her pre-pregnant state was highly considered. Polycystic ovaries cause increased sensitivity of the ovaries to gonadotrophin leading to augmentation of androgen production by the theca cell causing bilateral enlargement of the ovaries. The increase in growth hormone as well as IGF 1 also causes insulin resistance by decreasing the levels of sex hormone-binding globulins (SHBG), thus the circulating levels of free testosterone are also increased leading to hyperandrogenemia.

Hyperreactio luteinalis (Theca-lutein cysts) are benign ovarian lesions that result from exaggerated physiological follicle stimulation associated with markedly elevated serum levels of hCG.5 It is assumed that a certain pathological state of ovaries (e.g. PCOS or multiple corpora lutea) is the cause of internal sensitivity of the ovaries to gonadotropin effects.29 Although the cellular pattern of Hyperreactio luteinalis is similar to that of a luteoma, they are usually bilateral cystic ovaries. Theca-lutein cysts are found frequently with gestational trophoblastic disease because of high hCG levels. They are also more likely to be found with a large placenta such as with diabetes, D-isoimmunization, and multiple fetuses. Theca-lutein cysts have also been reported in chronic renal failure as a result of reduced hCG clearance, and in hyperthyroidism as a result of the structural homology between hCG and thyroid-stimulating hormone. But they also are encountered in women with otherwise uncomplicated pregnancies and are thought to result from an exaggerated response of the ovaries to normal levels of circulating hCG.

Although usually asymptomatic, hemorrhage into the cysts may cause abdominal pain. Maternal virilization may be seen in up to 25 percent of women. Changes including temporal balding, hirsutism, and clitoromegaly are associated with massively elevated levels of androstenedione and testosterone. The diagnosis typically is based on sonographic findings of bilaterally enlarged ovaries containing multiple cysts in the appropriate clinical settings. The condition is self-limited, and resolution follows delivery. In some women, increased ovarian responsiveness to gonadotropin can be confirmed by several weeks postpartum.16

Generally, these tumors are discovered incidentally during cesarean section or tubal ligation. Hyperreactio luteinalis occurs in primigravids and may occur any time during pregnancy. Hyperreactio luteinalis cannot be completely ruled out because of the ovarian mass that was seen in this case, bilateral cystically enlarged ovaries, as well as symptoms of virilization such as clitoromegaly, deepening of the voice, coarse hair growth pattern over the extremities.

Insulin resistance brought about by the increase in GH/IGF1 increases the incidence of gestational hypertension. Since insulin is a powerful regulator of potassium metabolism, for patients with hypertension and those with insulin resistance, there is shifting of extracellular potassium to intracellular space, causing increase in the excretion of potassium leading to hypokalemia.31

There are two probable theories for the resolution of acromegalic features post-partum. First, the pituitary gland returns to its normal size within 6 months post-partum. Thus, the decrease in size of the pituitary gland post-partum decreases the size of the pituitary adenoma to its pre-pregnancy size which may be small enough to cause hypersecretion of growth hormone, thus resolution of the patient’s acromegalic features. Secondly, Hyperreactio luteinalis is a self-limiting syndrome. There is spontaneous resolution of symptoms and regression of the ovarian cysts post-partum with decreasing level of human chorionic gonadotrophin.

Familial isolated adenoma is defined as occurrence of at least 2 cases of acromegaly in a family. This condition is due to loss of heterozygosity at chromosome 11q13. This should be considered since the patient had one sister with acromegalic features during pregnancy.
Final Diagnosis

G1P1 (1001) Pregnancy Uterine delivered Via Emergency Low Transverse Cesarean Section I secondaty to Failure in Descent secondary to Cephalo-Pelvic Disproportion. Acromegaly probably secondary to Growth-Hormone Secreting Pituitary Microadenoma Hyperreactio luteinalis Gestational Hypertension

CONCLUSION

This paper has presented a case of a 29 year old primigravid who developed acromegalic features during her pregnancy with subsequent resolution post partum. Biochemical studies and imaging tests have proven the presence of pituitary adenoma and hyperreactio luteinalis.

Pituitary adenoma particularly growth hormone-secreting tumor in women may cause infertility, but in this case pregnancy ensued. The clinicians must be aware of the possible changes that could affect the patient’s pregnancy. Close monitoring of the subsequent symptoms therefore is warranted. Post-partum, serial growth hormone determination is recommended. Serum IGF-1 determination is also excellent for screening, diagnosing and monitoring of acromegaly.

Counselling should be done not only to discuss treatment options (surgical, medical, radiation as well as psychological therapy) but also the pathogenesis and prognosis of the disease since, acromegaly as a symptom is associated with a spectrum of co-morbidities which may result in significant and debilitating clinical manifestations3.

It is prudent to investigate other family members for any occurrence of pituitary microadenoma because it may be a hereditary disease and patient’s education is warranted to prevent delay in the diagnosis.

REFERENCES

Lymphangiomyomatosis Originating in the Uterus*

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J.R. is a 47 year old, nulligravid, who presented with a two year history of prolonged and profuse menstrual episodes consuming up to 10 pads a day, lasting up to 2 weeks. Ultrasound was done revealing a huge pelvo-abdominal mass, to consider a uterine primary lesion, most probably a myoma with cystic degeneration. Exploratory laparotomy was done revealing a well-delineated multi-cystic mass in the posterior myometrial wall approximately measuring 12cm x 10cm x 6cm with straw-colored fluid upon rupture of each cyst. The mass was sent for histopath revealing lymphangiomyomatosis of the uterus.

Key words: lymphangiomyomatosis, lymphangioleiomyomatosis

Lymphangiomyomatosis is a rare disease that is characterized by proliferation of abnormal smooth muscle-like cells. The majority of cases primarily occur in the lungs, but extrapulmonary regions such as the pelvis and retroperitoneal spaces are occasionally primary sites. We offer in this report information that lymphangiomyomatosis which is known as a rare pulmonary disease can develop in the pelvic cavity, particularly in the uterus.

THE CASE

J.R., is a 47 year old, nulligravid who presented with a two year history of prolonged and profuse menstrual episodes consuming up to 10 pads a day with passage of blood clots lasting for up to 14 days per cycle. The patient denied constitutional symptoms like fever and weight loss. There were no associated symptoms of headache, dizziness, chest pain, dyspnea, abdominal pain, or changes in urinary and bowel habits.

She is hypertensive with controlled blood pressure, on Metoprolol 50mg/tab twice a day. She was diagnosed with bipolar disorder in 2001 and was on Carbamazepine 200mg/tab once a day and Lithium Carbamate once a day. She is allergic to shrimp and shellfish. Her previous surgeries include rhinoplasty in 1982.

The patient is a nulligravid, who has been regularly menstruating since 13 years of age. She used to consume 3-4 pads per day, 7 days duration and does not experience dysmenorrhea. She has not used hormonal contraceptive. No previous pap smear was done. She is unemployed, previously a banker, denies smoking, alcoholic beverage drinking and illicit drug use.

On examination, her vital signs were stable, not in cardiorespiratory distress. She has no pallor, and cervicolympadenopathy. Upon chest examination, breath sounds were clear. She has a normal cardiac rate, regular rhythm, no murmur. Abdomen was soft, had normoactive bowel sounds, with a firm, non-tender mass spanning the hypogastric area up to the level of the umbilicus. On rectal examination, sphincteric tone was intact, empty rectal vault, no nodularities, uterus enlarged to 20 weeks size, solid, firm, movable, non-tender. There were no adnexal masses and tenderness.

Transabdominal and transrectal sonology were done. The uterus was anteverted, midline, with heterogenous echopattern and smooth contour. It was enlarged and measured 15.2cm x 13.0cm x 13.2cm (Figure 1). From the posterior wall appears

* 3rd Place Winner, 2013 Midyear Residents' Interesting Case Paper Presentation Contest last 11 April 2013, Ballroom 2, The Oriental Hotel, Legaspi City.
to be a multiloculated cystic mass filled with anechoic fluid. The septa measured 0.12 cm, and is not vascular by color flow. The cystic portion measured 13.3cm x 10.2cm x 10.7cm (Figure 2). The endometrium measured 0.7cm, is hyperechoic, with irregular borders. The subendometrial halo was not seen. The cervix measured 2.1cm x 2.4cm x 2.4cm. Both ovaries were not visualized due to the large pelvic mass occupying almost the whole pelvis. The cul-de-sac was smooth without free fluid. Impression on ultrasound was a huge pelvo-abdominal mass, to consider a uterine lesion probably a myoma with cystic degeneration.

Other laboratory exams done were CBC, urinalysis, FBS, ASL, ALT, Na, K, creatinine, serum lithium level which revealed values within normal. Chest X-ray was done revealing a clear chest. She also had 12L ECG, 2D echo and treadmill stress test for her hypertensive work-up which also revealed normal results.

Our initial impression was, Gravida 0, Uterine mass probably myoma with cystic degeneration.

The patient underwent exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy with frozen section. Upon opening, the uterus was globularly enlarged which measured 16cm x 15cm x 10.5cm with a smooth surface (Figure 3). The cervix measured 4cm x 3cm x 4cm. The right and left ovaries appeared normal. On cut section of the uterus, the endometrium was 0.4cm thick, smooth and devoid of masses. The anterior myometrial wall was 3cm thick while the posterior myometrial wall was 2cm thick. There was a well- delineated multi-cystic mass in the posterior myometrial wall approximately measuring 12cm x 10cm x 6cm with straw colored fluid upon rupture of each cyst. The cyst wall was smooth (Figure 4).

The uterus was sent for histopathology. Microscopic examination revealed that the tumor was composed of atypical smooth muscle cells (LAM cells) arranged in short fascicles around dilated lymphatics and a ramifying network of endothelium-lined spaces (Figures 5 & 6). Immunohistochemical staining showed that the tumor cells were diffusely
positive for smooth muscle actin and positive for human melanin black-45 (HMB-45). Final histopathologic diagnosis was lymphangiomyomatosis of the uterus.

**DISCUSSION**

Lymphangiomyomatosis (LAM), is a rare idiopathic disease affecting primarily women that is characterized by abnormal proliferation of smooth muscle-like cells (LAM cells). It is an autosomal dominant syndrome characterized by hamartoma-like tumor growths in various organs. The disease is very rare with a prevalence of 1 per million in the general population of France, UK, and the USA.\(^1\) It predominantly affects the lungs, comprising 87% of cases.\(^2\) The clinical course of pulmonary LAM is characterized by progressive dyspnea on exertion, recurrent pneumothorax, and chylous fluid collections. Lung function declines up to 3 fold. CT scan findings demonstrate thin-walled cystic changes. On work-up of this patient, there was no lung involvement seen. Chest x-ray was clear.

Uterine involvement of lymphangiomyomatosis is extremely rare, and only 8 cases of pathologically proven uterine LAM have currently been reported.\(^3\) Based on researches from POGS and PGH, there were no cases reported in the Philippines.

LAM occurs mainly in women, usually during their reproductive ages. The exact pathogenesis of lymphangiomyomatosis is still unclear. According to literature, steroid receptors for estrogen and progesterone have been identified in tissues affected by LAM. Therefore, a hormonal cause has been suggested.\(^2\)

Lymphangiomyomatosis was also found out to occur in about 40% of woman with the tuberous sclerosis complex, a genetic disorder of highly variable penetrance associated with seizure, brain tumors and cognitive impairment.\(^3\) LAM may be classified as a tuberous sclerosis associated form or a sporadic form. Both are associated with mutations

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**Figure 4.** There was a well-delineated multi-cystic mass in the posterior myometrial wall approximately measuring 12cm x 10cm x 6cm with straw colored fluid upon rupture of each cyst. The cyst wall was smooth.

Her postoperative course was unremarkable and the patient was discharged on the 5th postoperative day without complications.
in the tuberous sclerosis gene, TSC1, TSC2. LAM is also seen in association with a variety of neoplasms, including renal angiolipomas, soft tissue tumors and endocrine tumors. Our patient however, showed none of the other manifestations of tuberous sclerosis.

Figure 1 shows a model of effect of LAM on lymphatics. The figure shows a normal lymphatic vessel with unidirectional valve and normal direction of lymph flow (A), then there is proliferation of abnormal smooth-muscle cells (LAM cells) causing mural thickening and luminal narrowing (B), until there is obstruction of the lymph flow that results in the dilatation of lymphatic proximal to obstruction, creating lymphangiomyoma (C).

Clinical and radiologic presentations may suggest the diagnosis of LAM. Classical feature on ultrasound of LAM is a finding of multiple thin-walled cysts distributed evenly through the affected organ, with normal intervening parenchyma. However, such presentation would not solely differentiate the case from other large cystic uterine lesions such as cystic degeneration of uterine leiomyoma, cystic adenomyosis, congenital uterine cysts, cervical nabothian cysts, echinococcal cysts, intramyometrial hydrosalpinx, and cystic metastasis from an occult tumor. Thus, final diagnosis of LAM is confirmed by histopathology.

The effective treatment mode for lymphangiomyomatosis is still obscure. Earlier management of LAM consisted of symptomatic treatment. The current treatment modality is primarily based on the antagonism of estrogen action. Hormonal manipulations such as progesterone, gonadotropin-releasing-hormone (GnRH) agonists, tamoxifen, and oophorectomy, have been used in an effort to prevent and control progressive affected organ destruction.

Lymphangiomyomatosis is a slowly-processing disease. A report showed mortality within 10 years after diagnosis. Severe lung involvement is usually the cause of mortality. In a study of Matsui K, et al. the diagnosis of pulmonary LAM is established after that of extrapulmonary LAM usually within 2 years.

Extrapulmonary LAM should be carefully followed up to discover any lung lesions that may develop after the initial diagnosis. The patient had several follow-ups and showed no signs and symptoms suggestive of pulmonary lymphangiomyomatosis. Plan for the patient is to be cautious for pulmonary symptoms and to regularly request for diagnostic chest X-ray every 6 months for the initial 2 years and yearly thereafter.

Recorded patients with uterine lymphangiomyomatosis were usually diagnosed postoperatively upon histopathology of uterine specimens. It is difficult to obtain a correct preoperative diagnosis. In this case, our preoperative diagnosis was a degenerative myoma uteri. Although smooth muscle proliferation in LAM is considered benign, it causes considerable morbidity and mortality once there is lung involvement due to progressive respiratory insufficiency. Although LAM is a rare uterine condition, it must be distinguished from a variety of uterine tumors.

SUMMARY AND CONCLUSION

Recorded patients with uterine lymphangiomyomatosis were usually diagnosed postoperatively upon histopathology of uterine specimens. It is difficult to obtain a correct preoperative diagnosis. In this case, our preoperative diagnosis was a degenerative myoma uteri. Although smooth muscle proliferation in LAM is considered benign, it causes considerable morbidity and mortality due to progressive respiratory insufficiency. It is often seen in association with tuberous sclerosis and a variety of neoplasms, including renal angiolipomas, soft tissue tumors, and endocrine tumors. Although LAM is a rare uterine condition, it must be distinguished from a variety of uterine tumors.

REFERENCES

