

Retrospective study on 43 patients with diagnosis of ectopic pregnancy

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SUMMARY: Retrospective study on 43 patients with diagnosis of ectopic pregnancy.

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Aim. This study aims at outlining the parameters of eligibility to lean toward conservative treatment rather than surgery in case of diagnosis of GEU.

Materials and methods. We retrospectively analyzed the data of 43 patients hospitalized at our facility between January 1, 2010 and June 30, 2012 with a diagnosis of GEU. We divided our sample into six groups: patients who underwent surgery within the first 24 h (A), and after the first 24 h (B), treated with methotrexate with positive results (C) and without success (D), and treated with watchful waiting with spontaneous resolution (E) or followed by surgery (F). Descriptive statistics methods were used, and also χ^2 (Chi-square) and analysis of variance.

A transvaginal transducer of 7.5 MHz was used for ultrasound examination. The analyzed parameters were values of beta-hCG, adnexal mass, endometrial thickness and presence and extent of Douglas pouch fluid.

Results. Considering the percentage of patients in groups C+E, conservative treatment was possible in 11 patients (25.5%), 4 patients of group C and 7 of group E. Watchful waiting has been successful in 87.5%. Instead, medical therapy has been successful in 57.1% of cases.

Conclusions. Therefore we propose a thorough laboratory (beta-hCG < 3000 mIU/ml) and ultrasonographic (adnexal mass < 3.5 cm) evaluation, always considering the clinical context of the patient in question.

Beta-hCG < 600 mIU/ml, associated with stable clinical condition of the patients, can direct to watchful waiting (laboratory and ultrasound monitoring).

Beta-hCG < 3000 mIU/ml, adnexal mass < 3.5 cm, patient in stable conditions and absence of heart rate have been proved to be good cut-off to direct the patient towards a conservative choice (treatment with Methotrexate) rather than invasive (surgery).

RIASSUNTO: Studio retrospettivo su 43 pazienti con diagnosi di gravidanza extrauterina.

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Scopo. Questo studio ha come scopo la delineazione di parametri di eleggibilità per propendere verso un trattamento conservativo piuttosto che chirurgico in caso di diagnosi di gravidanza extrauterina (GEU).

Materiali e metodi. Abbiamo analizzato retrospettivamente i dati relativi a 43 pazienti ricoverate presso la nostra struttura tra il 1° gennaio 2010 e il 30 giugno 2012 con diagnosi di GEU. Le abbiamo divise in sei gruppi: pazienti sottoposte a intervento chirurgico entro le prime 24h (A), e dopo le prime 24h (B), trattate con methotrexate con esiti positivi (C) e senza esiti positivi (D), e sottoposte a condotta di attesa con risoluzione spontanea (E) o seguita da intervento chirurgico (F). Per tale studio sono stati utilizzati metodi di statistica descrittiva. È stato eseguito il χ^2 (CHI-quadro) e l'analisi della varianza. Per l'esame ecografico è stato utilizzato un trasduttore transvaginale da 7.5 Mhz. I parametri analizzati sono stati i valori di beta-hCG, la massa annessiale, lo spessore endometriale e la presenza e l'entità di falda liquida nel cavo del Douglas.

Risultati. Considerando la percentuale di pazienti dei gruppi C+E, il trattamento conservativo è stato possibile in 11 pazienti (25.5%), 4 pazienti del gruppo C e 7 del gruppo E. La condotta di attesa ha avuto successo nell'87.5% dei casi. Invece, la terapia medica ha avuto successo nel 57.1% dei casi.

Conclusioni. Proponiamo dunque un'attenta valutazione laboratoristica (beta-hCG < 3000 mIU/ml) ed ecografica (massa annessiale < 3.5 cm), che però vada contestualizzata alla situazione clinica della paziente in esame.

Un valore di beta-hCG < 600 mIU/ml, associato a condizioni cliniche stabili della paziente, indirizza, indubbiamente, verso una condotta di attesa (monitoraggio laboratoristico ed ecografico).

Valori di beta-hCG < 3000 mIU/ml, massa annessiale < 3.5 cm, condizioni stabili della paziente e assenza di battito cardiaco si sono rivelati dei buoni cut-off per indirizzare la paziente verso una scelta conservativa (trattamento con methotrexate) piuttosto che invasiva (chirurgia).

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Finally, Beta-hCG > 3000 mIU/ml and presence of adnexal mass > 3.5 cm as well as presence of fetal heart rate and patient in critical clinical conditions require an emergency surgical approach.

Infine, valori di beta-hCG > 3000 mIU/ml e presenza di massa annessiale > 3.5 cm oltre che presenza di battito cardiaco fetale e condizioni cliniche critiche della paziente impongono un trattamento chirurgico d'urgenza.

KEY WORDS: Extrauterine pregnancy - Methotrexate - Adnexal mass - Beta-hCG.
Gravidanza extrauterina - Methotrexate - Massa annessiale - Beta-hCG.

Introduction

Ectopic pregnancy (GEU) means the implantation of the gestational sac outside the uterine cavity. More correctly, when the ectopic implantation occurs outside the uterus is called ectopic pregnancy (tubal pregnancy, ovarian pregnancy, primitive abdominal pregnancy); when the implantation occurs within the confines of the uterus but in an improper site, it names, depending on the case, angular pregnancy (implantation at tubaric corner level) and cervical pregnancy (implantation into the cervical canal).

The annual incidence is 16 cases out of 10,000 with a decreasing trend in the last three decades (1).

Ectopic pregnancy (GEU) is an obstetric emergency of great importance, which early diagnosis is crucial in both therapy and prognosis. The diagnosis of an ectopic pregnancy is based on clinical and instrumental procedures (β -hCG dosage, steroids dosage, transvaginal ultrasound).

The clinical objectivity of ectopic pregnancies can be very variable going from asymptomatic to acute abdomen with hemodynamic shock. The initial symptoms typically occurs with the combination of pelvic pain and menstrual abnormalities; abdominal pain is present in over 90% of cases even in the absence of tubal rupture. Metrorrhagia is present in approximately 50-80% of cases.

β -hCG is detectable in serum from the 8th day after fecundation.

The values of serum β -hCG, however, are lower in GEU than in normally implanted pregnancies, although about 20% of GEU presents a rate of β -hCG normal for the gestational age. In 93% of GEU, the increase of β -hCG serum title is less than 66% after 48 h.

The transvaginal ultrasound with standard 5-MHz probe becomes essential in diagnosis of its location, providing high-resolution images of uterus (endometrial thickness, gestational pseudosac), adnexal bodies and Douglas pouch (fluid presence). An expert sonographer should be able to identify all intrauterine pregnancies in regular evolution with transvaginal ultrasound when β -hCG is > 1000-1800 mIU/ml, the so-called "discriminatory zone" (2, 3).

In presence of β -hCG greater than 3000 mIU/ml, non-displaying the gestational sac in uterus is extremely suggestive for GEU, pointing out that the threshold expressed by these values lose credibility in case of multiple pregnancies.

When it is possible to determine with good reliability conceptional age, this has a correlation with ultrasound better than the correlation between β -hCG and ultrasound, assuming then clinical relevance. A recent survey showed that only 53% of the GEU are diagnosed at the time of first obstetric consultation. Of these, 60% are already in an advanced stage with urgency. Consequently, the choice of type of treatment depends greatly on the timeliness of diagnosis. To date, treatment may be surgical, medical with methotrexate administration, or watchful waiting, and the choice obviously depends on patients clinical condition as well as position and characteristics of the gestational body (4-11).

Our study is based on identification of limits within it may be feasible a watchful waiting or a medical therapy rather than surgical treatment.

Materials and methods

For our study were retrospectively evaluated patients with diagnosis of ectopic pregnancy, which came to our obstetric emergency center and were later hospitalized, during the period between January 1, 2010 and June 30, 2012, for a total of 43 patients. Of these 43 GEU, in 40 cases it was a tubal pregnancy, in 1 case an angular pregnancy, and in 2 other cases ovarian pregnancies. Diagnosis of ectopic pregnancy was set on the basis of clinical (pelvic pain, Douglas pouch fluid, ultrasound images suspicious for GEU) and biochemical (dosage of β -hCG) criteria. We obtained data on patients and their medical conditions by accessing medical records.

We collected data on age, parity and personal history, with particular reference to the presence of multiple abortions, previous ectopic pregnancies, previous abdominal surgery.

The patients were analyzed by evaluating symptoms present at diagnosis, gestational age, β -hCG

levels, ultrasonographic findings and subsequent treatment undertaken based on these parameters. The sample was divided into 6 groups: patients candidated for surgery within the first 24 h after diagnosis (GROUP A), patients who underwent surgery after the first 24h after diagnosis (GROUP B), patients who had undergone successful treatment with methotrexate (GROUP C), patients in whom treatment with methotrexate has not been successful (GROUP D), patients candidated to watchful waiting that ended with a spontaneous resolution of GEU (GROUP E), patients treated surgically after a watchful waiting not resolved successfully (meaning success a decrease of β -hCG to below 100 mIU/ml). Descriptive statistics methods were used, and also χ^2 (Chi-square) and analysis of variance. A transvaginal transducer of 7.5 MHz was used for ultrasound examination.

Results

The average age of the 43 patients observed was 33 years with a range between 21 and 45 years. The gestational age, determined by history, was 6w + 4d with a range from 5w + 2d to 9w + 6d. Six patients had a history of previous ectopic pregnancy. Of these, 3 had spontaneous resolution and 3 were treated in videola-

paroscopy (2 salpingectomies and 1 salpingotomy). Patients who had a history of previous abdominal surgery were 19.

Of the 43 patients studied, 3 had received their pregnancy with assisted reproduction techniques, and 5 patients had a history of multiple abortions.

On arrival to the emergency room 37 patients showed pelvic pain and metrorrhagia, 4 patients had typical symptoms of acute abdomen accompanied by hypovolemic shock, while 2 patients did not show any symptoms, but they had a positive pregnancy test (Gravindex / β -hCG serum) beyond the normal limits. Twenty-five patients had a positive test of the β -hCG in serum or urine done before admission (Fig. 1).

We took into account for the choice of treatment, biochemical parameters (β -hCG and hemoglobin) and ultrasonographic findings such as endometrial thickness, presence of Douglas pouch fluid and adnexal mass.

A pseudocamera was detected by ultrasound in 3 of 43 observed patients.

Patients treated with surgery were 28, including 18 treated with immediate intervention (GROUP A) and 10 with surgery performed after the first 24 hours of observation (GROUP B).

The treatment with methotrexate was adopted in 7 patients: 6 patients with single dose treatment and 1

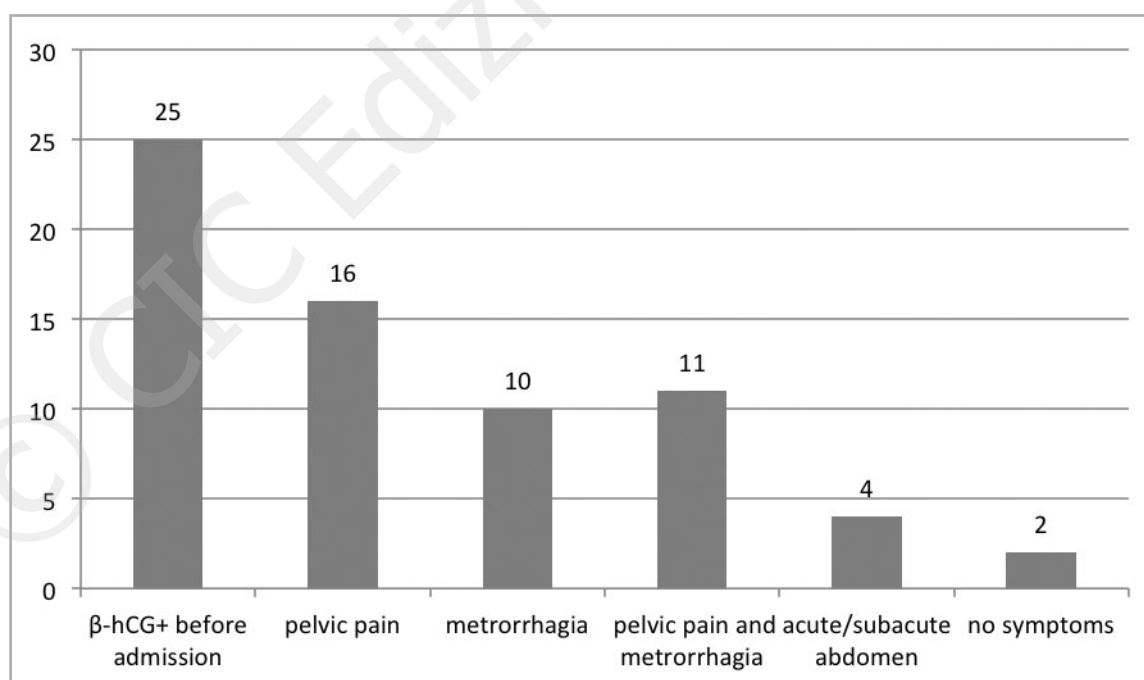


Fig. 1 - Clinical presentation of patients with GEU.

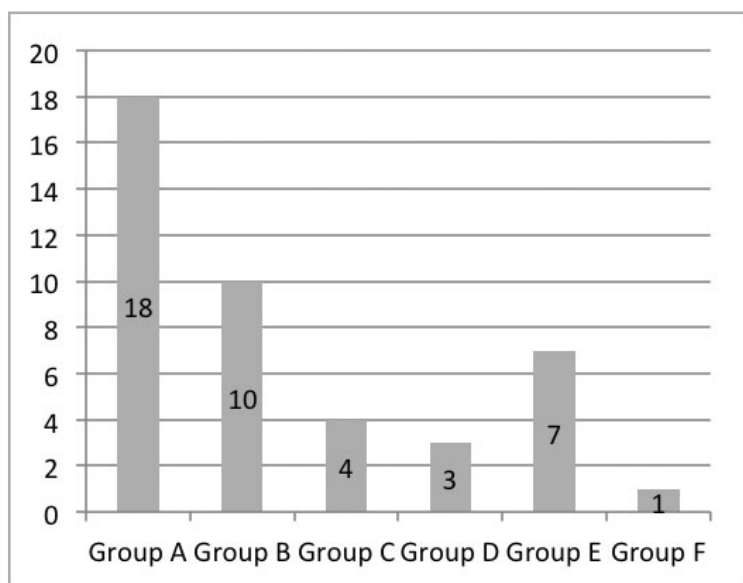


Fig. 2 - Groups.

patient with a subsequent administration 7 days after (administration schedule in variable dosage).

In 4 patients, medical therapy had been successfully applied (GROUP C).

In the others 3 cases, medical therapy had not yielded positive results (GROUP D) or an acute symptomatology arose and then had gone to surgery (2 laparoscopic salpingectomies and 1 laparotomy with angular resection).

Eight patients were candidates for conservative treatment, 7 of which resolved successfully (GROUP E) and 1 instead with unsuccessful result, that resolved after laparoscopic salpingectomy (GROUP F) (Fig. 2).

In total, surgical treatment, was it immediate, delayed, or after therapy with methotrexate or watchful waiting, had been necessary for 32 patients.

Discussion

In the past, the treatment of an ectopic pregnancy was predominantly surgical.

At present, an important alternative is represented by medical or conservative treatments of GEU, which have the considerable advantage of avoiding invasive surgical treatments and to preserve the reproductive physiology of a woman.

International guidelines indicate as risk factors for GEU, a previous abdominal surgery or a previous GEU. Our data agree with guidelines, having abdominal surgery a confirmation percentage of 44.1% (19/43) and a previous ectopic pregnancy a confirmation percentage of 13.9% (6/43).

The conservative treatment was possible in 11 patients (25.5%), 4 patients of group C and 7 of group E.

The watchful waiting was successful in 87.5% (Fig. 3).

Medical therapy was successful in 57.1% of cases (Fig. 4) (12-14).

It remains to define what are the criteria to candidate some patients to a particular therapeutic approach rather than another.

As already described in literature, we can refer to β -hCG levels to predict failure or success of conservative treatment.

Analyzing the data of our study, it shows that patients who had undergone immediate surgery had β -hCG significantly higher than those treated conservatively with watchful waiting (4105.4 mIU/ml compared to 444.5 mIU/ml) (Fig. 5).

If we analyze data reported in literature, the failure rates in conservative treatment with methotrexate proved to be higher if this type of treatment is reserved to patients who have higher β -hCG levels (15).

On the basis of these considerations, it has been proposed a cut-off value of β -hCG to identify all those patients who may be candidate to watchful waiting or to conservative treatment. From data of our study, the value of β -hCG proposable for watchful waiting is 600 mIU/ml.

In fact, considering the group E + F, where watchful waiting was provided, 6 patients (75%) had a value of β -hCG less than this cut-off.

For patients undergoing therapy with methotrexate (GROUP C + D) the value of β -hCG fell below that cut-off in only 1 patient (14.28%) and in those

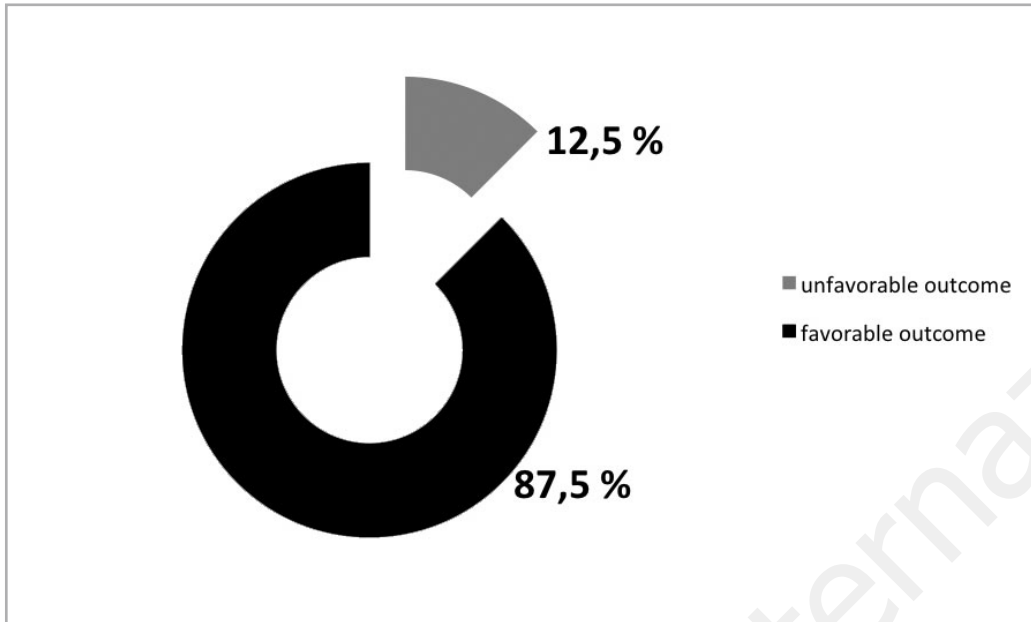


Fig. 3 - Watchful waiting percentage results.

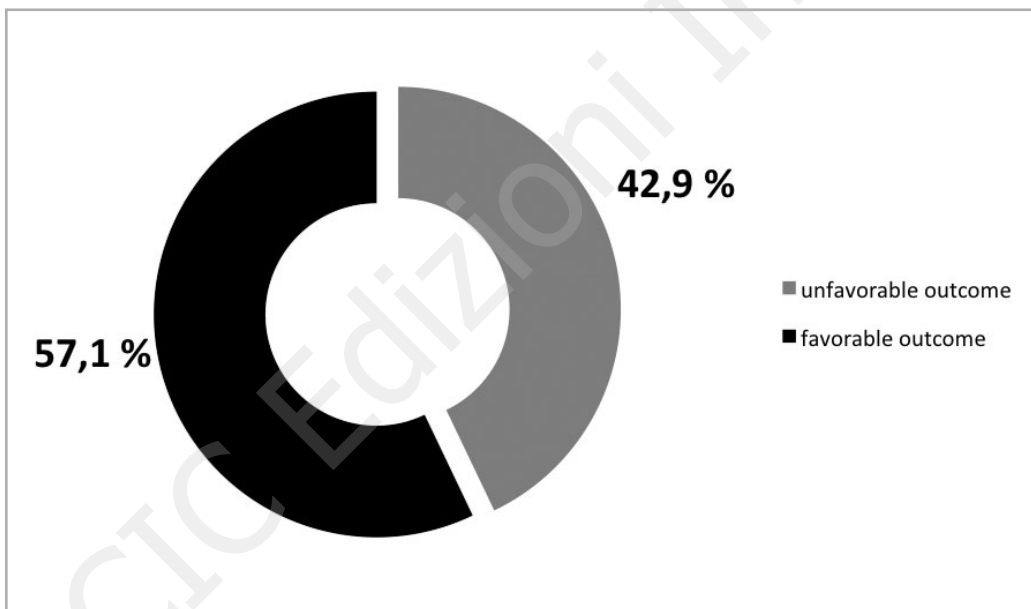


Fig. 4 - Medical therapy percentage results.

who had undergone surgical treatment, the value of β -hCG fell below this cut-off in 4 cases out of 28 (14.28%). One of these latter cases (3.5%) was a patient, who for ultrasonographic findings and laboratory had not been immediately addressed to surgical management (GROUP B).

With regard to treatment with methotrexate, Menon and Collins (16) in an important review in 2007, reported a safety threshold value of β -hCG of

5000 mIU/ml, whereas Royal College of Obstetricians and Gynecologists (RCOG) guidelines of 2004 set this limit to 3000 mIU/ml (17). A study carried out in 2009 (18) indicates as limit for a successful medical therapy 1800 mIU/ml.

In our study, patients treated successfully with methotrexate had a median value of β -hCG equal to 2515 mIU/ml (GROUP C), while those that had been treated with methotrexate but without success (GROUP

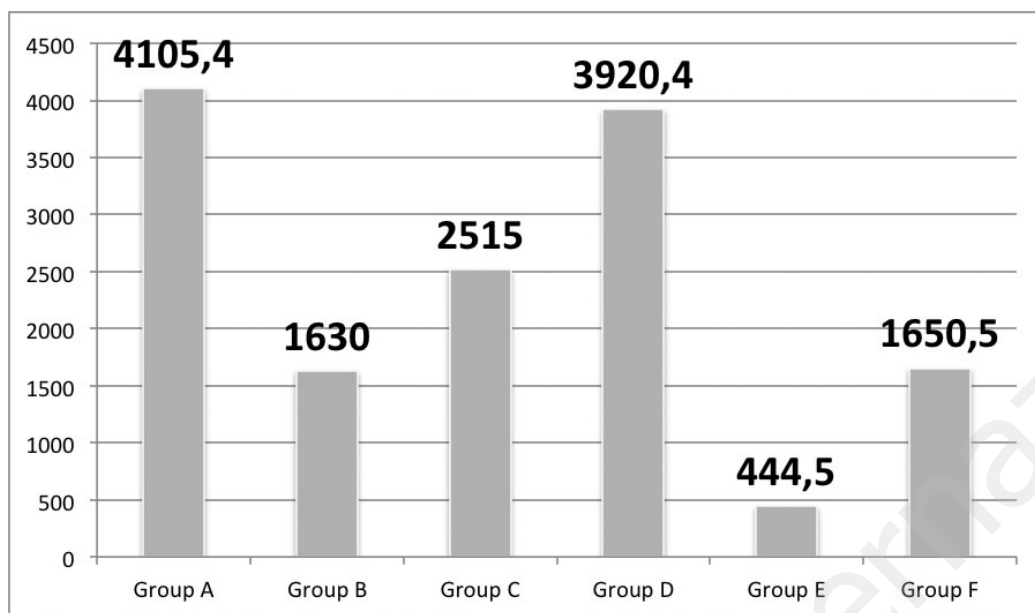


Fig. 5 - Median β -hCG value in different groups.

D) had a median value of β -hCG equal to 3920 mIU/ml (Fig. 5).

Therefore, we can consider as reference value to candidate patients to treatment with methotrexate a value of B-hCG equal to 3000 mIU/ml.

As regards the presence of Douglas pouch fluid, the incidence of patients, in which was observed, ranged from 33% to 100% in different groups, without any correlation with the severity of the clinical status of the patients. So, this parameter cannot be considered useful for therapeutic counselling.

Evaluating the ultrasound data, also, it has emerged as endometrial thickness cannot be used to direct patients towards surgical treatment rather than conservative, because the range of endometrial thickness is found to be extremely variable both in the group of patients treated conservatively than in those undergoing surgical treatment.

Finally, with regard to the ultrasound evaluation of adnexal mass, from the data at our disposal, which confirm those found in literature, you can say that the diameter of this mass equal to or less than 3.5 cm can lead towards watchful waiting or treatment with methotrexate, provided that there are no signs of tubal rupture or hemodynamic imbalance, that there is no embryonal cardiac activity and that patients are clinically stable.

In fact, of 3 patients who had been candidated for methotrexate but without success (GROUP D) and then treated surgically, 2 (66%) had a adnexal mass greater than 3.5 cm. Even the patient in which

there had been failure of watchful waiting (GROUP F) had an adnexal mass greater than 3.5 cm. Of patients who underwent surgery within or after 24 h since diagnosis, 26 (92%) had an adnexal mass greater than 5 cm. No patient candidated for treatment with methotrexate which resolved successfully, and no patients in whom watchful waiting resolved successfully, had an adnexal mass greater than 3.5 cm (Fig. 6) (Table 1).

Conclusions

Analyzing data retrospectively collected regarding values of β -hCG, presence of Douglas pouch fluid, endometrial thickness and diameter of adnexal mass, we can conclude by proposing a thorough laboratory (β -hCG < 3000mUI/ml) and ultrasound (adnexal mass < 3.5 cm) evaluation, but that should be contextualised to the clinical status of the patient in question.

A value of β -hCG < 600 mIU/ml, associated with stable clinical condition, direct, no doubt, to watchful waiting (laboratory and ultrasound monitoring).

Values of β -hCG < 3000 mIU/ml, adnexal mass < 3.5 cm, stable clinical conditions and absence of heart rate have proved to be good cut-off to direct the patient towards a conservative choice (treatment with Methotrexate) rather than invasive (surgery).

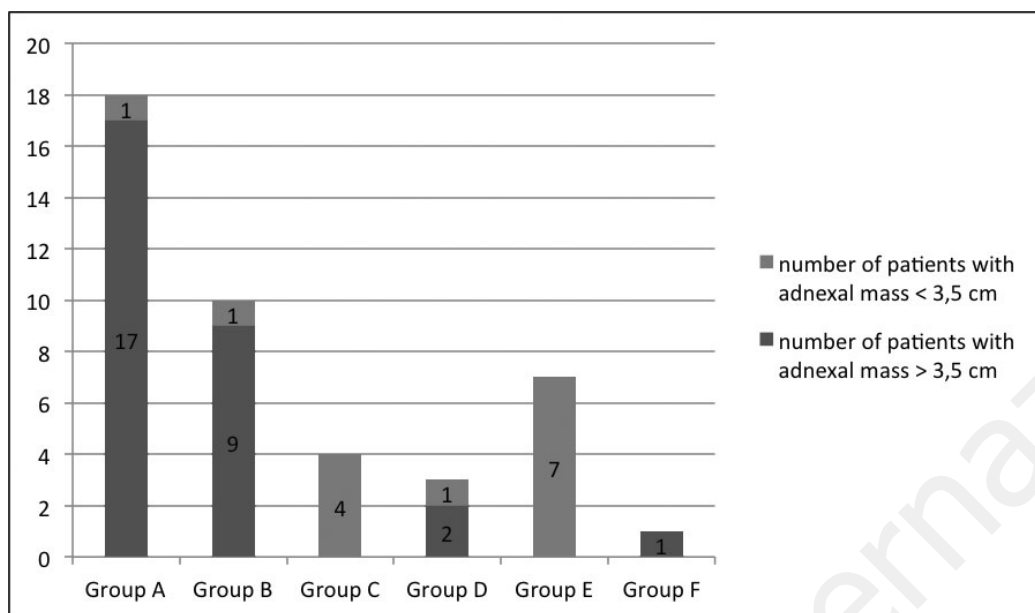


Fig. 6 - Adnexal mass dimension in different groups of treatment.

TABLE 1 - BIOCHEMICAL AND ULTRASOUND PARAMETERS.

	Group A	Group B	Group C	Group D	Group E	Group F
β -hCG (mUI/ml)						
• Median	4105,4	1630	2515	3920,4	444,5	1650,5
• Range	244-178296	52-25380	1175-5318	571-16733	0,44-1580	
Endometrial thickness (mm)						
• Median	9	13	8	9	8	3.9
• Range	2-21	6-25	4-18	5-19	2-19	
Douglas pouch fluid (pts)	7(38.8%)	6 (60%)	2 (50%)	1 (33,3%)	4 (57,1%)	1 (100%)
Adnexal mass >3,5 cm (pto)	17 (94%)	9 (90%)	0	2 (66%)	0	1 (100%)

Otherwise, the presence of Douglas pouch fluid and endometrial thickness seem necessary but not sufficient to ensure positive outcome in case of conservative choice rather than surgical.

Finally, values of β -hCG > 3000 mIU/ml and adnexal mass > 3.5 cm, as well as presence of fetal heart rate and critical clinical conditions require a surgical emergency.

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