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Medical Treatment of Ectopic Pregnancy in Douala: Indications, Results and Outcome

Traitement Médical de la Grossesse Ectopique à Douala : Indications Résultats et Évolution

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ABSTRACT

Introduction. Ectopic pregnancy is a serious gynaecological complication. Methotrexate is used to treat ectopic pregnancies. In Cameroon, surgery is the treatment of choice. We therefore studied the epidemiology, indications, outcome and success rate of medical treatment of ectopic pregnancy in three reference hospitals in Douala. **Materials and methods.** A five-year cross-sectional study was carried out in three hospitals in Douala from January 2018 to December 2022. All files presenting an unruptured ectopic pregnancy treated with methotrexate were recruited. Variables included sociodemographic, obstetric history, clinical presentation, paraclinical examinations and complications. Bivariate analysis was used to test the association between predictor variables and medical treatment success. **Results.** 66 participants received methotrexate as treatment for ectopic pregnancy. The average age was 30.05 ± 5.33 years and the gestational age was 49.88 ± 16.73 days. The most common clinical signs were pelvic pain, abnormal vaginal bleeding and amenorrhea (30.3 %). All patients had a pelvic ultrasound and b-hcg dosage. The prevalence of medical treatment was 13%, a success rate of 63.6 %. The age of the mother, the nulliparous woman, a primigravida, having a cumulative sexual partner, a gestational sac of 1 cm, beta-HCG <5000 miu/ml increased the chances of success of medical treatment. 18.2 % of adverse effects. **Conclusion.** Few ectopic pregnancies are treated medically. The effectiveness of the treatment is acceptable with few adverse effects.

RÉSUMÉ

Introduction. La grossesse extra-utérine est une complication gynécologique grave. Le méthotrexate est utilisé pour traiter les grossesses extra-utérines. Au Cameroun, la chirurgie est le traitement de choix. Nous avons étudié l'épidémiologie, les indications, l'issue et le taux de réussite du traitement médical de la grossesse extra-utérine dans trois hôpitaux de référence à Douala. **Matériels et méthodes.** Une étude transversale sur cinq ans a été réalisée dans trois hôpitaux de Douala de janvier 2018 à décembre 2022. Tous les dossiers présentant une grossesse extra-utérine non rompus traitées par méthotrexate ont été recrutés. Les variables comprenaient des variables socio-démographiques, les antécédents obstétricaux, la présentation clinique, les examens cliniques para cliniques et complications. Une analyse bivariée a été utilisée pour tester l'association entre les variables prédictives et le succès du traitement médical. **Résultats.** 66 participants ont reçu du méthotrexate comme traitement pour la grossesse extra-utérine. L'âge moyen était de 30,05 ± 5,33 ans et l'âge gestationnel de 49,88 ± 16,73 jours. Les signes cliniques les plus représentés étaient la douleur pelvienne, saignement vaginaux anormaux et aménorrhée (30,3 %). Toutes les patientes ont fait une échographie pelvienne et dosage de béta-HCG. La prévalence du traitement médicale était de 13%, un taux de réussite de 63,6 %. L'âge de la mère, la nullipare, une primigeste, avoir un partenaire sexuel cumulé, un sac gestationnel de 1 cm, béta-HCG <5000 mUI/ml augmentaient les chances de succès du traitement médical. 18,2 % des effets indésirables. **Conclusion.** Peu de grossesses extra-utérines sont traitées médicalement. L'efficacité du traitement est acceptable avec peu d'effets indésirables.

KEY MESSAGE

The prevalence of medical treatment was low (13%) in our study, while its success rate was high (63.6%).

INTRODUCTION

The blastocyst usually implants in the endometrial lining of the uterus after fertilisation and fallopian tube transit. Any other place is termed ectopic for implanting [1]. The incidence of ectopic pregnancy (EP) is currently rising globally, with an estimated 1-2% incidence in the USA. [2]. According to Olamijulo et al, the incidence of EP has tripled across Africa over the previous 30 years, with an incidence of 2.2% of EP in the Lagos University Teaching Hospital [3].

In Cameroon, studies revealed a 2.8% prevalence in 2020 at the Douala Laquintinie hospital and a 0.79% incidence at the Yaoundé University Teaching Hospital in 2000 [4; 5].

Tanaka et al. published the successful use of methotrexate in treating interstitial pregnancy in 1982. Since then, medicinal treatment for EP has established itself as a viable alternative to surgery [6].

In a Senegalese setting with limited resources, Ndour et al. reported a frequency of 6.8% for medical treatment of EP, with a success rate of 61.1% [7].

The success percentage of medical treatment according to Foumane et al.'s study on the use of minimally invasive or non-invasive treatment in the management of ectopic pregnancy at the Gyneco-Obstetrics and Pediatric Hospital of Yaoundé was 62.71% [8].

The fallopian tube is responsible for more than 95% of all ectopic pregnancies. [9].

All of the identified risk factors are maternal, including smoking, Chlamydia trachomatis infection, use of an intrauterine device (IUD) for contraception, use of assisted reproductive technologies (ARTs), prior abortions, and history of pelvic surgery. [10; 11].

Case mortality rates are reported between 1 and 3%, but are subject to bias due to frequent misdiagnosis [12]. In high-income nations, early diagnosis is frequently possible using ultrasound and serum levels of the human chorionic gonadotropin, whereas in low-income nations, getting the correct diagnosis is more challenging and relies mostly on history-taking and physical examination results.

The treatment option typically entails surgical intervention by a laparotomy or laparoscopy. It can also be treated medically or with expectant treatment [13]. Due to its effectiveness and minimal side effects, methotrexate is recommended over surgery for management [14; 15].

In Cameroon like many other low-income countries, numerous studies exist on the management of EP, but very few focused on the medical management. The purpose of this study therefore is to determine the prevalence, indications, success rate and outcomes of the medical treatment of EP.

METHODOLOGY

Study design

This was a cross sectional analytic and retrospective study.

Study period

This study was carried out over a period of five years from 1st January 2018 to the 31st December 2022.

Study duration

This research began from 12th November 2022 and ended on the 8th June 2023.

Study site

This study took place in the town of Douala in three reference Hospitals:

- The Douala Gynaeco-obstetrics and paediatrics Hospital (DGOPH);
- The Douala Laquintinie Hospital (DLH);
- The Douala General Hospital (DGH).

Study population and sampling

The target population in this study included files of patients who were diagnosed with EP in the DLH, DGOPH and DGH from January 2018 to December 2022.

Sampling method

Exhaustive consecutive sampling method was used.

Inclusion Criteria

Files of patients diagnosed with ectopic pregnancy.

Files of patients treated medically.

Exclusion Criteria

- Files of patients with ruptured ectopic pregnancy.
- Files of patients with heterotopic pregnancy.
- Files of patients with abdominal pregnancy.
- Files of patients loss to follow-up.

Study procedure

Ethical and Administrative Clearance

After approval of the protocol by the research panel of the Faculty of Medicine and Pharmaceutical Sciences Douala, ethical clearance was obtained from the Institutional Review Board of the Faculty of Medicine and Pharmaceutical Sciences, University of Douala.

Both the ethical clearance and the administrative approval documents was used to obtain an approval to carry out the study in the DLH, the DGOPH and the DGH.

Data collection

The files or registries of patients diagnosed with ectopic pregnancy and managed in the DLH, the DGOPH and the DGH were reviewed. After identification of patients in the registers, their files were retrieved from the achieves to fill questionnaires designed by the researcher and confirmed by a biostatistician. Data concerning epidemiology, demographics, relevant past history, risk factors of ectopic pregnancy, term of pregnancy, diagnostic methods, indication of treatment or management (medical), site effects and evolution.

- Independent variables: socio-demographic factors, social factors, gynaecological and obstetric factors.
  - Patient's socio-demographic data including: age, marital status, occupation, level of education, religion, residence and region of origin.
  - gynaecological and obstetrical history including; gravidity, parity, age of first coitus, STIs, use of pills, IUDs, previous abortion, antecedent of EP, number of cumulated sexual

partners, previous abortion, history if pelvic surgery
- Past medical history including: smoking.

➢ Dependent variables: signs and symptoms, medical management.
- Signs and symptoms during diagnosis; amenorrhea, pelvic pain, pelvic mass, vaginal bleeding, rebound tenderness, hemodynamic instability, culdocentesis.
- Diagnostic examination; Dosage of beta HCG, transvaginal sonography, serum progesterone, blood workup.
- Treatment received; medical (methotrexate, leucovorin)\.
- Site effects and evolution.

Data management and analysis

Data Analysis

Data collected using the KOBOTOCOL application was entered into SPSS version 26 for analysis. Binary logistic regression analysis/chi square test was used to test association between dependent variable and independent variables and reported as Crude odd ratios with 95% confidence intervals. A two-tailed p-value less than 0.05 was considered statistically significant . This was done by accessing patients' files and also interrogating patients using various means of communication like cell phones through calls, WhatsApp and direct communication.

Ethical considerations.

To obtain an ethical clearance, we presented the research protocol to IRB/UD. Both the ethical clearance and the administrative approval documents were used to obtain an approval to carry out a study in the DLH, DGOPH and DGH. Patient's confidentiality was respected by not collecting patients names, phone number and identity card number. Also, data collected for all patients was kept only by researcher.

RESULTS

Prevalence of medically treated ectopic pregnancy

In our study, we found 492 patient files with Ectopic Pregnancy and a total of 66 received medical treatment, giving a prevalence of 13%. All the 66 participants who received medical treatment had a Fernandez score ≤13.

Sociodemographic characteristics

The participants' ages varied from 18 to 41 and the mean age was 30.05±5.33 years. The median age was 29 years, with the age range of 21 to 30 years having the highest representation (53%) (Table I).

Table I: sociodemographic characteristics of participants

Variables		n	%
Age group	≤20	2	3.0
	]20 to 30]	35	53.0
	]30 to 40]	27	41.0
	>40	2	3.0
Employment Status	Employed	32	48.5
	Unemployed	12	18.2
	Self employed	15	22.7
	Student	7	10.6
Matrimonial Status	Single	41	62.1
	Married	25	37.9
Religion	Muslim	5	7.6
	Christian	61	92.4
Residence	Out of Douala	4	6.1
	Douala	62	93.9

Obstetrical and gynecological factors

The majority of participants had as period of amenorrhea less than or equals to 7 weeks (37.9%) with a mean value of 7.02 ± 2.52. The minimum was 35 days and the maximum of 121 days of amenorrhea (Table II).

Clinical Presentation

Signs and Symptoms

In our study, amenorrhea, pelvic pain, and abnormal vaginal bleeding were the most common symptoms.

Table II: Period of Amenorrhea

Variables		n=66	%
Mean ± SD	49.88 ± 16.73		
Min – Max	35 – 121		
Period of Amenorrhea range (Days)	≤42	**25**	**37.9**
	]42 – 49]	18	27.3
	>49	23	34.8

SD: Standard Deviation. Min: Minimum. Max: Maximum

The majority of participants presented with an association of abnormal vaginal bleeding, pelvic pain, and amenorrhea (30.3%), and 16 had both amenorrhea and pelvic pain (24.2%) (Figure 1).

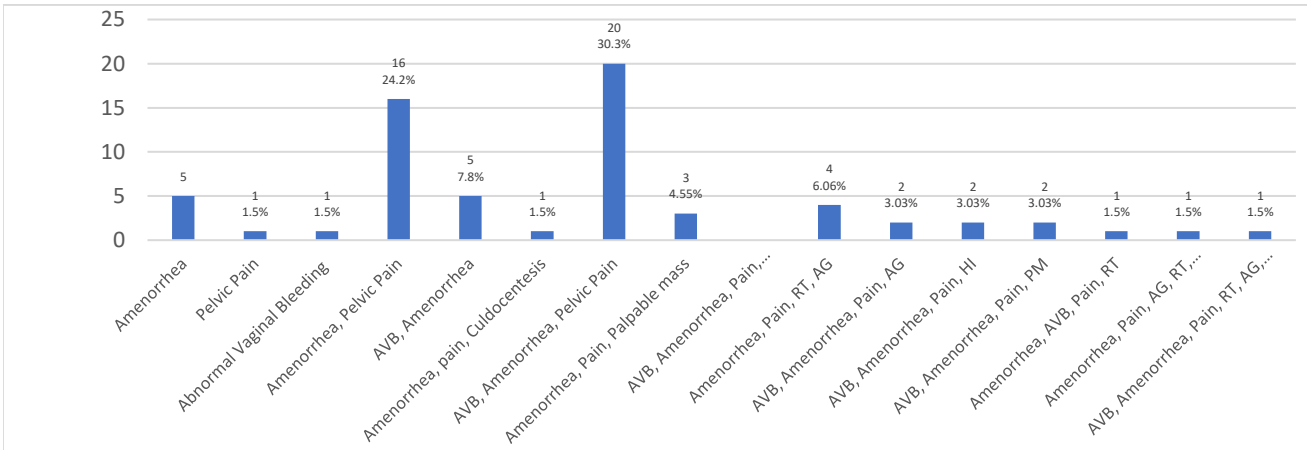

Figure 1: Representation of Signs and Symptoms upon Diagnosis

measuring between 1 and 3 cm, with a maximum of 9.4 cm (Table III).

Table III: Paraclinical results

Variables		n	%
Sonography	Yes	**66**	**100**
	No	0	0.0
Hematosalpinx (cm)	Mean ± SD	1.99 ± 1.78	
	Min – Max	**0.16 – 9.40**	
Hemoperitoneum (mL)	<1	23	34.8
	1 to 3	**34**	**51.6**
	>3	9	13.6
	Yes	16	24.2
	No	**51**	**75.8**

Blood Work-up

A sizable portion (62.8%) had human chorionic gonadotropin levels below 5000. The majority (66.7%) did not test their serum progesterone, whereas amongst the 22 who did 17 (25.8%) was greater than10.

Here, 30 participants did a full blood count (45.5%) whereas just 10 did liver and renal functions (15.25).

Treatment

In the study, all participants had Fernandez scores below 13. Methotrexate was administered to a large percentage of patients (87.9%) at doses of 50 mg/m2 (77.3%) and 1 mg/kg (22.7%). A single dose was given to 40 participants (60.6%), whereas repeated doses were given to 39.4.

Table IV: Representation of the indication and dosage of methotrexate used

Variables		n	%
Fernandez's Score	≥13	0	0.0
	<13	66	100
Medical Treatment	Methotrexate	58	87.9
	Leucovorin, Methotrexate	8	12.1
Methotrexate (Dosage used)	50mg/m^2	51	77.3
	1mg/kg	15	22.7

Success rate of medical Treatment

The medical treatment with methotrexate was successful with a percentage of 63.6.

Majority of correspondents did not have side effects. 5 had abdominal pain (7.7%) and a participant (1.5%) had stomatitis

A majority of participants did not require surgery (63.64%) as compared to 21.21% who were operated for ruptured ectopic pregnancy. Increase in B-hCG, hemodynamic instability and foetal cardiac activity were indication for surgery in 10.61%, 1.51% and 3.03% respectively.

Factors Associated to Success of Medical Treatment

There was a significant association between the age group less than or equals to 20years(p= 0.003, OR= 2.78, CI= 1.22 – 15.46) to the success of medically treated EP.

Some variables associated with the success of medical treatment were assessed using bivariate logistic regression analysis that showed that, being primigravida (p=0.02, OR=2.5, CI =1.47 – 13.39) and nulliparous (p =0.006, OR = 4.35, CI = 1.23 – 14.8) increased the chances of successful medical treatment while a past history EP (P = 0.04, OR = 0.26, CI = 0.07 – 0.99) reduced the chances.

Women who had just 1 cumulated sexual partners (p = 0.01, OR = 22, CI = 1.86 – 26) increased the chances of a successful medical treatment of EP with MTX.

We found out that, participants with no past surgical history and those who had tubal surgery were significantly related to the success of the medical treatment. No past surgical history (p = 0.005, OR=5.08, CI = 1.56 –16.52) increased the chances while tubal surgery (p = 0.005, OR = 0.12, CI = 0.02 – 0.65) reduced it.

In the study, abnormal vaginal bleeding (p = 0.04, OR = 0.66, CI = 0.43 – 0.95) decreases the odds of a successful medical treatment of EP with MTX. The dosage of B-hCG < 5000 (p=0.005, OR=1.61, CI=1.33–1,94), gestational sac less than 1cm (p=0.001, OR=5.33, CI=1.01–25.93) were positively associated. Whereas, a gestational sac greater than 3cm (p=0.002, OR=0.55, CI = 0.17 – 0.95) reduced the chances of success.

DISCUSSION

We carried out a cross-sectional study which set out to determine the prevalence, describe the sociodemographic, clinical and paraclinical presentation, evaluate the results and evolution of medical treatment as well aa to identify the factors associated to the success of the medical treatment of ectopic pregnancy.

The prevalence in this study was 13% which is similar to that of Foumane et al in two different studies Yaoundé Cameroon [13][55] found that 13.17% and 14% of the ectopic pregnancies diagnosed were treated medically. In contrast, this prevalence is lower than that reported by Garbin et al [56] in France (74%).The prevalence found by Ndour et al [12] in Senegal (6.8%) is lower than that in our study.

The success rates of the medical treatment of ectopic pregnancy with methotrexate in our study was 63.6%. This is in accordance with the studies of Foumane et al [13] in Yaoundé Cameroon and Zhang et al [58] in China that the other hand, this success rate was lower than that found by Almutairy et al [16] in Saudi Arabia (85.1%).

Socio-demographic features

Age

The mean age in our study was 30.05±5.33 years. Women within the ages of 21-30years made up the greatest proportion, accounting for 53.0% of the study population. Analysis of the trend of age group showed that ≤20years of age (p= 0.003, OR= $9*10^{-9}$, CI= $9*10^{-9}$ – $9*10^{-9}$) had a greater chance of success and the likelihood decreased as the age increased. These findings were similar to the study conducted by A. Panti et al [62] in Nigeria, Horne et al [63] in the. On the contrary, a study by Bonin et al [64] in France showed that older women had a higher chance of a successful medical treatment of ectopic. Assoumou et al found an average age of 32,8 ans years, with extremes ranging from 19 to 42 years.(hsd management of ectopicpregnancy at centre hospitalier universitaire mere et enfant foundation Jeanne Ebori of Libreville).

Marital Status

We found out that 62.1% of the participants were single. This is similar to a study carried out by Essome et al [6] and Fouedjio et al [65] in Cameroon that revealed that a

majority women were single in 57.4% and 80.4% respectively. On the other hand, this study was in contrast with a study carried out by in Nigeria and Cameroon that showed that 76.4% and 79.7% of the women with EP were married women. [15] [55].

Past history

Gravidity

This study found out that being primigravida was significantly associated with the success rate of the medical treatment of ectopic pregnancy. Women who were successfully treated with methotrexate were more likely to be pregnant for the first time (OR = 2.5, 95%CI = 1.4 – 13.39, p = 0.02). In contrast, a study carried by Khalil et al [66] in Saudi Arabia showed that there was no relationship between gravidity and the success of medically treated EP.

Parity

A low parity of 0 was significantly associated with the success rate of the medical treatment of ectopic pregnancy. The odds of the success rate were 4.35-fold greater in women who had never given birth before (OR= 4.35, 95%CI, 1.28 – 14.8, p = 0.006). This is similar to a study carried out by Bonin et al [64] in France in contrast with a study carried out by Dhar et al [57] in Oman that showed that pauciparous women had a higher rate of successfully medically treated ectopic pregnancy.

Gestational Age

The most represented gestational age range in this study was ≤42 days. The mean gestational age was 49.9 days. This is similar to a study by Zhang et al [58] in China that showed a similar mean of 47.2days.

Previous Ectopic Pregnancy

Past history of ectopic pregnancy was associated with success of medical treatment of EP. Our findings revealed that success of medically treated ectopic pregnancy was lesser in women with previous EP (P = 0.04, OR = 0.26, CI = 0.07 – 0.99). This finding s in line with other studies which equally reported that methotrexate regimen was less effective as a treatment for women with previous EP [67][68]. This is different from a study carried out by Khalil et al [66] in Saudi Arabia that found no association between a past history of EP with successful reduction in β-hCG after MTX treatment.

Past History of Pelvic Surgery

This study found that, there was a significant relationship between past history of tubal surgery, no history of pelvic surgery and the success rate of medically treated EP. Past tubal surgery (p = 0.005, OR = 0.12, CI = 0.02 – 0.65) was found to reduce the chances of a successful treatment of EP with MTX. This is different from a study carried out in France by Nazac et al [69] that showed no relation between tubal surgery and success with MTX treatment.

Clinical presentation

Abnormal Vaginal Bleeding

The most represented symptomatic triad (amenorrhea, pelvic pain and abnormal vaginal bleeding) was found in 30.3% similar to a study carried out by Essome et al [6] in Cameroon and Obiegbu et al [15] in Nigeria that showed this same triad in 46.1% and 45.6% respectively. Analysis of the trend of clinical presentation showed that abnormal vaginal bleeding (p = 0.04, OR = 0.66, CI = 0.43 – 0.95) was associated to the success rate of medically treated EP. This finding is similar to the study of Tawfiq et al [70] in the USA, that revealed that abnormal vaginal bleeding reduces the odds of the success of MTX treatment.

Paraclinical presentation

Gestational Sac

Gestational sac less 1 and greater than or equals to 3 were significant predictors for the success of medical treatment of EP. Our findings revealed that women with gestational sacs <1cm (p=0.001, OR=5.33, CI=1.01–25.93) increases the odds of a successful MTX treatment. Similar to this study is one carried out in France by Bonin et al [64] that showed that hematosalpinx at diagnosis was a predictive factor of methotrexate treatment success.This is in opposition to a study by Dhar et al [57] that said a gestational sac size of 2 – 3 cm had a higher success rate.

B-hCG Level

C-This study revealed that human chorionic hormone was a significant predictor for the MTX treatment success. Most of the participants received 50mg/m^2 and in single dose. B-hCG < 5000mIU/ml (p=0.005, OR=1.61, CI=1.33–1,94), was identified to increase the odds for MTX treatment success. This study resembles that of Dhar et al [57] and Almutairy et al [16] who found out that a success rate of 80% by treating 12 out of 15 women with single dose MTX with initial β-hCG levels equal to 5000mIU/ml. In a study carried out in France by Bonin et al [64], that said initial hCG values <1000 IU/l were associated with a success rate of 90% this can be explained by the fact that the smaller the β-hCG levels the higher response rate to methotrexate.

Evolution of medical treatment with mtx

In the study, just 18.2% of participants had secondary effects. In descending other these adverse effects were abdominal pain, vaginal bleeding and stomatitis. Similar to a study carried out by Dhar et al [57] in Oman, where 25.2% of women had side effects.

In a study 36.36% participant later received a surgical treatment after the failure of the medical treatment, mostly because these EP ruptured (21.21%). This was higher than a proportion of 23.9% in a study carried out in Turkey [71]

CONCLUSION

The prevalence of medical treatment was low.

Majority of the patients were young, single, nulliparous, with past history of PID and previous abortion. The mean gestational age was 7weeks (49days) and mostly presented with pelvic pain and abnormal vaginal bleeding. They all had an indication for medical treatment as Fernandez score <13. Diagnosis was done by sonography and dosage of B-hCG. Also, we noticed that many patients did not complete the pretherapeutic work-up.

The success rate after medical treatment was 63,6%. We observed very little side effects and surgery was done in 36.2% of cases with failure of medical treatment. This was mainly due to the ruptured nature of the EP.

The predictors of success in our study were low β-hCG and adnexal mass less than 1 cm, B-hCG < 5000mIU/mL, 1 cumulative sexual partner, age ≤ 20years, no past history of pelvic surgery, being nulliparous or a primigravida. Single dose methotrexate offers a safe and effective non-surgical method of treating selected patients and one important

advantage of medical therapy is the potential for considerable savings in treatment costs.

Study Strengths

- Provision of data on the medical treatment of ectopic pregnancy in our setting.
- Pilot study which may be used for future research.

Study Limitations

- The study population was not truly representative of the medically treated ectopic pregnancy in Cameroon, as the study was limited to patients of three hospitals.
- The retrospective nature of this study, data may be missing, inaccurate, or inconsistently recorded, which can compromise the reliability and validity of study findings.
- The fact that very little progesterone dosage was performed in our context, it could constitute a bias in the choice of management for ectopic pregnancies.

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