Serum CA-125 for early prediction of miscarriage

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Abstract:

Background: Miscarriage is defined as the loss of a pregnancy before 20 weeks of gestation or before the fetus reaches 500 g of weight. It is estimated that 30% of all pregnancies end in abortion. 20% occurs in subclinical form (before evidencing it with ultrasound) and 10% later of his clinical detection.

Objective: To assess the level of Serum CA-125 in pregnant with threatened miscarriage.

Patients and method: A case control study carried at Al-Zahra Teaching Hospital in the period from 1st of October 2018 to the 1st of April 2019, in which 167 pregnant respondents at 6-12 weeks of gestation (were calculated from last menstrual period), with regular cycles) were enrolled in the study, and divided into two groups: Case group (n=58) pregnant with threatened abortion and control group (n=109) normal pregnant women.

Results: The mean serum level of CA-125 in case group (threatened miscarriage) was (51.2±22.9 IU/ml) and for control group was (22.3±6.7 IU/ml). It was found that the serum level of CA-125 were highly significantly increased in threatened miscarriage group than in normal healthy group (P<0.001). In the cutoff value at (30.6 IU/dl) of serum CA-125 the sensitivity of the test to diagnose the miscarriage was (80%), sensitivity (87%), PPV (91.5%), NPV (88%) and the accuracy of the test was (83.5%).

Conclusion: The level of Serum CA-125 was highly increasing in threatened miscarriage patients.

Keyword: Miscarriage, CA-125, gestation


INTRODUCTION

Miscarriage is defined as the loss of a pregnancy before 20 weeks of gestation or before the fetus reaches 500 g of weight (¹). It is estimated that 30% of all pregnancies end in abortion. 20% occurs in subclinical form (before evidencing it with ultrasound) and 10% later of his clinical detection. Classically, Recurrent Abortion is defined as the loss of three or more clinically recognized pregnancies consecutively, ectopic pregnancies and molar pregnancies are excluded. This happens in approximately 1% of the population. However, others consider two or more abortions, this form is more frequent and it will occur to approximately 5% of the population (²,³).
Incidence of spontaneous abortions is between 10 and 18% of pregnancies \((4)\). It is associated with chromosomal defects \((5)\), endocrine, immunological, infectious maternal diseases and malformations of the genital tract or placental dysfunction \((6)\). According to Palacio R et al, one third of all women have miscarriage at some time in their reproductive years \((7)\).

**EPIDEMIOLOGICAL FACTORS**

The maternal-paternal age and the number of previous abortions are the most powerful risk factors of abortion. Advanced maternal age (it reaches 51% for the 40-44 year interval) has been associated with a deficiency in the number and quality of oocytes. The age of the father is important in couples where both are over 35 years of age or when the father's age is over 40 years \((1)\). Previous history of abortion is an independent predictor; the risk of a next abortion increases, reaching approximately 40% after three consecutive abortions. The participation of other risk factors is controversial given the difficulty in isolating the presence of confusing variables. While the tobacco, caffeine and alcohol have been linked to abortion in dose-dependent, the evidence has been considered still insufficient \((8)\).

Recent studies have linked obesity with an increased risk of recurrent abortion: \([0.4% \text{ [BMI 30 or more] versus 0.1% [BMI 25-29]}]\); Odd ratio (OR): 3.51; Confidence interval (CI) 95%, 1.03-12.01) \((9)\).

**Aim of the study**: To assess the level of Serum CA-125 in pregnant with threatened miscarriage.

**Patients and method:**

A case control study carried at Al-Zahraa Teaching Hospital in the period from 1st of October 2018 to the 1st of April 2019, in which 167 respondents were enrolled in the study. 167 pregnant women within gestational age between 6-12 weeks (measured by calculating from the last menstrual period of the respondents in a regular cycle) were enrolled in the current study.

58 patients were previously diagnosed as threatened miscarriage with presence of bleeding (vaginal or spotting) but with viable fetus were diagnosed by ultrasonography. The other 109 presented with no bleeding (past or now) in the existing pregnancy.

Exclusion criteria: included missed abortion, blighted ovum, molar or ectopic pregnancy, pregnancy with high-order, and tumor of the ovary with pregnancy, previous pelvic disease history.

After thorough and careful history, physical examination, then the ultrasound examination were carried to confirm gestational age, viability of the fetus, intrauterine single gestation and absence of exclusion criteria, the respondents were divided into two groups: 58 women in group I (those with threatened miscarriage) and 109 women as control (group II). The patients were following until the gestational age reach the 20th weeks to record if there is any abortion happened in both groups.

**Method**: 5 cc of venous blood were collected from all respondents and after blood was clotting then we put in centrifuge for to separate the serum and then stored for one day at refrigerator (4-8 °C) then by chemiluminescent immunometric method the serum levels of CA-125 markers were assayed. All samples were analyzed at private biochemistry lab in Al-Najaf city.
Ethical concept: All respondents gave their consent to participate in this study in agreement with the Helsinki Declaration. Demographic information was collected including age, gender, dates and source of admission.

Statistical analysis:
Data were described statistically as: mean ± SD and frequency. One-way ANOVA test was used to make a comprised of numerical variables between the two groups of the study. Accuracy of the test was calculated after calculating the sensitivity and specificity of the test to diagnose the threatened abortion. Receiver operator curve used to conclude the ideal cut off value of the CA-125, and P values equal or less than 0.05 considered as statistically significant. The analysis was done using computerized programs (SPSS version 25) for Microsoft Windows.

Results: Out of 167 pregnant respondents were enrolled in the current study, 58 pregnant with threatened abortion and 109 was normally pregnant women. The mean age of the case group was (27.4±2.1) years and mean age for healthy group was 27.1±1.8 years, with no significant difference between both groups (P-value=0.3). Furthermore, no significant differences were found between the studied groups regarding parity and gestational age (P>0.5) (table 1).

<table>
<thead>
<tr>
<th></th>
<th>Threatened Miscarriage group (n=58)</th>
<th>Normal pregnant group (n=109)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean±SD/years</td>
<td>27.4±2.1</td>
<td>27.1±1.8</td>
<td>0.3 NS</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P 0</td>
<td>12</td>
<td>29</td>
<td>0.8 NS</td>
</tr>
<tr>
<td>P 1-2</td>
<td>17</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>≥ P 3</td>
<td>29</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Gestational age mean/week</td>
<td>9</td>
<td>10</td>
<td>0.5 NS</td>
</tr>
</tbody>
</table>

Table 2 show that the serum mean level of CA-125 in case group (threatened miscarriage) was (51.2±22.9 IU/ml) and for control (Normal pregnant group) was (22.3±6.7 IU/ml). It was found that there is highly significant increase in serum level of CA-125 in threatened miscarriage group than in normal healthy group (P<0.001).

Table 2: Relation between the studied groups regarding the serum level of CA 125

<table>
<thead>
<tr>
<th></th>
<th>Threatened Miscarriage group (n=58)</th>
<th>Normal pregnant group (n=109)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 125 IU/ml</td>
<td>51.2±22.9</td>
<td>22.3±6.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
After follow up of the respondents to the end of 20 weeks of gestation the current study showed that in threatened group about 17/58 (29.3%) of the women was ended with miscarriage and 41/58 (70.7%) was continued with pregnancy (table 3). While in normal pregnancy group 11/109 (10.1%) of the pregnancy were ended with miscarriage and the rest were continued. Highly significant increase in serum level in miscarriage than in continued pregnancy in both tables (table 3 and 4).

Table 3: Serum CA 125 level in threatened abortion group (n=58) at 20 wks. of gestation

<table>
<thead>
<tr>
<th></th>
<th>Miscarriage (n=17)</th>
<th>Continued pregnancy (n=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 125 IU/ml</td>
<td>57.6±18.3</td>
<td>34.4±4.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4: Serum CA 125 level in normal pregnancy group (n=109)

<table>
<thead>
<tr>
<th></th>
<th>Miscarriage (n=11)</th>
<th>Continued pregnancy (n=98)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 125 IU/ml</td>
<td>27.5±9.2</td>
<td>19.2±3.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Regarding to the validity test for prediction of miscarriage in case group, it was found that the sensitivity was 80%, specificity (87%), Negative predictive value (88%), Positive predictive value (91.5%) and the accuracy (83.5%) (Table 5).

Table 5: Validity test of the CA 125 in prediction of Miscarriage in threatened group

<table>
<thead>
<tr>
<th></th>
<th>Cutoff value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum CA 125</td>
<td>58.0 IU/ml</td>
<td>80%</td>
<td>87%</td>
<td>88%</td>
<td>91.5%</td>
<td>83.5%</td>
</tr>
</tbody>
</table>

As for control group (normal pregnancy) the validity test for prediction of miscarriage, it was found that the sensitivity was (94%), specificity (100%), Negative predictive value (86%), Positive predictive value (98%) and the accuracy (97%) (Table 6).
Table 6: Validity test of the CA 125 in prediction of Miscarriage in normal pregnancy group

| Cutoff value | Serum CA 125 > 30.0 IU/ml | Sensitivity 94% | Specificity 100% | NPV 86% | PPV 98% | Accuracy 97% |

Discussion: The most common finding in the current study is the serum level of CA-125 was highly increase in threatened abortion women than that in normal pregnant women (p<0.001) which is in agreement with that mentioned by Al Mohamady M et al. (10) in his study revealed a significant difference were found between the group of pregnant respondents that continued and the miscarriage group (P<0.001). Moreover it is in agreement with that found by Sweed MS et al. (11).

But it is not in agreement with a previous study by Mahdi B who found that there was no statistically significant difference in serum level of CA-125 in miscarriage patients compared with those pregnant that continued pregnancies in spite of its higher leveland in his study revealed that CA-125 serum level in the first trimester are not predictive of threatened miscarriage and failed to distinguish among threatened miscarriages and normal pregnancies. (12)

In the present study the serum level of CA-125 was used as predictor for threatened miscarriage, when the cutoff value of serum CA-125 at (30.6 IU/dl) the sensitivity (80%), specificity (87%), PPV (91.5%), NPV (88%) and the accuracy of the test was (83.5%).

In Al Mohamady M et al study, (10) and when he considered the cut-off limit of CA-125 at 31.2 IU/ml, found that sensitivity was 96.2% and specificity 100%. While in a study carried by Schmidt et al used a cutoff value at 65 IU/ml and found that the sensitivity was (50%). (13) Azougi et al. used a cutoff value of CA-125 at 125 IU/dl stated a 100% sensitivity and specificity. (14) Moreover it is in agreement with that found by Katsikis I. et al, (15) and by Fiegler P et al. (16)

Conclusion

The level of Serum CA-125 was highly increasing in threatened miscarriage patients. Conflict of interest: The authors declare that no conflict of interest. This research was self-funding source. Ethical clearance was taken from the scientific committee of the Iraqi Ministry of health.

References:


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15. Katsikis I, Roussos D, Farmakiotis D, Kourtis A, Diamanti-Kandarakis E, Panidis D. Receiver operator characteristics and diagnostic value of progesterone and CA-125 in the prediction of ectopic