

CROSS CORRELATION STATISTICAL STUDY OF ULTRASONIC CHANGES IN CONSERVATIVE TREATMENT FOR TUBAL ECTOPIC PREGNANCY

Xiaojuan Liao, Wenhui Wang, Xinke Huang, Hanlin Shuai*

Department of Gynaecology, the First Affiliated Hospital of Jinan University, Guangzhou, 510630 China

*Corresponding E-mail: L8808104@126.com

Abstract: Objectives: To study the correlation between tubal ectopic pregnancy ultrasound imaging changes (mass size, type, blood flow signal, and so on) and the outcome for its conservative treatment, in order to explore the predictive value of ultrasound examination in the conservative treatment of tubal pregnancy. Methods: Ninety cases of tubal pregnancy were selected, seventy-four of which were treated conservatively by methotrexate (MTX) with Mifepristone (Ru486). In all cases, the ultrasound examination and serum β -HCG value were measured before treatment, Doppler ultrasound was performed on the 7th day of treatment, and serum β -HCG value was measured on the 4th, 7th, and 14th day of treatment. And we proceeded to analyze the correlation between the size, the type of tubal pregnancy mass, and serum β -HCG level, mass flow signal before and after treatment and the outcome of treatment. Results: Different types of masses were positively correlated with the levels of β -HCG before treatment and the different levels of Doppler ultrasound signals ($r = 0.631$, $P < 0.05$). The conservative treatment outcomes of different types of masses are different, and the conservative treatment on heterogeneous masses had the highest success rate ($X^2 = 24.38$, $P < 0.001$). The size of the tubal ectopic pregnancy mass had no significant relationship to the treatment outcome ($X^2 = 1.83$, $P = 0.38$). Conclusion: The ultrasound examination has significant application value in predicting the conservative treatment outcome of tubal pregnancy.

Keywords: Tubal ectopic pregnancy, β -HCG, ultrasound, conservative treatment, correlation.

1. INTRODUCTION

Ectopic pregnancy is a common gynecological disease, and its incidence has been on the rise for nearly a decade. Among them, tubal pregnancy accounts for more than 95% of ectopic pregnancy [1-3]. Once there is a rupture or miscarriage, it can lead to internal abdominal hemorrhage that could be life-threatening. Due to the rapid development of B-ultrasound, serum and urine β -HCG measurement technology, ectopic pregnancy can be diagnosed early [4-6]. Therefore, it has changed the way of relying mainly on surgical treatment in the past, so that conservative treatment has been paid more and more attention. It has become one of the main methods in the treatment of ectopic pregnancy [7]. However, there are no uniform standards for conservative treatment indications and testing methods, and there is controversy. Therefore, the investigation of predictive and monitoring indicators for conservative treatment of tubal ectopic pregnancy has significant importance. This article presents an analytical investigation of 90 cases showing the relationship between

changes in ultrasound imaging and treatment outcome, the report is as follows.

2. METHODS

Ethics statement

The study was approved by the medical ethics committee of the First Affiliated Hospital of Jinan University, Guangzhou. All participants provided written informed consent and their records/information were anonymized and de-identified prior to analysis.

Clinical Data

A total of 90 patients participated in the study, which with tubal ectopic pregnancy, without obvious intra-abdominal bleeding or bleeding cessation, admitted to the First Affiliated Hospital of Jinan University from October, 2014 to December, 2016. In all cases, the ultrasound examination, serum progesterone and β -HCG values were measured before treatment, 74 of which were conservatively treated and 16 were surgically treated. They were aged from 20 to 42 years old, with an average of (29.2 ± 5.8) years

old; menopause for 25 - 78 days, with an average of (47.3 ± 9.9) days; mass sizes of 12.0 mm to 75.0mm, with an average of (34.8 ± 13.7) mm.

Conservative treatment inclusion criteria: the patients with evident history of amenorrhea, positive urine pregnancy test, normal increased β -HCG values, and transvaginal ultrasound of the adnexa area diagnosing a characteristic tubal ectopic pregnancy mass. Voluntary acceptance of conservative treatment, not limited of the mass size and the β -HCG value.

Conservative treatment exclusion criteria [8]: the patients presenting signs of uterorectal effusion accompanied with obvious internal hemorrhage; iliac fossa and hepatorenal recess both present with large amount of effusion; prominent abdominal pain, fever; BRT shows decrease in white blood cells and platelets and hepatorenal insufficiency.

Conservative treatment success criteria: after one course of treatment, β -HCG value continuously decreases till normal or On the 7th day, the level of β -HCG decreased by $>15\%$ before treatment, then continue to fall to normal. During this period, there is no prominent internal bleeding, abdominal pain or any other kind of acute abdominal disease; normal blood routine analysis, no blood loss appearance.

Tubal ectopic pregnancy miscarriage diagnosis criteria: during surgery there is presence of blood effusion in the pelvis or abdomen; presence of hematoma or fresh bleeding in the fallopian tubes.

Instruments and Apparatuses

V730 Tridimensional Doppler diasonograph (USA) and I2000 chemoluminescence detector, ultrasound examination was enforced with the help of experienced and skilled gynecology sonography doctors; β -HCG titers tests were done by chemoluminescence (American Abbott Company Reagent), the blood is taken and examined by a special inspector of nuclear medicine on every morning.

Treatment plane

All conservative treatment patients, using a unified treatment plan: MTX 20 mg/d for 5 days, intramuscularly, and Ru486 25 mg for 3 days, twice daily. Enhanced treatment method: MTX 50mg, intramuscularly. Ultrasound before conservative treatment and on the 7th day of treatment. Color ultrasound is performed to determine the blood flow signal on the mass, to find the side with the highest blood flow signal, record the blood flow signal's shape and size: no blood flow signal, globular blood flow signal, rhabditiform blood flow signal, dendritic blood flow signal, 1/4 annular blood flow signal, 1/2 annular blood signal, 3/4 annular blood flow signal, full annular blood flow. Divided into 5 grades: Grade 0, no blood signal; Grade 1, globular blood flow signal; Grade 2, rhabditiform blood signal, 1/4 to 1/2 annular blood flow signal;

Grade 3, more than 1/2 to incomplete annular blood flow signal; Grade 4, full annular blood flow signal.

Observation index

Serum β -HCG values were measured on 1st, 4th, 7th, 10th and 14th day, respectively. If on the 7th day, the β -HCG values (compared to the ones before the treatment) have a decrease of $> 15\%$, then the course of treatment can be stopped. Patients with β -HCG values that decreased $< 15\%$ (compared to the ones before treatment). If the color ultrasound showed a decrease in the blood flow signal level, it was temporarily observed for 3 days, and if the decrease was still $< 15\%$ before the treatment and the patient insists on requiring medication, then intensive treatment can be taken. After discharge, all patients returned to the hospital every week to check the β -HCG levels until normal. Patients who failed medical treatment changed to surgical treatment.

Statistical method

The data were statistically analyzed using the SPSS 11.5 software package. Use the Rank sum test, X^2 test, and other related analysis. P values of < 0.05 were considered statistically significant.

3. RESULTS

Correlation and Differences between adnexal mass types and β -HCG value before treatment

Analysis of rank correlation showed that different types of gestational masses were positive correlation with β -HCG values ($r = 0.631$, $P < 0.05$). Rank sum test between different types of gestational masses and β -HCG values were significantly different ($P < 0.05$). See Table 1.

Rank correlation between types of gestational mass and Doppler ultrasound blood flow signal before treatment

Rank correlation analysis showed that before treatment, Doppler ultrasound blood flow signal were positive correlation with adnexal mass type ($r = 0.406$, $P < 0.001$). See Table 2.

Different types of gestational mass and treatment outcome.

The data analyzed by X^2 test showed that after one course of treatment, the success percentage of different types of gestational mass were significantly different ($X^2 = 24.38$, $P < 0.0001$). Success percentage in heterogeneous masses was significantly higher than gestational cysts, germ and plumule with blood vessel pulse types. See Table 3.

Sizes of gestational mass and treatment outcome

X^2 test showed that there was no significant difference in the treatment success percentage of the different sized gestational masses after a course of medication. See table 4.

Table 1. Correlation of the pretreatment adnexal mass type and β -HCG value.

| Mass type | β -HCG (IU/L) | $\bar{X} \pm S$ | Cases |
|-------------------------------|---------------------|-------------------|-------|
| Heterogeneous | 100 - 23738 | 2788 \pm 4610 | 63 |
| Gestational sac | 505 - 40347 | 12620 \pm 11886 | 20 |
| Plumule with cardiac activity | 15000 - 41712 | 24951 \pm 11484 | 7 |

Table 2. Rank correlation between Doppler ultrasound blood signals and types of gestational masses before treatment.

| Mass type (shape) | Blood Flow signal (Grade) | | | | | N |
|--------------------|---------------------------|-------|-------|-------|-------|----|
| | 0 (n) | 1 (n) | 2 (n) | 3 (n) | 4 (n) | |
| Heterogeneous | 18 | 16 | 7 | 13 | 9 | 63 |
| Gestational sac | 0 | 5 | 2 | 5 | 8 | 20 |
| Plumule with pulse | 0 | 1 | 1 | 0 | 5 | 7 |

Table 3. Treatment outcome for different types of gestational masses after one course of conservative therapy.

| Mass (Shape) | Succeeded (cases) | Failed (cases) | Total | Percentage (%) |
|--------------------|-------------------|----------------|-------|----------------|
| Heterogeneous | 44 | 11 | 55 | 80 |
| Gestational sac | 3 | 14 | 17 | 17.6 |
| Plumule with pulse | 0 | 2 | 2 | 0 |
| Total | 47 | 27 | 74 | 63.5 |

Table 4. Treatment outcome for different sizes of gestational mass after one course of conservative treatment

| Mass size (cm) | Succeeded (case) | Failed (case) | Total | Percentage (%) |
|----------------|------------------|---------------|-------|----------------|
| ≤ 3 | 21 | 16 | 37 | 56.7 |
| 3 - 5 | 23 | 9 | 32 | 71.9 |
| > 5 | 3 | 2 | 5 | 60 |
| Total | 47 | 27 | 74 | 63.5 |

4. CONCLUSION

Ultrasound imaging is very valuable to determine the diagnosis, monitoring and lapse of treatment of ectopic pregnancy, thus it has a lot of scholars to carry out research on this field. The ultrasound detection of a gestational sac and plumule with blood vessel pulsation is the characteristic of the embryo's early normal growth period. The presence of an annular ectopic pregnancy nourishing arterial blood flow signal explains the existence of life, and it marks a neonatal vascular signal in normal pregnancy, while a decreased blood flow signal is a sign of miscarriage or life cessation signal of ectopic pregnancy. In general, the blood flow signals below Grade 2 indicate that the trophoblastic cells of the ectopic pregnancy lesions are weak, and the blood flow signals above grade 3 indicate that the trophoblastic cells are strong in ectopic pregnancy lesions. Tubal ectopic pregnancy will eventually result in spontaneous abortion or rupture of the gestational mass [9-10]. Because of the different type, degree, timing of miscarriage, and abnormal embryo development, the ultrasound examination presents different types of masses and the β -HCG values

are also have significant difference [11-12]. This research found that tubal ectopic pregnancy masses can be divided in 3 types: heterogeneous, gestational sac, plumule with pulse. Among the heterogeneous type, 10% of cases had β -HCG values more than 5000 IU/L and the gestational sac type had 80% of β -HCG values more than 5000 IU/L. The plumule with pulse type had an average β -HCG of 15000 to 41712 IU/L. Rank sum test analysis showed the 3 types of β -HCG values have significantly difference, and analysis of rank correlation showed that different types of gestational masses have positive correlation with β -HCG values ($r = 0.631$, $P < 0.05$).

D. Jurkovic reported that 94% of ectopic pregnancies focus on the exploration of trophoblastic arterial circulation [8]. In our research, we were able to explore the blood flow signal of the gestational mass in 80% of ectopic pregnancy cases, as for the rest, there was no result because of the possibility of different pregnancy timing or inaccuracy during ultrasound examination. For the plumule with pulse type, 71% presented Grade 4 blood flow signal, gestational sac type presented 65% cases with Grade 3 - 4 blood flow signals, and heterogeneous type had 65% cases with Grade 2 or less blood

flow signals. Further studies have demonstrated that the nature of gestational mass and their blood flow signal are positive correlation ($r = 0.406$, $P < 0.001$). We analyzed that heterogeneous mass was related to tubal ectopic pregnancy miscarriages and gestational cyst damage lessened trophoblastic activity. Therefore, the β -HCG values decreased and the color Doppler flow imaging showed less blood supply and a blood flow signal below Grade 2. And medical conservative treatment has high success rate (80% success rate for single-course conservative treatment). However, gestational sac and plumule with pulse types with strong trophoblastic activity, high β -HCG value, active embryonic growth, color Doppler showing a rich blood supply and a blood flow signal of Grade 3 or more, higher failure rate of conservative treatment (the success rate of 17.6% and 0 for single-course conservative treatment, respectively).

If referring to immediate treatment result information, color ultrasound may be most conventional monitoring method. For example, in heterogeneous type, high levels of β -HCG would normally mean recent miscarriage, but there is no response because of the long half-life of β -HCG [13]. If there is no obvious internal hemorrhage, conservative treatment can be taken. In this research, the cases with no blood flow signal and successful single-course treatment had a β -HCG value up to 4390 IU/L. But for the gestational sac type with low levels of β -HCG, were probably related to an already and long-timed miscarriage. Among the successful single-course treatment patients, the β -HCG values of 3 gestational sacs were 541 IU/L, 552 IU/L, and 1765 IU/L, respectively, and the ultrasound examination also showed that the gestational sacs were located among the heterogeneous masses, with little effusion in the pelvic cavity.

Tubal ectopic pregnancy mass is mainly characterized for its disproportion, irregular shape. If the mass size is judged only by the diameter of the block, the error will be large. Therefore, in this research three average diameters were chosen to classify the mass size, of which 90% of cases had a mass diameter of > 5 cm. There was no statistical significance in the size of the mass and the percentage of successful treatment of the mass, the level of β -HCG and the level of blood flow signal, and the logistic regression analysis between mass size and its treatment outcome was not significant either ($X^2 = 1.83$, $P = 0.38$).

In conclusion, the size of the mass does not determine the activity and blood supply of the trophoblast cells separately. It needs to be considered in combination with serum β -HCG value, size of the mass and color flow signal.

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