

Evaluation of Vaginal Fluid Urea, Creatinine, Prolactin and Beta Human Chorionic Gonadotrophin for Diagnosis of Premature Rupture of Membranes

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Abstract: Background: Pre-term pre-mature ruptures of membranes (PPROM) complicate (2-20) % of all births. The non attendance of a non invasive gold standard technique for the diagnosing PROM has result in looking for the substitute bio-chemical biomarkers which existing with high concentration sin amniotic fluids. **Objectives:** Evaluation of the consistency of vaginal fluids human chorionic gonadotropin, urea, creatinine and prolactin for PROM-diagnosis. **Patients and methods:** At Azhar University Hospitals of Assuit branch, a prospective case-control study was conducted. We involved 150-pregnant cases ranging from 20 to 40-wks of pregnancy separated into 3 groups: Group-I consisting of 50-cases with affirmative vaginal leaking history and positive fluids leaking detected by sterile Cusco speculum. Group II consisted of 50 pregnant women with suspected PROM. Group III consisted of 50 were attended to outpatient clinic for antenatal care without any complications. All cases experienced complete history taking, general examinations, abdomen examinations and sterile Cusco speculum examinations. **Results:** The best cutoff value was a vaginal β -hCG level of >25.44 mIU/ml which had a sensitivity of 92% with specificity 90%, accuracy 91%. Vaginal prolactin had cut-off value of >14.98 μ IU/ml, with sensitivity 86% and specificity 82%, accuracy 84%. Vaginal urea had cutoff value of >3.7 mg/dl, with sensitivity 94% and specificity 70%, accuracy 82%. Vaginal creatinine had cutoff value of 0.265mg/dl, with sensitivity 96% and specificity 74%, accuracy 85%. **Conclusion:** Although urea and creatinine are highest sensitivity but B-hcg is the most diagnostic and specific then prolactin for PROM-diagnosing, and may be utilized in suspected patients.

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Key Words: Fetal membranes, amniotic fluid, premature rupture of membranes, urea, creatinine, prolactin

1. Introduction

Pre-mature Rupture of Membranes (PROM) refer to embryonic membranes rupture earlier to the beginning of labor. If it happens earlier to 37-wks of gestation, it is named pre-mature PROM (1).

Ultrasound (US) examinations with amniotic fluid determining isn't a preferred testing as it could not distinguish PROM from other patients of oligohydramnios (2).

For this cause, a noninvasive, easy, and cheap technique for diagnosing PROM is needed like urea, prolactin, creatinine, α -fetoprotein and Beta-human chorionic gonadotropin (β -HCG). Urea as well as creatinine were excreted via glomerular filtrations. These markers are as well accessible in amniotic fluids and were inspected for detecting PPRM (3). In a research connected to vagina washing fluids urea and levels of creatinine, urea measurements and creatinine of cervico-vaginal washing-fluid approves a precise diagnosis for PROM (4).

Prolactin (PRL) is a 199-aminoacid solo polypeptide chain and identified as a lactogenic hormone that is secreted throughout gestation from fetus & mother pituitary and decidua. so PRL can be

supportive in PROM-diagnosing (5). β -HCG is glycoprotein existing in amniotic fluids in addition to mother urine & blood. β -HCG is a dependable examination at 2nd and 3rd trimesters in PROM patients and is inexpensive and simpler, therefore it has been more feasible for PROM-diagnosing (6).

The aim of this work is to detect the diagnostic role of vagina fluids urea, creatinine, prolactin and beta-human chorionic gonadotrophin in PROM-diagnosing.

2. Subjects and Methods

This prospective case-control investigation was done at the Outpatient Clinics of Department of Obstetrics and Gynecology, Azhar University Hospitals of Assiut Branch. It was based on clinical and bio-chemical parameters. It was accomplished on 150-pregnancies.

Patients were separated into 3 groups as follows:

➤ **Group A (definite rupture of membranes):**

It included 50 pregnant women with the following conditions for inclusion criteria:

1. Weeks of gestation is between (20 - 40 weeks).
2. Singleton gestation.
3. History of watery vagina leaking.

4. Visualizations of amniotic fluids leaking (sterile cusco speculum examination: positive fluid leakage).
5. Reduced amniotic fluids index (AFI was determined in accordance to 4 quadrants method) (AFI = 5–10 cm).

➤ **Group B (suspected but not definite PROM):**

It included 50 pregnant women with Suspected rupture of membranes with the following condition for inclusion criteria:

1. Weeks of gestation is between (20 - 40 weeks).
2. Singleton gestation.
3. History of vagina fluids leaking.
4. Average amount of amniotic fluids index (AFI > 10 cm).
5. No visualization of amniotic fluids leaking (sterile cusco speculum test: negative fluids leaking).

➤ **Group C (control group):**

It comprised 50-pregnancies who were joined the out-patient clinic for routine pregnancy check with the following inclusion criteria:

1. Gestational age between (20 - 40 weeks).
2. Singleton gestation.
3. There is no history of vaginal fluid leakage.
4. Average amount of amniotic fluids index (FI > 10 cm).

Inclusion criteria:

- 1- Ages from 18-35-yrs.
- 2- Gestational age between (20 - 40 weeks).
- 3- Absence of regular uterine contractions.
- 4- Absence of vaginal bleeding.
- 5- Absence of vaginal infection.
- 6- No history of coitus 48 hours before examination.

Exclusion criteria:

- Meconium stained amniotic fluid.
- Patients who have visible blood in vagina secretions.
- Having inter-course in the previous night.
- Using vagina medications.
- Presence of fetal anomalies.
- Patients in labor.
- Intra-uterine fetal mortality and pre-natal complications.
- Oligohydramnios.

Methods:

➤ **Complete history taking:**

Involving individual history, the previous menstrual period, history of amniotic fluids leaking (beginning, quantity, period and color of the fluids), history of amniotic fluids leaking in preceding gestations, history of vagina blood loss and obstetrical history.

➤ **General examinations:**

Involving vital marks (pulse, temp., blood pressure, and breathing rates), jaundice, pallor, cyanosis, oedema (generalized or localized), chest and heart testing.

➤ **Abdominal examinations:**

Involving fungal levels, uterine contractions, embryonic heart sounds, abdomen tender and stiffness.

➤ **Complete clinical test results of speculum test:**

Including pooling test, nitrazine test and fern test.

- Transabdominal ultrasonography.
- Vaginal wash urea measurement by enzymatic urease method.
- Vaginal wash creatinine measurement test by RATE JAFFE method.
- Vaginal wash fluid prolactin measurement by ELISA method.
- Measurement of β -HCG in the amniotic fluid by ELISA method.

Statistical analyzing:

The mean, standard deviation (SD), and range were used to depict quantitative data. Numbers and percentages were used to describe qualitative data. One way ANOVA test (F) is a technique used to compare means of two or more groups. this technique can be used only for numerical data.

Quantitative variables analyzing was done via nondependent students t-testing and qualitative data via Chi-squared testing. Diagnostically accuracies was evaluated via sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Receiver operating characteristic (ROC) curve has been utilized to find the best cutoff concentration.

P-value was used to quantify the idea of statistical significance of evidence and a guideline to ignore data that did not reach a specific level: The significance level was established as $P < 0.05$. $P > 0.05$ was considered insignificant. $P < 0.001$ was considered high significance.

3. Results

There is nonsignificant change among the study groups in regard to ages, gestational ages, gravidity, parity or abortion (table 1).

A statistically significant change was found among the three groups in regard to amniotic fluid index. On LSD comparison, the difference is significant between each two individual groups (table 2).

A statistically significant change was found among the three groups in regard to results of fern and nitrazine paper tests (the difference is significant between control groups and both definite and suspected PROM groups regarding fern and nitrazine paper tests) (table 3).

A statistically significant change was found among the three groups in regard to beta subunit of hCG. On pairwise comparison, the difference is significant between each two individual groups (Table 4).

A statistically significant change was found among the three groups in regard to prolactin. On pairwise comparison, the difference is significant between each two individual groups (table 5).

A statistically significant change was found among the three groups in regard to urea. On pairwise comparison, the difference is significant between control and each other group. The difference is non-significant between suspected and definite PROM groups (table 6).

A statistically significant change was found among the three groups in regard to creatinine. On pairwise comparison, the difference is significant between control and each other group (table 7).

The best cutoff of beta hCG subunit in PROM-diagnosing is ≥ 25.44 mlu/ml with area under curve 0.986, sensitivity 92%, specificity 90%, PPV 90.2%, NPV 91.8%, positive probability ratio 9.2, negative probability ratio 0.09 and accuracy 91% ($p < 0.05$) (Figure 1).

The best cutoff of prolactin subunit in PROM-diagnosing is ≥ 14.98 with area under curve 0.965, sensitivity 86%, specificity 82%, PPV 82.7%, NPV 85.4%, positive probability ratio 4.78, negative probability ratio 0.17 and accuracy 84% ($p < 0.05$) (Figure 2).

The best cutoff of urea subunit in PROM-diagnosing is ≥ 3.7 with area under curve 0.947, sensitivity 94%, specificity 70%, PPV 75.8%, NPV 92.1%, positive probability ratio 3.13, negative probability ratio 0.09 and accuracy 82% ($p < 0.05$) (Figure 3).

The best cutoff of creatinine in PROM-diagnosing is ≥ 0.265 with area under curve 0.902, sensitivity 96%, specificity 74%, PPV 78.8%, NPV 94.9%, positive probability ratio 3.69, negative probability ratio 0.05 and accuracy 85% ($p < 0.05$) (Figure 4).

Table (1): Comparing amongst the three patients in regard to age and obstetric history

| Parameters | Groups | | | Test | |
|------------------------------|------------------|------------------|----------------------|-------|-------|
| | Control group | PROM group | Suspected PROM group | F/KW | p |
| Age: | | | | | |
| Mean \pm SD | 28.44 \pm 5.35 | 26.54 \pm 4.5 | 27.9 \pm 3.69 | 2.298 | 0.104 |
| Range | 22 - 35 | 23 - 35 | 23 - 35 | | |
| Gestational age (Ws): | | | | | |
| Mean \pm SD | 29.98 \pm 6.36 | 31.72 \pm 1.75 | 30.82 \pm 3.41 | 2.059 | 0.131 |
| Range | 20 - 40 | 29 - 34 | 26 - 36 | | |
| Gravidity: | | | | | |
| Mean \pm SD | 2.94 \pm 1.13 | 3.1 \pm 0.76 | 2.86 \pm 1.01 | 0.858 | 0.651 |
| Range | 3 (1 - 5) | 3 (2 - 5) | 3 (1 - 4) | | |
| Parity: | | | | | |
| Mean \pm SD | 1.7 \pm 1.18 | 1.7 \pm 0.74 | 1.58 \pm 0.91 | 0.328 | 0.849 |
| Range | 2 (0 - 5) | 2 (1 - 3) | 2 (0 - 3) | | |
| Abortion: | | | | | |
| Mean \pm SD | 0.36 \pm 0.6 | 0.4 \pm 0.49 | 0.28 \pm 0.45 | 1.609 | 0.447 |
| Range | 0 (0 - 3) | 0 (0 - 1) | 0 (0 - 1) | | |

F One way ANOVA KW Kruskal Wallis test

Table (2) Comparing amongst the three patients in regard to amniotic fluid index

| Parameters | Groups | | | Test | |
|-----------------------|-------------------------|-------------------------|-------------------------|---------|----------|
| | Control group | PROM group | Suspected PROM group | F | p |
| Age: | | | | | |
| Mean \pm SD | 12.68 \pm 1.1 | 7.26 \pm 1.61 | 11.3 \pm 0.54 | 290.114 | <0.001** |
| Range | 11 - 14 | 5 - 10 | 11 - 13 | | |
| LSD comparison | P ₁ <0.001** | P ₂ <0.001** | P ₃ <0.001** | | |

F One way ANOVA ** $p \leq 0.001$ is statistically highly significant

Table (3): Comparing amongst the three patients in regard to Fern and nitrazine paper tests

| Parameters | Groups | | | Test | |
|------------------------|---------------|---------------------|----------------------|----------|----------|
| | Control group | Definite PROM group | Suspected PROM group | χ^2 | p |
| | N=50(%) | N=50(%) | N=50(%) | | |
| Fern test: | | | | | |
| Negative | 43 (86) | 10 (20) | 16 (32) | 49.758 | <0.001** |
| Positive | 7 (14) | 40 (80) | 34 (68) | | |
| Nitrazine test: | | | | | |
| Negative | 43 (86) | 18 (36) | 17 (34) | 34.776 | <0.001** |
| Positive | 7 (14) | 32 (64) | 33 (66) | | |

**p≤0.001 is high significance

Table (4): Comparing amongst the three patients in regard to β -hCG

| Parameters | Groups | | | Test | |
|--------------------------------|-------------------------|-------------------------|-------------------------|---------|----------|
| | Control group | Definite PROM group | Suspected PROM group | KW | |
| β-hCG: | | | | | |
| Mean \pm SD | 12.67 \pm 6.19 | 399.28 \pm 83.43 | 150.56 \pm 68.54 | 130.855 | <0.001** |
| Median | 10.7 | 400.5 | 150.6 | | |
| Range | 6.9 – 30.9 | 230.5 – 500.4 | 10.99 – 230.4 | | |
| Pairwise comparison | P ₁ <0.001** | P ₂ <0.001** | P ₃ <0.001** | | |

**p-value≤0.001 is high significance KW Kruskal Wallis testing

Table (5): Comparison between the studied patients regarding prolactin

| Parameters | Groups | | | Test | |
|----------------------------|-------------------------|-----------------------|-------------------------|-------|----------|
| | Control group | Definite PROM group | Suspected PROM group | KW | |
| Prolactin: | | | | | |
| Mean \pm SD | 10.44 \pm 5.19 | 83.61 \pm 38.87 | 45.27 \pm 26.81 | 83.87 | <0.001** |
| Median | 9.5 | 78.5 | 43.98 | | |
| Range | 6 – 29.89 | 7.2 – 130.4 | 14.56 – 120.65 | | |
| Pairwise comparison | P ₁ <0.001** | P ₂ 0.006* | P ₃ <0.001** | | |

*p<0.05 is statistically important **p-value≤0.001 is statistically high significance KW Kruskal Wallis test

P₁ difference between control group and definite PROM groupP₂ difference between definite and suspected PROM groupsP₃ difference between control group and suspected PROM group**Table (6)** Comparing amongst the three patients in regard to urea:

| Parameters | Groups | | | Test | |
|----------------------------|-------------------------|---------------------|-------------------------|--------|----------|
| | Control group | Definite PROM group | Suspected PROM group | KW | |
| Urea: | | | | | |
| Mean \pm SD | 3.17 \pm 1.3 | 10.93 \pm 5.63 | 7.3 \pm 2.21 | 81.667 | <0.001** |
| Median | 2.5 | 10.6 | 7.15 | | |
| Range | 1.88 – 5.9 | 3.6 – 20.5 | 3.4 – 10.6 | | |
| Pairwise comparison | P ₁ <0.001** | P ₂ 0.14 | P ₃ <0.001** | | |

*p-value<0.05 is statistically important **p≤0.001 is statistically high significance KW Kruskal Wallis test

P₁ difference between control group and definite PROM groupP₂ difference between definite and suspected PROM groupsP₃ difference between control group and suspected PROM group

Table (7): Comparison between the studied patients regarding creatinine:

| Parameters | Groups | | | Test | |
|----------------------------|-------------------------|-------------------------|-------------------------|--------|----------|
| | Control group | Definite PROM group | Suspected PROM group | KW | |
| creatinine: | | | | | |
| Mean ± SD | 0.21 ± 0.1 | 1.03±0.58 | 0.48 ± 0.17 | 91.267 | <0.001** |
| Median | 0.18 | 0.95 | 0.39 | | |
| Range | 0.1 – 0.13 | 0.35 – 2.1 | 0.19 – 0.68 | | |
| Pairwise comparison | P ₁ <0.001** | P ₂ <0.001** | P ₃ <0.001** | | |

*p-value<0.05 is statistically important **p-value≤0.001 is statistically high significance KW Kruskal Wallis test

P1 difference between control group and definite PROM group
 P2 difference between definite and suspected PROM groups
 P3 difference between control group and suspected PROM group

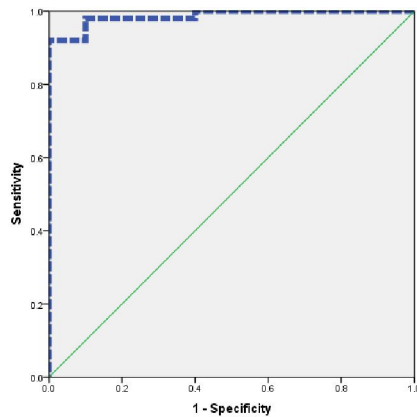


Figure (1): ROC curve presenting performance of β-hCG in PROM-diagnosing among the studied patients

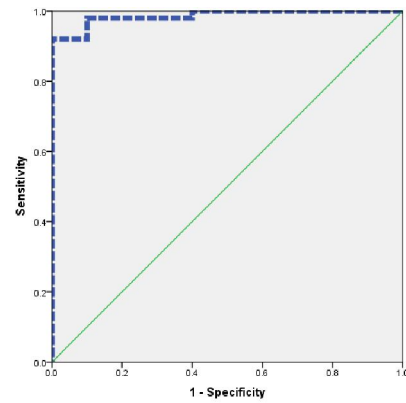


Figure (3): ROC curve presenting performance of urea in PROM-diagnosing among the studied patients

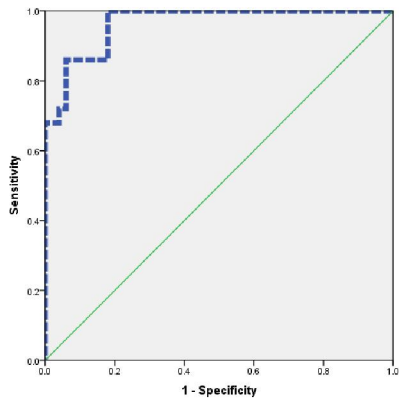


Figure (2): ROC curve presenting performance of prolactin in PROM-diagnosing among the studied patients

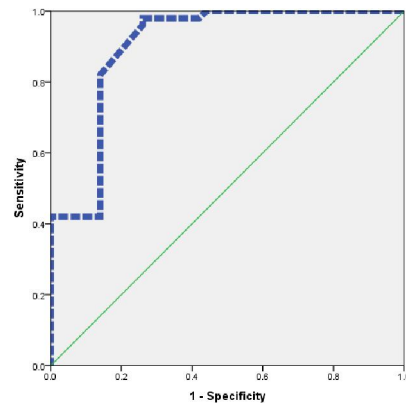


Figure (4): ROC curve presenting performance of creatinine in PROM-diagnosing among the studied patients

4. Discussion

PROM denotes to embryonic membrane ruptures earlier to the beginning of labor. Pre-term PROM is rupture of embryonic membranes earlier to 37-wks. PROM happens in 10 % of all pregnancies and around (2 to 4) % of pre-term

gestations, with complications like infections and pre-term delivery ⁽⁷⁾.

In the urine, urea has a crucial role in the nitrogenous chemical metabolism. Creatinine is a derivative of creatine phosphate in muscle that is produced at a

relatively constant rate and cleared out of the blood by the kidneys. Vagina urea and creatinine can be beneficial in PROM-diagnosing as in the second half of pregnancy, embryonic urination is the most important source of amniotic fluids ⁽⁸⁾.

PRL is a 199-aminoacid single polypeptide chain and recognized as a lactogenic hormone. PRL is coded by a single gene placed on the short arm of chromosome six Throughout gestation PRL is made via the maternal and embryonic hypo-physes and the decidua. PRL concentration increase gradually in mother blood during gestation to around 10-fold the nonpregnant values. PRL of amniotic fluid is (5-10)-fold elevated than that of either mother blood ⁽⁹⁾.

B-HCG presents in amniotic fluids in addition to mother urine & blood. In a research done by the measurements of β -HCG levels in vagina fluids for PROM diagnosing at 3rd trimester, sensitivity, specificity, and PPV and NPV were reported as 100-, 96.5-, 88.9- and 100-%, respectively. It was highlighted that β -HCG is a dependable examination at 2nd and 3rd trimesters in PROM patients. Presence of this substance in vagina secretion at low concentration and the rise of vagina concentrations afterward amniotic drainage at PROM mean that it can be beneficial to utilize these substances in the PROM-diagnosing ⁽¹⁰⁾.

This work was conducted to evaluate the diagnosing value of vagina fluids urea, creatinine, prolactin and beta-human chorionic gonadotrophin levels in patients with PROM. The research was done at the Out-patient Clinics of Department of Obstetrics and Gynecology, Azhar University Hospitals of Assiut Branch. A number of 150-pregnant cases have been comprised in the work, from (20-40)-wks of pregnancy, allocated into 3 groups: 50-pregnancies with definite PROM, 50-pregnancies with suspected PROM and 50-pregnancies who visited the outpatient clinic for ante pregnancy check with no history of vagina discharge.

The study showed that there are nonsignificant changes among the study groups in regard to ages, gestational ages, gravidity, parity and history of abortion. **Effat et al.** ⁽¹¹⁾ compared the diagnosis value of vagina fluids creatinine and β -HCG for the PROM-diagnosing. This prospective case-control investigation was performed at Al-Zahraa hospitals comprised 75-pregnancies ranging from 24 to 36-wks of pregnancy, grouped into 3 groups. Group-1; the established group is comprised 25-pregnancies with PROM. Group2; suspected PROM group is included 25-pregnancies. Group-3; controls comprised 25-pregnancies who visited the outpatient clinic for pregnancy checking. A nonsignificant alterations were found

among three groups in age, gestational ages, gravidity and mode of delivery (P-value > 0.05).

In terms of AFI, the study indicated a statistically important difference between the three groups. On LSD comparison, the difference is significant between each two individual groups. Our findings support those of **Effat et al.** ⁽¹¹⁾ who discovered that the cases number with AFI 5cm was 34% in approved group, 14%in suspected group and no cases in controls. In contrast the AFI-cases > 5CM was 68%, 84% and 100% patients respectively so, there was significant difference regarding AFI in study groups (p-value 0.001). Our findings are not reliable with the report made by **Kafali and Oksuzler** ⁽¹⁰⁾ who concluded that here was nonsignificant change among three groups regarding AFI.

Our study showed that a statistically significant change was found among the three groups in regard to beta subunit of hCG. On pairwise comparison, the difference is significant between each two individual groups. The best cutoff of beta hCG subunit in PROM-diagnosing is ≥ 25.44 mlu/ml with area under curve 0.986, sensitivity 92%, specificity 90%, PPV 90.2%, NPV 91.8%, positive probability ratio 9.2, negative probability ratio 0.09 and accuracy 91% (p<0.05).

Ghasemi et al. ⁽¹²⁾ evaluated the value of β -hCG, prolactin, urea and creatinine of vagina fluids for PPROM- diagnosing in pregnancy. The cutoff point for β -hCG was 20.5 mIU/mL. With that cutoff point, the specificity, sensitivity, PPV and NPV for PROM detection were 87.5%, 86%, 86.4%, and 87.3%, respectively.

Our study showed that a statistically significant change was found among the three groups in regard to prolactin. On pairwise comparison, the difference is significant between each two individual groups. The best cutoff of prolactin subunit in PROM-diagnosing is ≥ 14.98 μ IU/ml with area under curve 0.965, sensitivity 86%, specificity 82%, PPV 82.7%, NPV 85.4%, positive probability ratio 4.78, negative probability ratio 0.17 and accuracy 84% (p<0.05).

The power diagnosis of vaginal cleaning fluids PRL for PROM-diagnosing was assessed by **Kariman et al.** ⁽⁵⁾ and the cutoff value was 9.5 μ IU. The mean content vagina fluids prolactin level in the PROM-group were 851.22 \pm 425.74 μ IU/ml. This is notable (p<0.001) higher than the value found for controls (i.e., 8.20 \pm 0.67 μ IU/ml, ranging from 4.00 to 24.00). The AUC is 89.90% for prolactin. In accordance to the prolactin cutoff point sensitivity of 87.30%, specificity of 75.0%, PPV of 75.80%, NPV of 86.53% and accurateness of 83.33% were obtained respectively. They came to the conclusion that the concentrations of prolactin in the backward vaginal washing fluids fornix is dependable and noninvasive diagnosing examinations of PROM.

Our study showed that a statistically significant change was found among the three groups in regard to urea. On pairwise comparison, the difference is significant between control and each other group. The difference is non-significant between suspected and definite PROM groups. The best cutoff of urea subunit in PROM-diagnosing is ≥ 3.7 mg/dl with area under curve 0.947, sensitivity 94%, specificity 70s%, PPV 75.8%, NPV 92.1%, positive probability ratio 3.13, negative probability ratio 0.09 and accuracy 82% ($p < 0.05$).

A report by **Mohamed and Mostafa** ⁽¹³⁾. The specificity, sensitivity, PPV and NPV were 100% in PROM detection by evaluating the vagina urea concentrations with cutoff values of 13.2 mg/dl.

Our study showed that A statistically significant change was found among the three groups in regard to creatinine. On pairwise comparison, the difference is significant between control and each other group. The best cutoff of creatinine in PROM-diagnosing is ≥ 0.265 mg/dl with area under curve 0.902, sensitivity 96%, specificity 74%, PPV 78.8%, NPV 94.9%, positive probability ratio 3.69, negative probability ratio 0.05 and accuracy 85% ($p < 0.05$).

Kui et al. ⁽¹⁴⁾ found that the mean vagina fluids creatinine levels in confirmed PROM-group, suspected PROM and controls were 0.40 ± 0.20 , 0.16 ± 0.04 and 0.08 ± 0.01 , respectively, where the change was significant (p -value=0.001). ROC analyzing was utilized to confirm the optimal cutoff concentrations for vagina washing fluids creatinine level and it was formed that cutoff value 0.14 mg/dl was optimum. The sensitivity, specificity, PPV, and NPV were 98.7%, 100%, 100% and 98.8%, respectively, in PROM detection assessment of vagina fluids creatinine.

Osman and Elghazaly ⁽¹⁵⁾ evaluated and compared the accurateness of urea and creatinine in vagina fluids washing for PROM-diagnosing and to find out the cutoff values. They revealed that vagina fluids washing urea and creatinine level in vagina fluids washing were very precise, easy examinations for PROM-diagnosing.

Gezer et al. ⁽¹⁶⁾ determined if urea and creatinine levels in vagina fluids can be utilized for PPRM diagnosis and expect birth period afterward PPRM. They concluded that measurements of creatinine & urea levels in vagina fluids is a fast and dependable examination for diagnosis and as well for expecting birth period afterward PPRM.

Conclusion

Vaginal washing-fluid urea, creatinine, prolactin and β -HCG assays are cheap, fast and valid (with higher sensitivity) to establish accurate PROM-diagnosing. Although urea and creatinine are highest sensitivity but B-hcg most specific and

diagnostic then prolctin for PROM-diagnosing, and can be utilized in suspected patients.

Conflicts of Interest:

There are no conflicts of interest reported by the authors.

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