



Sonographic vascularity indices' study in ectopic pregnancies, after methotrexate treatment

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ABSTRACT

Objectives: Ectopic pregnancy is a crucial problem in Gynaecology. Previous studies concerning the medical treatment of ectopic pregnancies, have used only β -hCG (beta- human chorionic gonadotropin) values, to monitor the successful response to treatment. The current study was a PhD (Doctorate of Philosophy) thesis research, which has evaluated the vascularity indices' changes. The values of vascularity indices could be used, in combination with β -hCG values and the gestational sac dimensions, in every medically treated ectopic pregnancy. The results could be used, for monitoring the course of all medically treated ectopic pregnancies.

Study design: 72 women of reproductive age have taken part in the study. They have been admitted due to secondary amenorrhea, positive β -hCG test, with or without vaginal bleeding. The participants took part voluntarily and were allocated in two groups. The first group consisted of 37 women, who were possible normal or threatened intrauterine pregnancies (control group). The second group consisted of 35 women, whose sonographic findings suggested ectopic pregnancy, and qualified for methotrexate treatment (study group). Sonographic control and measurement of the vascularity indices (PI – RI) (Pulsatility index – Resistance index) of the ectopic pregnancy was conducted, in combination with β -hCG values for every admitted or outpatient woman.

The dimensions of the gestational sac of both groups were measured during four consecutive periods of time. The control group has shown progressively increasing sac dimensions, whereas, in the study group sac dimensions were more stable or growing gradually smaller. The exception where those ectopic pregnancies that ruptured, which have also shown a gradual enlargement of the sac.

Results: The endometrial thickness of the study group was gradually decreasing up to 76 % per day, and the more eminent, but not statistically significant decrease, was observed in the single dose regiment of methotrexate. Moreover, the quantitative PI and RI were evaluated, and the main finding was that there were no statistically significant decreases in any of the two groups. Concerning the study group, methotrexate treatment was successful, since there was a decrease of up to 80 %, whereas a clearly significant correlation was found between the β -hCG levels and the RI.

Conclusion: The vascularity indices could be used safely, in combination with β -hCG levels and the decrease of the gestational sac dimensions, as criteria for the evaluation of response to medical treatment of ectopic pregnancies.

1. Introduction

Ectopic pregnancy is the implantation of the embryo, elsewhere than the endometrial cavity. The most common implantation site are the tubes, and rarer sites are the ovary, the cervix, or the peritoneal cavity.

The signs that lead to an ectopic pregnancy possibility, are a positive β -hCG test, no signs of endometrial pregnancy, abdominal or cervical sensitivity, and possible intraperitoneal bleeding, according to NICE guidelines [1]. The differential diagnosis is made with TVS (Transvaginal Sonography), and β -hCG levels [2,3]. Doppler sonography is also

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helpful for diagnosing, as well as treatment course of ectopic pregnancies [4,5].

After the positive diagnosis, gold standard therapies consist of expectant management, surgical procedures with laparoscopy or laparotomy, or methotrexate treatment [6]. The proposed regimes are two: 1. The single-dose treatment, with an IM dose of 50 mg/m² of body surface, using the Mosteller type: $\sqrt{\text{height(cm)} \times \text{weight(Kg)}/3600}$. 2. The multiple-dose treatment, with IM doses of 1 mg/Kg every two days, and Leucovorin doses of 0,1 mg/Kg in between [7]. Both regimes are equally efficient [8]. The follow-up consists of consecutive β -hCG levels, Full Blood Count (FBC), clotting mechanism, renal and liver function, and ultrasound examination. Doppler sonography increases the sensitivity and specificity for ectopic pregnancy for up to 87 % [9]. Hence, the color doppler provides more benefits when a TVS is performed in early pregnancies [10,11].

Till now, Methotrexate treatment was considered successful when there was a β -hCG drop of > 15 % between day 4 and 7 [12], and the measurements continued until β -hCG < 10mIU/ml, as well as when the absorption of the pregnancy sac. This research has also used the vascularity indices, to decide whether they can contribute as a factor of success of Methotrexate treatment, despite the divergence from the international accepted criteria and the bibliography [13].

Barnhart et al. [14], Lermann et al. [15] and Saleh et al. [16], have widely studied the efficacy of single- and multiple-dose Methotrexate regimes, without proving the surpass of one over the other. The single dose is the mostly used, due to the simple technique and the fewer complications. Barnhart et al. [17] have proposed a 2-dose scheme as a good choice, whereas Alleyassin et al. [18], suggested that all schemes have the same result without complications.

2. Material and methods

The current research was a prospective clinic-laboratorial case – report study, that took place in the premises of the 2nd University Department of Obstetrics and Gynaecology, of the Aristotle University of Thessaloniki, at the Hippocrates's General Hospital of Thessaloniki, Greece. The patients were examined as inpatients or outpatients at the sonography department, and in laboratories of the Hospital or private laboratories, depending on the patients' choice, but in the same laboratory for each patient.

Seventy-two women of reproductive age have taken part in the study, during the preparation of the thesis. The required number, according to a biostatistics analyst, was at least 50 patients. They have been admitted due to secondary amenorrhea, positive β -hCG test, with or without vaginal bleeding. The participants took part voluntarily and were allocated in two groups. The first group consisted of 37 women, who were early, intrauterine pregnancies (control group). The second group consisted of 35 women, whose sonographic findings suggested ectopic pregnancy (all of them tubal pregnancies), and qualified for methotrexate treatment (study group). The single-dose protocol was used to most of them. Sonographic control and measurement of the vascularity indices (PI – RI) (Pulsatility index – Resistance index) of the ectopic pregnancy was conducted, measuring different vessels of the trophoblastic sac, in combination with β -hCG values for every admitted or outpatient woman (Pictures 2–6). All the sonographic and doppler measurements, have been conducted by the same sonographer, which was the PhD Researcher.

The parameters that were taken under control, were:

1. The patient's medical history,
2. Sonographic control, thus consecutive TVS, measurement of the sac, of the endometrial thickness, and the PI-RI,
3. Consecutive β -hCG levels according to the treatment protocol,
4. Blood tests according to the treatment protocol,
5. Routine check of vital signs and the clinical condition of the patients,

6. Pathological examination of possible histological specimens, in case of a Dilatation and Curetage (D&C) or surgical excision due to ectopic pregnancy rupture.

The study group was subdivided according to the β -hCG levels (raising, stable or dropping), and the methotrexate's dosage regime. All the participants were informed and gave a written and signed consent for their participation, as well as for the administration of Methotrexate (Picture 1). The collection and study of the data was conducted according to the 1964 World Medical Association (WMA) Declaration of Helsinki and its amendments [19]. No experimental procedure was performed on any patient. All the parameters and data were analyzed as following, and then were put in Microsoft Excel data sheets. SPSS v.24 was the used software. For normality control, we performed the Kolmogorov – Smirnov and Q-Q plots tests. For comparison of the quantitative variables, the chi-square test was applied, whereas for qualitative variables, we applied the One-way Analysis Of Variance (ANOVA), when the values were normally distributed. Linear regression was performed to determine whether the variables are related to the dependent variable, which ones have the greatest impact. Finally, the Pearson coefficient (in case of normal distribution) or Spearman coefficient (in case of non-normal distribution) were used for correlation between different variables [20].

The research was approved by the Bioethical Committee of the Aristotle University of Thessaloniki, and it took the following Greek National Registry of Clinical Trials: 2013–001258-24.

3. Results

During the current PhD thesis, we have developed the scientific approach an evaluated the change of the values of vascularity indices, in women of reproductive age, from the first day after the administration of Methotrexate due to Ectopic Pregnancy, till their final reduction, alongside the β -hCG values and the size of the sac. We started with the measurement of the pregnancy sac in 4 consecutive times of pregnancy (1st day of admission and methotrexate administration, 4th day, 7th day, 14th day) in the control and study groups, and we found growing sac sizes in women with endometrial pregnancies, whereas we had more stable or dropping sizes of sac in ectopic pregnancies after methotrexate. The growth of the GS (gestational sac) had almost linear correlation with the progress of a normal pregnancy.

The values of the β -hCG levels were significantly higher in women of the control group, compared to those of the study group. On the other hand, as the results have shown, higher values of β -hCG, do not necessarily lead to more methotrexate doses needed. We also observed, that, as expected, higher values of β -hCG, are associated with increased GS dimensions. We commenced, with the comparison of the total mean β -hCG values per day of count, both for the study as for the control group. We came up to a statistically significant result, which is easily explained, as in the study group, the values of β -hCG were dropping gradually, whereas in the control group they were raising. The endometrial thickness has been gradually dropping in the study group day by day, reaching up to 76 % drop, whereas significant but not statistically strong, has been the drop observed after single dose methotrexate.

Moreover, the PI and RI have been evaluated, taking in mind the flow velocity and the systolic/diastolic correlation. We came to a conclusion, that both in control (endometrial) group, as well as in study (ectopic) group, there have been no statistically significant drops between them. The PI, despite the fact that it is dropping in linear correlation with the β -hCG, is not statistically significant correlated with the β -hCG (p-value= 0,2256), as the RI. We have to annotate, that in the study group, methotrexate therapy showed to be quite effective, since its effectiveness was higher than 80 %, whereas the β -hCG values showed to have a strong significant correlation with those of the RI (p-value: 0,0001 (<0,05)) (Table 1). Therefore, if the null hypothesis is to have no changes in PI-RI values in comparison to the β -hCG, the sac diameter and



ΔΗΛΩΣΗ ΣΥΓΚΑΤΑΘΕΣΗΣ ΣΕ ΙΑΤΡΙΚΗ ΠΡΑΞΗ

1. Η υπογεγραμμένη _____
 Διεύθυνση _____
 Τηλέφωνο _____
 (σε περίπτωση ανικάνου προς δικαιοπρακτική δήλωση ασθενή, αναφέρεται το όνομα του κατά νόμο εκπροσώπου αυτού)
 Δίνω μετά από πλήρη ενημέρωσή μου, τη συγκατάθεση μου για την εφαρμογή των ακόλουθων ιατρικών πράξεων:
ΦΑΡΜΑΚΕΥΤΙΚΗ ΑΝΤΙΜΕΤΩΠΙΣΗ ΕΚΤΟΠΗΣ ΚΥΗΣΗΣ ΜΕ ΜΕΘΟΤΡΕΞΑΤΗ.

2. Ο ιατρός μου εξήγησε τα ακόλουθα:
 - α. Το είδος και το σκοπό της ιατρικής πράξεως που σε γενικές γραμμές είναι:
ΕΝΔΟΜΥΙΚΗ ΧΟΡΗΓΗΣΗ ΜΕΘΟΤΡΕΞΑΤΗΣ, ΠΛΗΡΩΝΤΑΣ ΤΑ ΚΡΙΤΗΡΙΑ ΧΟΡΗΓΗΣΗΣ.

 - β. Τους ενδεχόμενους κινδύνους που συνεπάγεται αυτή η ιατρική πράξη.
ΚΟΙΛΙΑΚΟ ΑΛΓΟΣ, ΟΡΟΓΟΝΙΤΙΔΑ (ΞΗΡΟΣΤΟΜΙΑ, ΞΗΡΟΦΘΑΛΜΙΑ, ΒΗΧΑΣ, ΔΥΣΠΝΟΙΑ, ΦΩΤΟΕΥΑΙΣΘΗΣΙΑ), ΛΕΥΚΟΠΕΝΙΑ, ΑΝΑΙΜΙΑ, ΑΛΩΠΕΚΙΑ, ΠΘΑΝΗ ΤΕΡΑΤΟΓΟΝΟΣ ΔΡΑΣΗ ΣΕ ΚΥΗΣΗ, ΠΘΑΝΗ ΑΠΟΤΥΧΙΑ ΤΗΣ ΜΕΘΟΔΟΥ.

 - γ. Τους εναλλακτικούς τρόπους θεραπείας.
ΧΕΙΡΟΥΡΓΙΚΗ ΑΝΤΙΜΕΤΩΠΙΣΗ ΜΕ ΛΑΠΑΡΟΤΟΜΙΑ Η ΛΑΠΑΡΟΣΚΟΠΗΣΗ.

3. Αποδέχομαι ότι κατά τη διάρκεια της πράξεως, απρόβλεπτες καταστάσεις μπορεί να απαιτήσουν επιπρόσθετη ή διαφορετική διαδικασία από αυτήν που μου εκτέθηκε παραπάνω. Για αυτό δίνω τη συγκατάθεσή μου και ζητώ όπως ο ιατρός και οι συνεργάτες αυτού εκτελέσουν όλες τις ιατρικές πράξεις που θα κρίνουν αυτοί αναγκαίες. Αυτή η συγκατάθεση περιλαμβάνει οποιοσδήποτε καταστάσεις γνωστές, άγνωστες, προβλέψιμες ή απρόβλεπτες στον ιατρό κατά το χρόνο ενάρξεως της ιατρικής πράξεως.

4. Συναινώ στην είσοδο παρατηρητών στο χώρο όπου πρόκειται να γίνει η ιατρική πράξη, για σκοπούς επιστημονικούς ή εκπαιδευτικούς.

5. Αναγνωρίζω ότι η Β' Μαιευτική – Γυναικολογική Κλινική του Α.Π.Θ. στο Γ.Ν.Θ. Ιπποκράτειο, μπορεί κατά τη δική της εκτίμηση να διατηρήσει και να χρησιμοποιήσει ΑΝΩΝΥΜΑ για επιστημονική έρευνα ή εκπαιδευτικούς λόγους, ή να εκθέσει οποιοδήποτε υλικό ή ιστούς τα οποία προέρχονται από το σώμα μου κατά τη διάρκεια νοσηλείας μου.

Υπογραφή ασθενούς

Ημερομηνία

Ωρα

Picture 1. Consent form given to every participant for them to sign, informing them on the use of methotrexate, and participation in the research.



Picture 2. Transvaginal axial image of the right ovary, with the ectopic pregnancy sac, day 1, right before the methotrexate administration.



Picture 4. Transvaginal axial image of the right ovary, with the ectopic pregnancy sac, day 14 after the methotrexate administration.



Picture 3. Transvaginal color Doppler image, measuring the vascularity indices in the ectopic pregnancy, day 1, right before the methotrexate administration.



Picture 5. Transvaginal color Doppler image, measuring the vascularity indices in the ectopic pregnancy, day 14 after the methotrexate administration.

the endometrial thickness, the hypothesis is rejected. Thus, the study hypothesis is confirmed since there have been correlated changes.

To sum up, the total estimate of the ectopic pregnancy patient's course after methotrexate injection, by measuring the PI and RI has provided a new aspect. PI-RI are two new values to be measured, as till now, all the research suggested measuring only β -hCG alongside the diameter of the sac and the patient's symptoms, in order to evaluate the follow-up of ectopic pregnancies treated with methotrexate.

4. Conclusion

As mentioned, this research has evaluated the changes of the vascularity indices from the first day of methotrexate treatment, till the final drop of their minimum values, in correlation with the β -hCG values, and the decrease of the sac. The aim was to use these results as evaluation criteria for the follow-up of medically treated ectopic pregnancy. The research sample might be small but has been a representative subject and the results have shown important conclusions for future use. The results showed that the single dose has been slightly more effective,

which agrees with other research, as those of Kilic et al. [21] and Klausner et al. [22]. The values of β -hCG between 4th and 7th day after methotrexate administration, seemed to have a crucial role in the efficacy of the treatment, as it has been more subjective for all regimes.

As far as the vascularity indices, have been evaluated, and even though their absolute values did not give statistically significant differences, there has been an important drop during the treatment. PI and RI are widely used for the fetal monitoring, as Maulik has stated at 2000 [23]. In normal pregnancies, they show a gradual drop from the beginning of the pregnancy till the term. When the vascularity differs from the regular, the possibility of a bad perinatal outcome is rising. The values of both indices have shown a drop during the treatment, and we have to note out, that the comparison of RI with β -hCG levels, showed a statistically significant correlation, which means that the vascularity indices, and especially the RI, can be considered as predictive indices of the efficacy of methotrexate treatment. It is the first time that such a correlation has been observed.

Therefore, a future aim could be to perform larger sample researches, consisting of women with different demographic characteristics and



Picture 6. Transvaginal axial image of the right ovary, with the ectopic pregnancy sac disappeared, day 26 after the methotrexate administration.

Table 1

Comparison of the RI (Resistance Index) of the ectopic pregnancy, to the β -hCG values, showing a strong correlation, as p-value: 0,0001 (<0,05).

z for 95 % CI = 1,96				
Invalid: 0				
Cases-N: 70				
r (var1.var2) = 0,4472				
p = 0,0001				
E(var2) = 2,117(se = 0,419)+ 801,04(0)*var1				
Anova Table				
Source	Σ of Sq.	%	Mean Σ -Sq	df
Explained	160,22	20	160,22	1
Unexplained	640,81	80	9,4237	68
Total	801,04	100 %		69
F-Value: 17,002; p-value: 0,0001				
Residual standard error: 25,314				

clinical data, and large observational studies, in order to conclude more safely if the vascularity indices can be used, alongside the β -hCG levels and the dimensions of the ectopic sac, as evaluation criteria for the efficacy of methotrexate as a medical treatment for ectopic pregnancies.

CRedit authorship contribution statement

Themistoklis Mikos: Validation, Data curation. **Angelos Daniilidis:** Supervision, Project administration, Formal analysis. **Menelaos Zafarakas:** Validation, Software, Resources. **Dimitrios Chitzios:** Writing – original draft, Investigation, Conceptualization. **Dimitrios Balaouras:** Methodology, Investigation, Formal analysis. **Panayiota Papasozomenou:** Writing – review & editing, Data curation. **Georgios Balaouras:** Writing – original draft, Validation, Investigation.

Declaration of Competing Interest

The authors hereby declare NONE conflict whatsoever.

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