Serum Beta HCG Level in Patients with Pregnancies of Unknown Location (PUL) and their Prognosis in A Tertiary Care Hospital

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ABSTRACT

Background: Pregnancy of unknown location (PUL) is defined as the situation when the pregnancy test is positive but there are no signs of intrauterine pregnancy or an extrauterine pregnancy via transvaginal ultrasonography (TVUS). PUL is not a final diagnosis and PUL does not mean an ectopic pregnancy. The final diagnosis is arrived at by transvaginal ultrasonography and measurement of serum human chorionic gonadotropin (hCG). It is not always possible to arrive at a final diagnosis, however identifying ectopic pregnancy in these patients at the earliest is very essential as ectopic pregnancy is a potentially lethal obstetric emergency. Women who were admitted with Pregnancy of unknown location PUL and followed up forms the cohort of this study.

Aim of the study was to study the prognosis of patients with pregnancies of unknown location in correlation with Serum Beta hCG levels and the rate of change of β hCG levels.

Methodology: This study was conducted at Sree Avittom Thirunal Hospital, Government Medical College, Trivandrum, a retrospective cohort of patients admitted with pregnancy of unknown location a tertiary care center for period of 1 year.

Statistical tests used are mean, SD, Percentage, chi square and Odds Ratio to assess association of the selected parameters with the Ectopic pregnancy.

Results: Of the 99 patients who met the inclusion criteria 26 were eventually diagnosed ectopic pregnancies, 34 were failing or self resolving pregnancy of unknown location, and 39 were viable intra uterine pregnancy. The majority of patients were in 25 - 29 yrs age group with mean age 26.87yrs. The patients in Intra Uterine pregnancy group where the maximum number of patients were in the group of 20 – 24 yrs. (X²=12.4, P =0.001)

The association of gravidity and outcome was found significant with Chi-square =20.58; P =0.008. The majority of patients in Intra Uterine group were primi gravidas.

Patients with PUL who had a past history of ectopic pregnancy and prior abdominal surgery were seen to be at statistically significant high risk for ectopic pregnancy.

51 out of 60 cases with Beta hCG <1500 or 85% were symptomatic and 15% were asymptomatic. The difference in the mean Beta hCG at the time of presentation was found to be significant statistically. (ANOVA, F=8.331, P=0.000) in that the mean value was significantly lower for failing PUL in comparison to the EP and IUP groups. However, these values are not adjusted to the gestational age at presentation, and hence no reliable conclusions can be drawn. In cases with Beta hCG below the discriminatory zone at the time of presentation, majority (48.33%) were non-viable failing PUL, 31.66% were eventually viable IUPs while 20% were ectopic. There was statistical significance to this finding. (X²=3.263, P=0.001)85.29% of failing PUL
presented with low Beta hCG.

Rate of change of Beta hCG from day 0 to day 2 was statistically significant with chi square $X^2=92.469$, $P=0.000$. Among cases showing more than 66% rise, 87.9% were IUP, 9.1% were EP and 3.0% were non-viable pregnancies. When rate of change of Beta hCG and Outcome was also studied with a Lower Cut Off of ‘Normal Rise’ in 48hrs. This association was also significant ($X^2=92.469$, $P=0.000$). A suboptimal rise of less than 50% detects a higher risk of an unfavorable outcome (73.9%) than a suboptimal rise of less than 66% (63%). Similar to the result with rate of change of Beta hCG between day 2 and day 0, the rate of change in serial values on day 4 and day 2 also yields statistically significant results. ($X^2=35.953$, $P=0.000$).

In fact the course of rate of change of serial serum hCG after the initial 48 hrs actually provides more diagnostic information, in that only 6.7% of cases mimicked the normal “doubling” of viable IUP as compared to the initial 11.5%.

**Conclusion:** The management of PUL is highly crucial, the definitive diagnosis of a woman with either a failed IUP or ectopic pregnancy has important clinical consequences. The PUL should be assessed by employing experienced doctors and using high quality ultra-sonography in early pregnancy units. Among the several hormones evaluated in the prediction of PUL outcome serum hCG level is the most useful hormone; however, evaluating the changes in hCG serum levels within 48 hours is a more reliable method than a single measurement. It is very important to follow-up the patients diagnosed with PUL until the final diagnosis is concluded.

**Keywords:** Pregnancy of unknown location (PUL), Beta Human Chorionic Gonadotropin, Ectopic Pregnancy, Failing PUL.

**Introduction**

A pregnancy of unknown location (PUL) is when, in a woman with a positive pregnancy test, an empty uterus is visualized on transvaginal ultrasound scan (TVS), with no signs of an intrauterine pregnancy (IUP) or an extra uterine (ectopic) pregnancy. Pregnancy of unknown location (PUL) is a descriptive term and not a definite diagnosis. The majority of women will subsequently be diagnosed with spontaneously resolving pregnancies (failing PULs) or IUPS that were too early to visualize on TVS, a proportion will be diagnosed with ectopic pregnancies that were too early to visualize or were missed on the initial TVS examination. The failing PUL group will include both failing IUP and extrauterine pregnancies, since the location of the pregnancy may never be determined. The reported rate of PUL among women attending early pregnancy units varies between 5 and 42% in the literature and the frequency of PUL incidents has increased in the recent years. Studies report that in women attending an early pregnancy unit (EPU) with a positive urinary pregnancy test, the location of the pregnancy may be confirmed in up to 90-92% of cases on the basis of the initial TVS findings. Also studies demonstrates that although more than 90% of ectopic pregnancies are visualized on transvaginal ultrasound scan prior to treatment, almost 75% can be visualized on the initial scan performed.

Published data demonstrate that whilst the majority of women (50-70%) will have spontaneously resolving pregnancies (failing PULs), 7-20% will subsequently be diagnosed with an ectopic pregnancy. A quarter of women with ectopic pregnancies will initially be classified as having a PUL. During the past decade, transvaginal ultrasonography has given an earlier and clearer picture of early pregnancies, by ruling out ectopic pregnancy if intra uterine pregnancy is identified or it may strongly suggest an ectopic pregnancy if an adnexal mass is seen or in the presence of pelvic fluid. However in 15% of cases the report may be indeterminate, that is empty uterus, ectopic pregnancy not ruled out. The management of PUL is highly crucial in obstetrics clinical practice. The definitive diagnosis of a woman with either a failed IUP or ectopic pregnancy has important clinical consequences, including prognosis as to the possibility of a repeat ectopic pregnancy, the need for assisted reproductive technologies or workup for potential recurrent pregnancy loss. Therefore,
attempts should be made to make a definitive diagnosis when possible.

An ectopic pregnancy is a common cause of morbidity and occasionally of mortality in women of reproductive age group. It is the implantation of fertilized ovum outside the normal uterine cavity.\textsuperscript{2,4}

Clinical examination findings and history were once the main stay in diagnosing ectopic Pregnancy. But today the transvagal ultrasonography and immunoassays of serum beta HCG levels is more discerning in patients with pregnancy of unknown location (PUL). However early detection of ectopic pregnancy can be challenging and a number of early ectopics are missed at the initial medical examination. The incidence of ectopic pregnancy in the general population is about 2 % ; and the prevalence of ectopic pregnancy in pregnant patients presenting to an emergency department with first trimester bleeding or pain or both is 6 % to 16 % .\textsuperscript{8,9}

The simplicity and non-invasiveness of transvaginal ultrasonography has transformed ultrasound into the principal imaging tool in diagnosis and decision making. In a normal intrauterine pregnancy a normal gestational sac, an ovoid collection of fluid adjacent to the endometrial stripe, can be visualized by means of the transvaginal probe at a gestational age of about 5 weeks. The yolk sac appears during the fifth week and the cardiac activity at 6 - 6.5 weeks.\textsuperscript{10}

Radioimmunoassays of HCG can detect pregnancy as early as 12 days post conception. The ability to document an intra uterine pregnancy by ultrasound has lagged behind by two to three weeks. Moreover the hormonal environment in ectopic pregnancy produces an intrauterine fluid collection that mimics a gestational sac, and hence called the “pseudo gestational sac”. Therefore a sac alone cannot confirm intrauterine pregnancy. Once the sac is implanted within the endometrium, its position relative to the endometrial wall changes, producing the ‘intra decidual-sac sign’ and then the ‘double decidual-sac sign’.\textsuperscript{10} The proportion of accurate preliminary ultrasound diagnosis in detecting intrauterine pregnancy was significantly higher in subjects who presented with beta-hCG levels above 1500 mIU/ml compared with levels below 1500 mIU/ml.\textsuperscript{11} For a normal viable intrauterine pregnancy, a gestational sac should be visualized under ultrasonography after a hCG level of 1500 mIU/L is noted. When the transabdominal approach is preferred, the threshold for hCG is up to 6500 mIU/L.

The spectrum of sonographic findings in ectopic pregnancy is broad and the diagnosis of ectopic pregnancy is usually based on one of the following grey- scale appearances.\textsuperscript{12}(1) An inhomogenous mass or ‘Blob sign’ adjacent to the ovary and moving separately from the ovary.\textsuperscript{(2)} A mass with a hyper-echoic ring around the gestational sac or ‘Bagel sign’.\textsuperscript{(3)} A gestational sac with a foetal pole with cardiac activity, i.e. a viable extra uterine pregnancy.\textsuperscript{(4)} A gestational sac with a foetal pole without cardiac activity, i.e. a non-viable extra uterine pregnancy.

In ectopic pregnancy a pseudo sac is seen in 20%, free pelvic fluid in 56%, non homogenous adnexal mass in 60%, gestational sac, embryo and foetal heart rate in 20% . Collection of fluid within the endometrial cavity, which is often called a pseudosac; has been reported in up to 20% of cases. It is not difficult to separate the pseudosac from early intrauterine gestational sac by using TVUS. A differentiating feature is the location of the fluid. An early intrauterine sac is intradecidual and is therefore seen as an eccentrically placed hyperechoic ring within the endometrial cavity, whereas a pseudosac develops within the uterine cavity and lacks a well-defined rim of surrounding echoes.\textsuperscript{13}

Banhart et al. suggested categorising the patients into 5 groups based on their ultrasonographic findings:\textsuperscript{14}

- **Definite ectopic pregnancy**: extraterine gestational sac with yolk sac and/or embryo with or without cardiac activity.
- **Probable ectopic pregnancy**: non-homogeneous adnexal mass.
• **PUL:** no finding for intrauterine pregnancy or ectopic pregnancy.

• **Probable intrauterine pregnancy:** intrauterine echogenic sac-like structure.

• **Definite intrauterine pregnancy:** intrauterine gestational sac with yolk sac and/or embryo with or without cardiac activity.

The change in serum hCG over time has been used to predict the outcome of PULs. Kadar et al. were the first to describe the minimal rate of increase for an IUP to be 66% over 2 days.\(^{15}\) This study was based on a small sample of 20 women and used an 85% confidence interval (CI). More recently, the minimal rise in serum hCG level in viable IUPs was reported to be 53%, on the basis of a 99% CI.\(^{16}\) However, in clinical practice, a more conservative cutoff of 35% has been suggested to minimize the potential risk of terminating a wanted pregnancy.\(^{17}\)

Serum hCG curves for expected hCG declines in spontaneous miscarriages have also been described.\(^{18}\) In addition, the change in serum hCG level over 48h has also been referred to as the 'hCG ratio' (hCG 48h:hCG 0h). An hCG ratio of less than 0.87 (or an hCG decrease >13%) has been demonstrated to have a sensitivity of 92.7% (95% CI: 85.6-96.5) and a specificity of 96.7% (95% CI:90.0-99.1) for the prediction of a failing pregnancy.\(^{19}\)

Single serum progesterone levels have been used to predict the outcome of PULs. A serum progesterone level below 20nmol/l has been shown to have a positive predictive value greater than 95% of predicting pregnancy failure.\(^{2}\) Levels above 25nmol/l are 'likely to indicate' and levels above 60nmol/l are 'strongly associated' with pregnancies subsequently demonstrated to be viable.\(^{20}\) Other serum markers that have been examined to determine if they are predictive of pregnancy outcome in the PUL population include cancer antigen (CA) 125, creatine kinase and activin A.\(^{21}\)

**Materials and Methods**

**Study Design:** Retrospective cohort

**Setting:** A tertiary care setting, Department of Obstetrics and Gynaecology, Sree Avittom Thirunal Hospital, Govt. Medical College, Trivandrum, Kerala.

**Study Duration:** One year

**Inclusion Criteria:** Patients who were admitted to Sree Avittom Thirunal Hospital with pregnancy of unknown location for a period of 1 year was included in this study. Patients were selected from the admission register.

**Exclusion Criteria:** Patients with incomplete follow up till a final diagnosis were excluded from the study and also patients who conceived with IVF were excluded as the transfer of multiple embryos could influence the beta hCG levels.

**Sample Size:** During the study period of 1 year 109 patients were admitted with pregnancy of unknown location were admitted of which 10 patients were excluded from the study because of incomplete follow up.

**Study Variables:** Includes Socio demographic variables like age, place of residence, socioeconomic status and also history of gravidity, parity, number of previous ectopic pregnancy, number of previous spontaneous abortions, number of previous induced abortions, history of pelvic inflammatory disease (requiring hospital admissions), history of documented tubal pathology, history of using intra uterine devices, history of abdominal or pelvic surgery, history of treatment for infertility or artificial reproductive technologies. Data was also collected on Serum Beta hCG at presentation and on serial measurements, transvaginal ultrasonography with endometrial thickness, adnexal mass or any co-existing pathology.

The data was collected using a proforma and patients were grouped into 3 categories: Category 1: Ectopic pregnancy. Category 2: Non viable pregnancy- failing or self resolving pregnancy of unknown location includes failing intra uterine pregnancy and intra uterine spontaneous miscarriage Category 3: Viable intra uterine pregnancy.

Data entry was done using Microsoft excel sheet, and data analysis was done with SPSS software.
**Observation and Results**

During the period of study 99 patients met the inclusion criteria of which 26 were ectopic pregnancies, 34 were failing or self resolving pregnancy of unknown location, and 39 were viable intra uterine pregnancy.

**Table: 1 Age distribution in each category**

<table>
<thead>
<tr>
<th></th>
<th>&lt;20 yrs</th>
<th>20-29</th>
<th>&gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>0%</td>
<td>61.50%</td>
<td>38.40%</td>
</tr>
<tr>
<td>Failing PUL</td>
<td>0%</td>
<td>58.80%</td>
<td>41.20%</td>
</tr>
<tr>
<td>IUP</td>
<td>7.70%</td>
<td>84.70%</td>
<td>7.70%</td>
</tr>
</tbody>
</table>

The distribution is statistically significant Chi-square =12.4, P =0.001

**Fig: 1 Age distribution of patients**

Age pattern was almost similar in patients with ectopic pregnancy and failing PUL. But there was a significant difference with women >30yrs having a bad outcome (88.9%) when compared to women with intra uterine pregnancy (11.1%). The difference in age and pregnancy outcome was statistically significant. Chi square 12.4, P value 0.001, OR 8.00. Among intra uterine pregnancy 92.3% were <30yrs and only 7.7% were more than or equal to 30 yrs. In pregnancies of poor outcome that is ectopic pregnancy and failing PUL, 60% were less than 30yrs where as 40% had an age of 30yrs or more.

**Table: 2 The mean age of the patients**

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Mean Age in yrs</th>
<th>Std Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>26</td>
<td>28.58</td>
<td>3.797</td>
</tr>
<tr>
<td>Failing PUL</td>
<td>34</td>
<td>28.88</td>
<td>4.125</td>
</tr>
<tr>
<td>IUP</td>
<td>39</td>
<td>23.97</td>
<td>3.558</td>
</tr>
<tr>
<td>TOTAL</td>
<td>99</td>
<td>26.87</td>
<td>4.453</td>
</tr>
</tbody>
</table>

The overall mean age of the patients at presentation was 26.87yrs.

The majority of patients were in 25 - 29 yrs age group, which was also true for ectopic pregnancy and Failing PUL but not for the patients in Intra Uterine pregnancy group where the maximum number of patients were in the group of 20 – 24 yrs. (X2 =12.4,P =0.001)

**Table: 3 Distribution according to Domicile**

<table>
<thead>
<tr>
<th></th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>69.20%</td>
<td>30.80%</td>
</tr>
<tr>
<td>failing PUL</td>
<td>64.70%</td>
<td>35.30%</td>
</tr>
<tr>
<td>IUP</td>
<td>46.10%</td>
<td>53.80%</td>
</tr>
</tbody>
</table>

There was no statistical significance noted between the place of residence and the final outcome. There was more number of referred cases in all the three categories. Overall 60% of the PUL were referred. Among the cases that were eventually ectopic pregnancy 65% were referred cases.
Domicile pattern of Pregnancies of unknown location according to their final outcome.

**Table: 4 Distribution according to Gravidity**

<table>
<thead>
<tr>
<th>Gravida</th>
<th>G1</th>
<th>G2</th>
<th>G3 or more</th>
<th>G4</th>
<th>G5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>7(26.9%)</td>
<td>10(38.5%)</td>
<td>7(26.9%)</td>
<td>1(3.8%)</td>
<td>1(3.8%)</td>
<td>26(100%)</td>
</tr>
<tr>
<td>Failing PUL</td>
<td>11(32.4%)</td>
<td>10(29.4%)</td>
<td>12(35.3%)</td>
<td>1(2.9%)</td>
<td>0</td>
<td>34(100%)</td>
</tr>
<tr>
<td>IUP</td>
<td>27(69.2%)</td>
<td>9(23.1%)</td>
<td>2(5.1%)</td>
<td>1(2.6%)</td>
<td>0</td>
<td>39(100%)</td>
</tr>
</tbody>
</table>

The association of gravidity and outcome was found significant with Chi-square =20.58; P =0.008. The majority of patients in Intra Uterine group were primi gravidas.

The overall incidence of prior miscarriage in our study population was around 21% and no significant statistical association of previous history of abortions either spontaneous or induced was not obtained in this study. History of Infertility and Outcome was also studied and in this study overall there were 14 (14.14%) patients with infertility. In the ectopic pregnancy group, 19.2% gave history of treatment for infertility while 80.8% did not have history of infertility treatment. A similar distribution was noted in both the other groups and hence the association was not statistically significant. Increased risk of infertility is for patients with tubal factor but this could not be studied as patients who conceived with Artificial reproductive techniques were excluded from this study.

**Table: 5 Past history of ectopic pregnancy and outcome**

<table>
<thead>
<tr>
<th>Past history of ectopic</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>3(11.53%)</td>
<td>23(88.46%)</td>
</tr>
<tr>
<td>Failing PUL</td>
<td>1(2.94%)</td>
<td>33(97.05%)</td>
</tr>
<tr>
<td>IUP</td>
<td>0</td>
<td>39(100%)</td>
</tr>
<tr>
<td>Total</td>
<td>4(4.04%)</td>
<td>95(95.95%)</td>
</tr>
</tbody>
</table>

11.53% of patients with ectopic pregnancy had past history of ectopic pregnancy while as there was none in the group of Intra Uterine Pregnancy.

Comparing the ectopic pregnancy as one group and non ectopics as the other group, History of ectopic pregnancy was found significant with Chi-square =20.58; P =0.008.
pregnancy is found to be a statistically significant risk factor for ectopic pregnancy with Chi-square = 5.11; P =0.024.

The numbers of patients with previous ectopic pregnancy were not large enough in this study population to get a significant result on the influence of treatment modality in the previous ectopic pregnancy. However in ectopic pregnancy group 42.3% gave history of prior abdominal surgery, while 57.7% did not have history of prior abdominal surgery. This was found to be statistically significant for ectopic pregnancy with Chi-square =8.23; P =0.016.

11 out of 26 patients in ectopic pregnancy group had previous abdominal surgery; of which 6 had previous tubal surgery, whereas only 2 in spontaneous abortion group and none in intra uterine pregnancy group had previous tubal surgery. This observation is statistically significant risk factor for ectopic pregnancy with Chi-square =5.238 ; P =0.022; odds ratio:12 making tubal ligation and partial salpingectomy important risk factor for ectopic pregnancy.

Table: 6 History of Pelvic inflammatory diseases.

<table>
<thead>
<tr>
<th>history of PID</th>
<th>yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>1(3.8%)</td>
<td>25(96.2%)</td>
</tr>
<tr>
<td>Failing PUL</td>
<td>2(5.9%)</td>
<td>25(94.1%)</td>
</tr>
<tr>
<td>IUP</td>
<td>1(2.6%)</td>
<td>25(97.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>4(4%)</td>
<td>25(96%)</td>
</tr>
</tbody>
</table>

No statistical significance was noted as only patients with history of hospital admission for PID was included.

Table: 7 Bleeding PV as presenting complaint

<table>
<thead>
<tr>
<th>Bleeding pv</th>
<th>yes</th>
<th>no</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>14(53%)</td>
<td>12(47%)</td>
</tr>
<tr>
<td>SAB</td>
<td>18(52.9%)</td>
<td>16(47.1%)</td>
</tr>
</tbody>
</table>

More than 50% of Ectopic as well as failing PUL group had bleeding per vaginum.

Bleeding per vaginum was the predominant symptom in abortion group. In ectopic pregnancy group 53% presented with irregular bleeding per vaginum. 11.5% of patients in ectopic group were asymptomatic but had indeterminate scans that caused suspicion of ectopic.

Table: 8 Symptoms and Beta hCG at presentation

<table>
<thead>
<tr>
<th>Symptoms and Beta hCG at Presentation</th>
<th>SYMPTOMATIC</th>
<th>ASYMPOTOMATIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BETA HCG &lt;1500mIU/mL</td>
<td>85%</td>
<td>15%</td>
</tr>
<tr>
<td>BETA HCG ≥1500mIU/mL</td>
<td>87.1%</td>
<td>12.9%</td>
</tr>
</tbody>
</table>

51 out of 60 cases with Beta hCG <1500 or 85% were symptomatic and 15% were asymptomatic. This is comparable to 34 out of 39 cases with Beta hCG ≥1500 or 87.1% who were symptomatic and a marginally smaller percent of asymptomatic percent. However this minor difference is not clinically or statistically significant.
Cervical movement tenderness and fornical tenderness could be elicited in only around 4% of cases overall, and were positive in only 3.8% of the EP group. There is no statistical significance to the predictive value of clinical signs in determining the outcome.

None of the cases had clinical evidence of abdominal rigidity, abdominal distension, and shifting dullness on physical examination. The cervical os was closed in all bimanual pelvic examination.

The difference in the mean Beta hCG at the time of presentation was found to be significant statistically. (ANOVA, F=8.331, P=0.000) in that the mean value was significantly lower for failing PUL in comparison to the EP and IUP groups. However, these values are not adjusted to the gestational age at presentation, and hence no reliable conclusions can be drawn. The mean gestational age of EP and IUP were comparable at 28.6 days.
More than half (60%) of the patients had hCG levels less than the discriminatory zone of Beta hCG at the time of presentation. In cases with Beta hCG below the discriminatory zone at the time of presentation, majority (48.33%) were non-viable failing PUL, 31.66% were eventually viable IUPs while 20% were ectopic.

In cases with Beta hCG above the discriminatory zone at the time of presentation, majority (51.28%) were viable IUPs, 35.89% were ectopic and 12.82% were failing PUL.

**Table: 10 β hCG at presentation (within each category)**

<table>
<thead>
<tr>
<th>Serum β hCG</th>
<th>β hCG &lt; 1500</th>
<th>β hCG ≥ 1500</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>12 (46.15%)</td>
<td>14 (53.84%)</td>
<td>26 (100%)</td>
</tr>
<tr>
<td>failing PUL</td>
<td>29 (85.29%)</td>
<td>5 (14.71%)</td>
<td>34 (100%)</td>
</tr>
<tr>
<td>IUP</td>
<td>19 (48.71%)</td>
<td>20 (51.28%)</td>
<td>39 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>39</td>
<td>99 (100%)</td>
</tr>
</tbody>
</table>

There was statistical significance to this finding. (X²=3.263, P=0.001) 85.29% of failing PUL presented with low Beta hCG.

**Fig: 7 Rate of change of Beta hCG (D₂ – D₀)**

Among cases showing more than 66% rise, 87.9% were IUP, 9.1% were EP and 3.0% were non-viable pregnancies.

Among cases showing less than 66% rise, 48.1% were EP, 37% were IUP and 14.8% were non-viable.

Among cases showing less than 50% fall, 52.6% were EP, 47.4% were non-viable pregnancies.

100% of the cases showing fall by more than 50% were eventually diagnosed as non-viable pregnancies.

**Fig: 8 Rate of change of Beta hCG and Outcome with a Lower Cut Off of ‘Normal Rise’ in 48hrs**
K.T. Barnhart et al in 2004 suggested that a 53% increase in hCG concentration in 2 days, rather than a 66% increase, should be considered the lower limit of normal in defining a viable intrauterine pregnancy. A slower rate of increase from this expectation suggests an increased possibility of a pregnancy. 

This association was also significant ($X^2=92.469$, $P=0.000$) 84.6% of viable IUPs showed a rise in Beta hCG of $>53\%$ over 2 days, as compared to only 74.4% that showed a rise of $>66\%$. A suboptimal rise of less than 53% detects a higher risk of an unfavourable outcome (73.9%) than a suboptimal rise of less than 66% (63%).

Table: 11 Course of rate of change of beta hCG and Outcome

<table>
<thead>
<tr>
<th></th>
<th>↑ by &gt;66%</th>
<th>↑ by &gt;50 - 66%</th>
<th>↓ by &lt; 50 %</th>
<th>↓ by &gt; 50 %</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>6.70%</td>
<td>46.70%</td>
<td>40%</td>
<td>6.70%</td>
<td>100%</td>
</tr>
<tr>
<td>failing PUL</td>
<td>0%</td>
<td>5.90%</td>
<td>17.60%</td>
<td>76.50%</td>
<td>100%</td>
</tr>
<tr>
<td>IUP</td>
<td>60%</td>
<td>40%</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Similar to the result with rate of change of Beta hCG between day 2 and day 0, the rate of change in serial values on day 4 and day 2 also yields statistically significant results. ($X^2=35.953$, $P=0.000$)

In fact the course of rate of change of serial serum hCG after the initial 48 hrs actually provides more diagnostic information, in that only 6.7% of cases mimicked the normal “doubling” of viable IUP as compared to the initial 11.5%.

**Discussion**

During the period of study 99 patients with pregnancy of unknown location who met the inclusion criteria were admitted, of these 26 were eventually ectopic pregnancies, 34 were Failing PUL (which includes both failing ectopic pregnancy and failing intra uterine pregnancy), and 39 were viable intra uterine pregnancy. That is 26% of the patients with PUL turned out to be an ectopic pregnancy.

The majority of patients were in 25 - 29 yrs age group, which was also true for ectopic pregnancy and Failing PUL but not for the patients in Intra Uterine pregnancy group where the maximum number of patients were in the group of 20 – 24 yrs. ($X^2=12.4,P =0.001$) The overall mean age of the patients at presentation was 26.87yrs. The risk of ectopic pregnancy increases with advancing maternal age, in a study by Farquhar CM. on Ectopic pregnancy; age over 35 years was found to be a significant risk factor.22

There was no statistically significant association of domicile pattern and the final outcome of Pregnanies of unknown location. The association of gravidity and outcome was found significant...
with Chi-square =20.58 ; P =0.008. The majority of patients in Intra Uterine group were primi gravidas. History of Infertility and Outcome was also studied and in this study overall there were 14 (14.14%) patients with infertility. In the ectopic pregnancy group, 19.2% gave history of treatment for infertility while 80.8% did not have history of infertility treatment. A similar distribution was noted in both the other groups and hence the association was not statistically significant. The overall prevalence of prior miscarriage in this study population was around 21% consistent with quoted incidence of 17% to 22% in a study by Barnhart et al and Poland et al.

Patients with PUL who had a past history of ectopic pregnancy were seen to be at high risk for ectopic pregnancy. History of ectopic pregnancy is found to be a statistically significant risk factor for ectopic pregnancy with Chi-square = 5.11 ; P =0.024. The number of patients with previous ectopic pregnancy were not large enough in this study population to get a significant result on the influence of treatment modality in the previous ectopic pregnancy. Women with a previous history of ectopic pregnancy also have an increased risk, which increases further in proportion to the number of previous ectopic pregnancies. In one study the OR for having an ectopic pregnancy was 12.5 after one previous ectopic pregnancy and 76.6 after two.23 However in ectopic pregnancy group 42.3% gave history of prior abdominal surgery this was found to be statistically significant for ectopic pregnancy with Chi-square =8.235 ; P =0.016.

51 out of 60 cases with Beta hCG <1500 or 85% were symptomatic and 15% were asymptomatic. This is comparable to 34 out of 39 cases with Beta hCG ≥1500 or 87.1% who were symptomatic and a marginally smaller percent of asymptomatic percent. However this minor difference is not clinically or statistically significant. Bleding per vaginum was the predominant symptom in abortion group. In ectopic pregnancy group 53% presented with irregular bleeding per vaginum. 11.5% of patients in ectopic group were asymptomatic but had indeterminate scans that caused suspicion of ectopic.

Cervical movement tenderness and forniceal tenderness could be elicited in only around 4% of cases overall, and were positive in only 3.8% of the EP group. There is no statistical significance to the predictive value of clinical signs in determining the outcome.

The difference in the mean Beta hCG at the time of presentation was found to be significant statistically. (ANOVA, F=8.331, P=0.000) in that the mean value was significantly lower for failing PUL in comparison to the EP and IUP groups. However, these values are not adjusted to the gestational age at presentation, and hence no reliable conclusions can be drawn. The mean gestational age of EP and IUP were comparable at 28.6 days.

More than half (60%) of the patients had hCG levels less than the discriminatory zone of Beta hCG at the time of presentation. In cases with Beta hCG below the discriminatory zone at the time of presentation, majority (48.33%) were non-viable failing PUL, 31.66% were eventually viable IUPs while 20% were ectopic. In cases with Beta hCG above the discriminatory zone at the time of presentation, majority (51.28%) were viable IUPs, 35.89% were ectopic and 12.82% were failing PUL. There was statistical significance to this finding. (X2=3.263, P=0.001)85.29% of failing PUL presented with low Beta hCG.

Rate of change of Beta hCG from day 0 to day 2 was statistically significant with chi square X2=92.469, P=0.000. Among cases showing more than 66% rise, 87.9% were IUP, 9.1 % were EP and 3.0% were non-viable pregnancies. Among cases showing less than 66% rise 48.1% were EP, 37% were IUP and 14.8% were non-viable. Among cases showing less than 50% fall, 52.6% were EP, 47.4% were non-viable pregnancies.100% of the cases showing fall by more than 50% were eventually diagnosed as non-viable pregnancies.

When rate of change of Beta hCG and Outcome was also studied with a Lower Cut Off of ‘Normal
Rise’ in 48hrs. K.T. Barnhart et al in 2004 suggested that a 53% increase in hCG concentration in 2 days, rather than a 66% increase, should be considered the lower limit of normal in defining a viable intrauterine pregnancy. A slower rate of increase from this expectation suggests an increased possibility of a pregnancy. This association was also significant (X²=92.469, P=0.000) 84.6% of viable IUPs showed a rise in Beta hCG of >53% over 2 days, as compared to only 74.4% that showed a rise of >66%. A suboptimal rise of less than 53% detects a higher risk of an unfavourable outcome (73.9%) than a suboptimal rise of less than 66% (63%).

Similar to the result with rate of change of Beta hCG between day 2 and day 0, the rate of change in serial values on day 4 and day 2 also yields statistically significant results. (X²=35.953, P=0.000)

In fact the course of rate of change of serial serum hCG after the initial 48 hrs actually provides more diagnostic information, in that only 6.7% of cases mimicked the normal “doubling” of viable IUP as compared to the initial 11.5%.

The changes in serum hCG levels over 48 hour have been defined as the hCG ratio. Kirk et al has reported that a serum hCG increase over 48 hours of more than 66% (the hCG ratio >1.66) is a good predictor of an intrauterine pregnancy. A decrease in hCG of >13% or a hCG ratio of <0.87 has been found to have a sensitivity of 92.7% and a specificity of 96.7% for the prediction of a failing PUL; these patients have only a minimal need of subsequent follow-up . In study the largest study of hCG levels to date, performed by Bignardi et al the sensitivity of hCG level for EP is found to be 85–100% and specificity is 28–97%..

In fact, in 21% of women with ectopic pregnancy, the hCG levels imitate intrauterine pregnancy levels and in 8% can imitate the spontaneous abortion hCG levels. Similarly, in 1% of women with intrauterine pregnancy and in 10% of women with spontaneous abortion, the hCG levels are similar to ectopic pregnancy hCG levels.

Conclusion
The management of PUL is highly crucial in obstetrics clinical practice. The definitive diagnosis of a woman with either a failed IUP or ectopic pregnancy has important clinical consequences, including prognosis as to the possibility of a repeat ectopic pregnancy, the need for assisted reproductive technologies or workup for potential recurrent pregnancy loss. Therefore, attempts should be made to make a definitive diagnosis when possible.

However, the PUL frequency should be kept under 15% by employing experienced doctors on this topic and using high quality ultra-sonography in early pregnancy units. Among the several hormones evaluated in the prediction of PUL outcome serum hCG level is the most useful hormone; however, evaluating the changes in hCG levels within 48 hours is a more reliable method than a single measurement. It is very important to follow-up the patients diagnosed with PUL until the final diagnosis is concluded.

Recommendation
Early diagnosis of ectopic pregnancy reduces the risk of tubal rupture and allows more conservative medical treatments to be employed. Ultrasonography should be the initial investigation for symptomatic women in their first trimester; when the results are indeterminate, the serum β human chorionic gonadotropin (β-hCG) concentration should be measured. Serial measurement of β-hCG and progesterone concentrations may be useful when the diagnosis remains unclear. Even though the hCG ratio is the best method for predicting ectopic pregnancy in patients with PUL, progesterone is the best indicator for viability. Mathematical models should developed and validated for routine use.

References
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