European Journal of Obstetrics & Gynecology and Reproductive Biology 236 (2019) 32–35

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Evaluation of a follow-up customized strategy for women treated with methotrexate for an ectopic pregnancy: An observational study

Magalie Barbier, Audrey Pivano, Claire Tourette, Sabine Poizac, Ludovic Cravello, Leon Boubli, Aubert Agostini*

Department of Gynaecology and Obstetrics, Conception University Hospital, 147 Boulevard Baille, 13005, Marseille, France

ARTICLE INFO

Article history:
Received 18 February 2019
Accepted 26 February 2019

Keywords:
Ectopic pregnancy
Methotrexate
Follow-Up strategy

ABSTRACT

Objective: To evaluate a follow-up customized strategy used in women treated with methotrexate for tubal ectopic pregnancy.
Study design: This observational monocentric study took place from November 2009 to December 2015 in the emergency unit at La Conception University Hospital in Marseille, France. 440 women were treated by methotrexate for tubal ectopic pregnancy. Women were assigned in a classic follow up protocol with a weekly hCG evaluation (conventional protocol) if the drop in hCG between D1 and D4 was inferior to 20% or in an alternative follow up (streamlined protocol) with a hCG evaluation at one month. The main outcome measures were the success rate, the proportion of women requiring several methotrexate injections, and the mean number of consultations per women and duration of the follow-up.
Results: During this period, the success rate was 348/440 (79.1%). The rate of women requiring 1, 2, or 3 injections and of women lost to follow-up were comparable between the two protocols. The mean number of consultations per woman was 3.6 ± 1.33 vs. 5.95 ± 2.25 days ($p < 0.0001$), and the follow-up was 27.5 ± 12 vs. 28.1 ± 15.4 ($p = 0.6$) respectively in the conventional protocol group and the streamlined.
Conclusion: Our customized strategy allows for a decrease in the number of consultations per woman without changing the success rate or the need for methotrexate injection. hCG count drop between D1 and D4 allows for the selection of a low-risk group that can benefit from appropriate aftercare.

Introduction

The treatment of ectopic pregnancy (EP) with methotrexate (MTX) is a first-line treatment that is inreasingly being used, attaining a rate of 27% in 2015 in the USA [1]. This treatment has a success rate of between 68 and 98%, depending on the initial level of choriogonadotrophic hormone (hCG) [2,3]. The protocol for follow-up that has been used, evaluated, and validated the most is the one described by Stovall and Lipscomb [4,5]. This is a single follow-up protocol that is applied to all women treated with MTX for a EP. Compliance is however low, depending on the study [6–8]. In order to determine the risk of failure during the follow-up of women with a EP treated by MTX, several authors have tried to evaluate the risk of failure as a function of the initial levels of hCG or the kinetics of hCG following the injection of MTX [2,3,9–15]. This evaluation of risk allows for selection of a population at high risk of failure for whom a conventional follow-up protocol is recommended and a population with a low risk for whom a more streamlined follow-up protocol can be considered. It would be interesting to evaluate this strategy of follow-up based on the risk of failure. Furthermore, the impact of implementing a selection of women into two groups (i.e. high risk and low risk) depending on the kinetics of hCG, with a different follow-up protocol according to the group (i.e. a conventional or a streamlined follow-up protocol) has not been evaluated relative to a conventional follow-up without selection of women. The aim of this study was to evaluate a strategy of follow-up based on the risk of failure ('customized strategy').

Materials and methods

This observational study took place from November 2009 to December 2015 at La Conception Hospital in Marseille, France. All women older than 18 years of age treated with MTX for an EP were included in this study after obtaining written informed consent. The Ethics Committee for Research in Obstetrics and Gynecology approved the study (CEROG 2009-030).

* Corresponding author.
E-mail addresses: magalie.barbier@ap-hm.fr (M. Barbier), Audrey.PIVANO@ap-hm.fr (A. Pivano), clairemarie.tourette@ap-hm.fr (C. Tourette), sabine.poizac@ap-hm.fr (S. Poizac), Ludovic.CRAVELLO@ap-hm.fr (L. Cravello), Leon.BOUBLI@ap-hm.fr (L. Boubli), aubert.agostini@ap-hm.fr (A. Agostini).

https://doi.org/10.1016/j.ejogrb.2019.02.037
0301-2115/

EP was diagnosed in women referred for pelvic pain, vaginal bleeding, or both, who met the following criteria: positive plasma hCG (a stable or rising plasma hCG level in separate measurements that were 48 h apart) with an empty uterus by sonography and other sonographic signs indicative of EP: an inhomogeneous adnexal mass, an empty gestational sac with a hyperechoic ring, or an extra uterine gestational sac containing a yolk sac or fetal pole with or without cardiac activity [16]. The indications for MTX treatment were: absence of embryonic cardiac activity detected by transvaginal ultrasonography, a plasma hCG level <5000 mIU/mL, EP < 4 cm in size as visualized by transvaginal ultrasonography, and the ability to participate in the follow-up. Contraindications for MTX treatment for EP were hepatic or renal failure, thrombopenia, anemia, or any suspicion of tubal rupture (e.g. hemodynamic instability, severe pain, or a large hemoperitoneum by ultrasonography).

The women received intramuscular MTX at a dose of 1 mg/kg. The day of injection was designated day 1 (D1) of the protocol. Women with non-tubal ectopic pregnancies and heterotopic pregnancies were excluded from the analysis.

If the drop in hCG between D1 and D4 was less than or equal to 20%, the women were assigned to the high-risk group and were monitored according to the conventional follow up protocol described by Stovall et al. [2,4]. Plasma hCG levels were measured on day 4 (D4) and day 7 (D7). If hCG levels decreased by ≥15% between D4 and D7, weekly monitoring continued until they fell below 15 mIU/mL. If they failed to decrease by 15% between D4 and D7 or between weekly hCG titers, the injection of MTX was repeated. After the second or third injection, hCG titers were followed using the same protocol with a new day 1 reading (D'1 or D''1). If they failed to fall appropriately after a total of three injections, the treatment was deemed to have failed, and surgical therapy was performed.

If the drop was more than 20%, the woman was assigned to the low risk group and they followed the streamlined protocol. In this protocol, the woman underwent a new hCG measurement at D28 without intermediate measurements. If at D28 the level was less than 15 mUI/mL, the treatment was deemed to be a success. If at D28 the level was more than 15 mUI/mL, it was compared to the theoretical values expected with a decrease of at least 15% at D7, D14, D21, and D28. If the level at D28 was higher than the expected theoretical level, a second injection of MTX was recommended with follow-up according to the conventional protocol, with the day of the second injection designated as D'1. If the level was less than the expected level, the woman underwent another measurement at D56. If the level at D56 was negative, the treatment was deemed to be a success, while if the level was still positive it was treated according to the same reasoning as the level of hCG at D28. This streamlined protocol was devised based on two prior studies from the same unit [11,17].

Women were informed prior to the administration of MTX of the need to have regular monitoring until a level of hCG < 15 mIU/mL and the need to consult in case of pain or if they felt unwell. Success of the medical treatment by MTX was defined as having achieved a level of hCG < 15 mUI/mL after 1, 2, or 3 injections of MTX. Failure of the medical treatment by MTX was defined as the need for surgical treatment for "suspected tubal rupture", or the absence of an "adequate decline in hCG levels after three injections", or the woman's refusal to undergo a second or third MTX injection. Women without a failure between D1 and D4 for whom the measurements of hCG at D1 were not available were excluded from the study.

We compared the mean age, the mean level of hCG at D1, the rate of EP treated by MTX, the success rate for the treatment with MTX, and the number of women lost to follow-up between the two protocols follow up.

Table 1
Distribution of the women between the conventional and the streamlined protocol.

Number of MTX[a] injections	Streamlined protocol n (%)	Conventional protocol n (%)	Odds ratio (OR)
1 injection			
Success rate	133 (89.9)	133 (76)	OR[b]: 6.56 [2.44; 22.21]
Failure rate	5 (3.4)	33 (18.9)	
Lost to follow-up	10 (6.7)	9 (5.1)	OR[c]: 1.34 [0.47; 3.85]
Total	148	175	
2 injections			
Success rate	2 (66.7)	75 (80.7)	OR[b]: 0.43 [0.02; 26,72]
Failure rate	1 (33.3)	16 (17.2)	
Lost to follow-up	0	2 (2.1)	OR[c]: NA
Total	3	93	
3 injections			
Success rate	0	5 (83.3)	NA
Failure rate	0	1 (16.7)	
Lost to follow-up	0	0	
Total	0	6	
Total			
Success rate	135 (89.4)	213 (77.7)	OR[b]: 5.26 [2.17; 15.44]
Failure rate	6 (4)	50 (18.2)	
Lost to follow-up	10 (6.6)	11 (4.1)	OR[c]: 1.69 [0.63; 4.5]
Total	151	274	

NA: Not assessable.
[a] MTX: methotrexate.
[b] Odds ratio women with success vs. women with failure.
[c] Odds ratio women lost to follow-up vs. the remainder of the women.

We compared the number of consultations per woman (i.e. the mean number of consultations per individual and the distribution of the women as a function of the number of consultations) between the two groups. Outcome for women according to the protocol that was followed initially (i.e. conventional or streamlined).

The quantitative variables were analyzed with the Student's *t*-test and the qualitative variables by the odds ratio with a 95% confidence interval or the Chi-squared and the Fisher's test, if needed, based on the context. The results were considered to be significant if $p < 0.05$.

Results

The number of EP treated by MTX over this period was 463/740 (62.6%). The mean age of the women was 30.6 ± 6.3 years and the level of hCG at D1 was 1,988 ± 1,986 (p = 0.12). The rates of women received one, two or three MTX injections were reported in Table 1.

Among the 440 women, there were 15 who experienced a failure prior to D4. Thus, there were 425 women who either had a conventional protocol (274 women (64.5%)) or a streamlined protocol (151 women (35.5%)) (Fig. 1). The outcomes for the women based on the protocol that was followed are shown in Table 1. The characteristics of follow-up were significantly different between the conventional protocol and the streamlined protocol (Table 2).

The causes for failures were a suspected rupture in 57/71 (80.3%), refusal of the 2nd or the 3rd injection in 13/71 (18.3%), and stagnation at the end of the three injections in 1/71 (1.4%). Concerning the causes of failures with the streamlined protocol, there were six surgical treatment for suspected ruptures that occurred between D4 and D7 for 5 women and at D38 for a woman who had two injections of MTX.

The mean number of consultations per woman was 3.6 ± 1.33 vs. 5.95 ± 2.25 days (p < 0.0001), and the follow-up was 27.5 ± 12

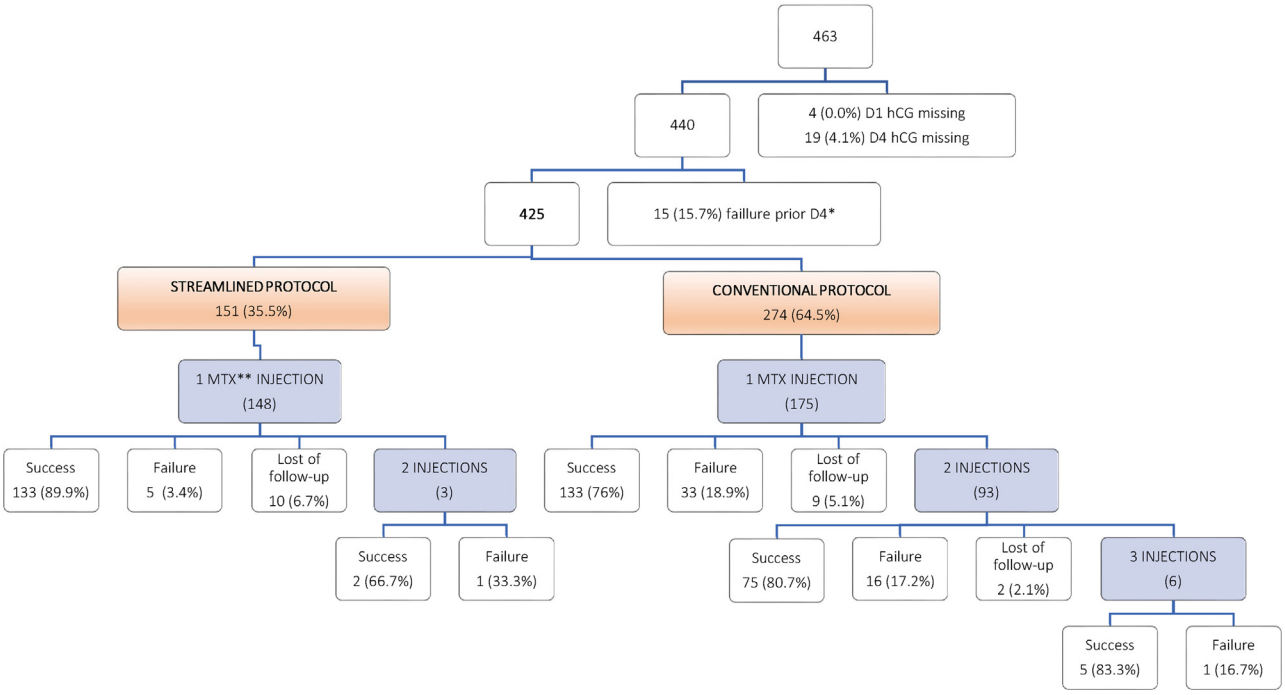

Fig. 1. Flowchart.
*Failure : surgical treatment.
**MTX : Methotrexate.

Table 2
Consultations number and follow up duration for the period according to the follow-up protocol.

Number of consultations (cs)	Streamlined protocol (N: 151)	Conventional protocol (N: 274)	Odds ratio (OR)
≤3	98 (64.9)	40 (14.6)	OR[a]: 10.69 [6.54 ; 17.8]
3 < cs≤5	40 (26.5)	93 (33.9)	
5 < cs≤9	12 (7.9)	121 (44.2)	
>9	1 (0.7)	20 (7.3)	

	Mean ± standard deviation	Mean ± standard deviation	p-value
Number of consultations per woman	3.6 ± 1.33	5.95 ± 2.25	<0.0001
Duration of the follow-up (days)	27.5 ± 12	28.1 ± 15.4	0.6

[a] Odds ratio women with n < 3 vs. the remainder of the women.

vs. 28.1 ± 15.4 (p = 0.6) respectively in the conventional protocol group and the streamlined.

Discussion

The implementation of a customized strategy comprising conventional follow-up for a group at high risk and a streamlined follow-up for a group at low risk did not appear to alter the overall success rate, or the number of injections of MTX, or the number of women lost to follow-up. On the other hand, this strategy appears to allow for a reduction in the mean number of consultations per woman, as well as the number of women with more than three consultations, albeit with an increase in the mean duration of the follow-up.

We chose a threshold of 20% for the drop in hCG in light of a preliminary study of 129 women [11]. In this study, the receiver-operator curve was analyzed to assess the performance of the hCG index in discriminating between an EP treated successfully with a single dose of methotrexate and an EP requiring repeated administration of MTX or surgical treatment. The threshold of 20% corresponded with a sensitivity, specificity, PPV, and NPV of 0.6, 0.92, 0.97, and 0.35, respectively. These results were confirmed by an initial preliminary study comprising a small number of women followed with the customized strategy [17]. Although the treatment of women with MTX is standardized, there are probably several factors aside from hCG levels that vary from one team to the next that influence the success. Although the rate of no or slightly progressive EPs treated with MTX differs between teams, it does also influence the rate of success [18]. Thus, it is likely that the variation in the level of hCG between D1 and D4 is a factor that is predictive of success, although the quantitative value is probably different from one team to the next [19,20]. We have defined treatment success as negativation of the hCG with a single injection of MTX. With the aim of streamlining the follow-up, it seems relevant to define a population at high risk of success with a single injection. Indeed, a streamlined protocol for follow-up should allow for the selection of women who do not require more scheduled care (i.e. a second or third injection) or urgent treatment (surgery). The main risk of relying on the streamlined follow-up is

undertreatment of women who ultimately require a surgical treatment that could have been avoided by a second injection of MTX that would have been indicated by a measurement of hCG at D7. In our population monitored according to the streamlined protocol, there were six failures that required surgical treatment, of which five occurred prior to D7. For these five women, there was no risk of undertreatment given that the measurement at D7 would not have been done if they had been monitored according to the conventional protocol since the surgical treatment was carried out prior to this time. It is possible that for the sixth woman, who had a second injection of MTX at D28 only, the treatment might have been avoidable if a measurement at D7 had not indicated an earlier and perhaps more effective second injection. The number of women excluded due a lack of hCG measurements at D1 and/or D4 in the absence of failure between D1 and D4 was higher for the second period (OR: 3.13 [1.15 ; 10.67]). For these women, this was most often due to an error of the protocol, with a measurement at D3 or D5 instead of D4. In practice, they were monitored based on the assumption that the measurement had been taken at D4. However, for the present study, it was necessary to exclude them for the analyses that were carried out.

The use of this customized strategy allowed the population of women treated with MTX for an EP to be divided into a population at high risk of failure in 2/3 of the cases (64.5%) and a population with a low risk in a third of the cases (35.3%). Thus, this customized strategy allows for streamlined follow-up of a third of the women without affecting the rate of success. On the other hand, the mean duration of the follow-up until negativation was longer in case of a strategy based on the risk. This was probably due to the fact that the women at low risk who will probably negativate rapidly do not undergo measurement until D28, while with conventional follow-up the negativation would have been noticed sooner.

Conclusions

The implementation of a strategy according to the risk is beneficial for the woman. Indeed, depending on the risk, the follow-up is streamlined without there being an a priori risk of undertreatment by MTX that would increase the risk of surgical treatment. For the women at high risk, a closer level of follow-up allows for treatment in keeping with conventional treatment. For the women lost to follow-up, efforts to recontact them could be prioritized for the women at high risk. Lastly, in terms of the activity of the hospital unit, this customized strategy decreases the amount of care that is provided per woman undergoing treatment.

Disclosure of interests

The authors report no financial or commercial conflicts of interest.

Contribution to authorship

All authors had a role in the conception of the study. AA conceived the idea. MB, AP, CT and SB carried out data extraction. MB, AP, CT, SP, LC, LB and AA carried out the analysis. All carried out interpretation of the data, revised the article critically for intellectual content and approved the final draft for publication.

Ethics statement

This study obtained an ethical approval from the institutional review board of the French college of Obstetricians and Gynecologists, CEROG-2009-030.

Funding

This research has not been funded.

References

[1] Hsu JY, Chen L, Gumer AR, Tergas AI, Hou JY, Burke WM, et al. Disparities in the management of ectopic pregnancy. Am J Obstet Gynecol 2017;217(July (1)) 49.e1–49.e10.
[2] Lipscomb GH, McCord ML, Stovall TG, Huff G, Portera SG, Ling FW. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. N Engl J Med 1999;341(December (26)):1974–8.
[3] Menon S, Colins J, Barnhart KT. Establishing a human chorionic gonadotropin cutoff to guide methotrexate treatment of ectopic pregnancy: a systematic review. Fertil Steril 2007;87(March (3)):481–4.
[4] Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. Obstet Gynecol 1991;77(May (5)):754–7.
[5] Kirk E, Condous G, Van Calster B, Haider Z, Van Huffel S, Timmerman D, et al. A validation of the most commonly used protocol to predict the success of single-dose methotrexate in the treatment of ectopic pregnancy. Hum Reprod 2007;22(March (3)):858–63.
[6] Nelson AL, Adams Y, Nelson LE, LaHue AK. Ambulatory diagnosis and medical management of ectopic pregnancy in a public teaching hospital serving indigent women. Am J Obstet Gynecol 2003;188(June (6)):1541–50.
[7] Jaspan D, Giraldo-Isaza M, Dandolu V, Cohen AW. Compliance with methotrexate therapy for presumed ectopic pregnancy in an inner-city population. Fertil Steril 2010;94(August (3)):1122–4.
[8] Dueñas-Garcia OF, Young C, Mikhail M, Salafia C. Compliance with follow-up in an inner-city population treated with intramuscular methotrexate for suspected ectopic pregnancy. Int J Gynecol Obstet 2013;120(March (3)):254–6.
[9] Dudley PS, Carson SA. Characterizing ectopic pregnancies that rupture despite treatment with methotrexate. Fertil Steril 2004;82(5):5.
[10] Natale A, Candiani M, Barbieri M, Calia C, Odorizzi MP, Busacca M. Pre- and post-treatment patterns of human chorionic gonadotropin for early detection of persistence after a single dose of methotrexate for ectopic pregnancy. Eur J Obstet Gynecol Reprod Biol 2004;117(November (1)):87–92.
[11] Agostini A, Blanc K, Ronda I, Romain F, Capelle M, Blanc B. Prognostic value of human chorionic gonadotropin changes after methotrexate injection for ectopic pregnancy. Fertil Steril 2007;88(August (2)):504–6.
[12] Cohen A, Bibi G, Almog B, Tsafrir Z, Levin I. Second-dose methotrexate in ectopic pregnancies: the role of beta human chorionic gonadotropin. Fertil Steril 2014;102(Dec (6)):1646–9.
[13] Rabischong B, Tran X, Sleiman AA, Larraín D, Jaffeux P, Aublet-Cuvelier B, et al. Predictive factors of failure in management of ectopic pregnancy with single-dose methotrexate: a general population-based analysis from the Auvergne Register, France. Fertil Steril 2011;95(January (1)) 401-404.e1.
[14] Nguyen Q, Kapitz M, Downes K, Silva C. Are early human chorionic gonadotropin levels after methotrexate therapy a predictor of response in ectopic pregnancy? Am J Obstet Gynecol 2010;202(June (6)) 630.e1–630.e5.
[15] Girija S, Manjunath AP, Salahudin A, Jeyaseelan L, Gowri V, Abu-Heija A, et al. Role of day 4 HCG as an early predictor of success after methotrexate therapy for ectopic pregnancies. Eur J Obstet Gynecol Reprod Biol 2017;215 (August):230–3.
[16] Condous G, Okaro E, Khalid A, Lu C, Van Huffel S, Timmerman D, et al. The accuracy of transvaginal ultrasonography for the diagnosis of ectopic pregnancy prior to surgery. Hum Reprod 2005;20(May (5)):1404–9.
[17] Bottin P, Gnisci A, Crochet P, Butzbach P, Cravello L, Gamerre M, et al. Valeur pronostique de la cinétique précoce du taux d'hCG après injection de méthotrexate pour grossesse extra-utérine. Gynécologie Obstétrique Fertil 2014;42(January (1)):3–7.
[18] Levin I, Tsafrir Z, Sa'ar N, Lessing J, Avni A, Gamzu R, et al. "Watchful waiting" in ectopic pregnancies: a balance between reduced success rates and less methotrexate. Fertil Steril 2011;95(March (3)):1159–60.
[19] Crochet P, Agostini A. Prognostic value of human chorionic gonadotropin levels 4 days after a single dose of methotrexate for ectopic pregnancy: correspondence. BJOG Int J Obstet Gynaecol 2012;119(March (4)):506.
[20] Skubisz MM, Lee J, Wallace EM, Tong S. Decline in βhCG levels between days 0 and 4 after a single dose of methotrexate for ectopic pregnancy predicts treatment success: a retrospective cohort study. BJOG Int J Obstet Gynaecol 2011;118(13):1665–8.