

Widening the Field of Indication of Conservative Management of Unruptured Tubal Pregnancy in Low Resources Settings: Lessons Learnt from 10-year Experience in Three University Teaching Hospitals in Yaoundé (Cameroon)

Mve Koh Valere^{1, *}, Essiben Felix¹, Essome Henri², Dang Atanga Danielle², Mbu Enow Robinson¹

¹Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon

²Faculty of Medicine and Pharmaceutical Sciences, University of Douala, Douala, Cameroon

Email address:

vmvekoh@yahoo.com (M. K. Valere), essibenx@yahoo.fr (E. Felix), essometocky@yahoo.com (E. Henri), dang_danielle@yahoo.com (D. A. Danielle), robinsonmbu@gmail.com (M. E. Robinson)

*Corresponding author

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Abstract: Ectopic pregnancy is the leading cause of maternal mortality in the first trimester. When a patient is admitted before rupture, organ-preserving management which keeps a higher fertility rate than ablative surgery can be done. The incidence of Unruptured Ectopic Pregnancy (UTP) on admission is unknown. In the study facilities, methotrexate treatment was given to most of UTP regardless of Fernandez score. The aim of this study was therefore to assess the lessons learnt from that experience. Methods: It was a cross sectional study over a 10 years period, conducted in four university teaching hospitals affiliated to the University of Yaoundé I, Cameroon. Included patients were managed either by therapeutic abstention, single or multidose intra muscular MTX. Onset of clinical acute abdomen was the only indication of failure of conservative management and prompted emergency laparotomy. Results: We included 153 UTP cases. The incidence of UTP on admission was 0.46%, the mean age 28.4 ± 4.9 , 88.2% were admitted at a gestational age <9 weeks, 19% had no pelvic pain. Medical treatment by MTX success rate was 81.7% but was not related to mono or multiple-dose ($p=0.87$), the success rate when β -hCG value was ≥ 10000 mIU/ml was 63.3% ($p=0.004$). When Fernandez score was ≥ 13 , 21/25 (84%) were still successful including 3/7 with cardiac activity. ($p=0.007$). Conclusions: The incidence of UTP on admission is approximately 1/10th of all EP. Some UTP patients should be given MTX treatment opportunity even when Fernandez score recommends surgical management.

Keywords: Unruptured Ectopic Pregnancy, Widen Indication, Acute Abdomen

1. Introduction

Ectopic pregnancy (EP) defined as the implantation of the fertilized ovum outside of the uterine cavity [1] is a life-threatening gynecological emergency with a risk of death 10 times higher than death after vaginal delivery and 50 times more than induced abortion [2]. It is the leading cause of

maternal mortality in the first trimester accounting for 10%–15% of all maternal deaths [3]. EP is indeed the most frequent cause of first trimester maternal death in developed countries and in sub-Saharan Africa [4]. The maternal mortality rate due to its complications increased from 2.8% in 2001-2003 to 4.2% 2004-2006 in France, and it was 6% in the USA [5-6]. The mortality rate in a study in Cameroon was 12.5%, three times higher than in France and was the

third maternal mortality cause [7], and, EP can lead to lower chance of conception when compared to those who had miscarriage [8]. More than 95% of EPs occur in the fallopian tubes. [9]. The majority of patients are admitted late after rupture and hemodynamic instability in developing countries [10]. Surgery is then the most appropriate treatment and is usually an ablative surgery like partial or total salpingectomy, but after surgical management, 30% of EP cases won't be able to have another pregnancy and 15 to 30% may experience another episode of EP [11].

When a patient is admitted before rupture, organ-preserving management like Methotrexate (MTX) administration, the first option for medical therapy can be given, avoiding the rupture of the concerned tube when successful, and keeping potential fertility. Organ-preserving management keeps indeed a higher fertility rate than ablative surgery. [12]. This is an important advantage as some of EP are suffering from infertility, an established risk of EP and cases of tubal re-permeability after MTX have been described [12-13].

The incidence of ectopic pregnancy is approximately 1.5 to 2% of all pregnancies [14], but the incidence of Unruptured Ectopic Pregnancy (UTP) on admission is unknown in our milieu. Systematic medical treatment had been applied to cases of UTP in some study facilities, regardless of the Fernandez score, with capability of prompt surgical take-over in case of rupture. The aim of this study was therefore to assess the lessons learnt from that experience, mainly, the profile of EP patient admitted before rupture and the relation between Fernandez score value and MTX treatment success in low resources settings.

2. Methods

It was a cross sectional study over a 10 years period, from January 1st 2006 to of December 31st 2015. The study was conducted over a four months period, from the first of January to April 30th 2016. This study took place in the services of gynecology and obstetrics of four university teaching hospitals affiliated to the University of Yaoundé I, namely, the University Teaching Hospital, the Gynecology-Obstetric and Pediatric Hospital, the Central Hospital and the General Hospital, all of them in Yaoundé, the capital city of Cameroon, a sub-Saharan African country in the gulf of Guinea with a population of 25 million. They are the only ones conducting conservative medical management of unruptured tubal pregnancy (UTP). We included all files of women hospitalized for UTP, diagnosed through both serum β -hCG > 10ml/IU and pelvic or vaginal ultrasound without the presence of intrauterine pregnancy and the presence or not of a tubal sac or embryo, with or without cardiac activity, managed by methotrexate injection or expectant management regardless of β -hCG value with hemodynamic stability on admission. Files without ultrasound and β -hCG results before admission, serial β -hCG after admission and management by

MTX, clinical outcome (laparotomy or not) and discharge note were excluded, so were cases of UTP with the absolute contra-indication below: unstable hemodynamic state, contra indications to MTX: (breast feeding, immunodeficiency, ASAT or ALAT values twice higher than normal, kidney failure, thrombopenia (<100000/mm³), leucopenia (<2000/mm³), hemoglobin concentration <11g/dl. We also excluded files without surgical findings of laparotomy in case of rupture of the previously unruptured tubal pregnancy and non-tubal extra-uterine pregnancies.

Because of the difficulties to assess progesteronemia, the evaluation of Fernandez score was done assuming a maximum value of P > 10ng/ml. All the diagnosed patients were hospitalized and managed there until discharge. Full blood count, liver function test and blood type and Rh factor were done prior to the beginning of MTX treatment.

Expectant management was done in some of the cases (β -hCG value <500 IU/ml, but monodose was given on day one of admission 1mg/kg intra muscularly, two protocols of multi-dose were used, MTX 1mg/kg day 1, 3 and 5, or 100mg intra muscularly on day 1, 3 and 5 when they were cardiac activity, but in some cases, the choice of protocol was physician dependent. Successful outcome designated dropping of serial β -hCG after MTX treatment or watchful waiting (medical abstention), discharge without acute abdomen and final β -hCG value <10UI/ml, during serial outdoor monitoring. Onset of clinical acute abdomen (rebound tenderness) was the only indication of failure of conservative management, and failure was confirmed by laparotomic rupture tubal pregnancy after at least one intra muscular injection of a total dose of 1mg/kg MTX. All the rupture cases were surgically managed in the same health facilities.

The minimum sample size was 35 according to Lorentz formula. The data of interest were sociodemographic, (maternal age, occupation, marital status, ethnicity), contributing gynecological and obstetrical past history (Gravidity, parity, risk factors of UTP, the clinical manifestations on admission (referral case or not, gestational age, clinical signs on admission), para-clinical imaging and biological assessment results, (Pelvic/endovaginal ultrasound β -hCG values), therapeutic management and maternal outcome.

Data collected were processed by Cs Pro 6.1 and SPSS 20.0. Differences in baseline characteristics between different modalities were assessed by X^2 , the threshold of significance was $P \leq 0.05$. This study received the ethical clearance of the ethical committee of the university of Douala in Cameroon and the authorization of the directors of the four University teaching Hospitals.

3. Results

We included 153 cases of UTP corresponding to inclusion criteria. There was no fatal outcome.

Table 1. Incidence of UTP on admission.

Hospital	Number of UTP	Total number of deliveries	Frequency (%)
GOPH	163	25884	0.60
UTH	156	18996	0.80
CH	62	39060	0.10
GHD	45	7777	0.57
Total	426	91717	0.46

GOPH: Gyneco-Obstetric and Pediatric Hospital

UTH: University Teaching hospital

CH: Central Hospital

GHD: General Hospital

The incidence of UTP was 0.46% (4, 6 cases for 1000 births).

Table 2. Sociodemographic and clinical parameters distribution of UTP.

Variables	n	Percentage (%)
Ages (years)		
[16-20]	5	3.2
[20-25]	45	29.4
[25-30]	57	37.2
[30-35]	32	20.9
[35-40]	12	8
[40-45]	2	1.3
Marital status		
Married	57	27
Single	96	63
Gestivity		
1	29	19
2-3	69	45
4	41	27
≥5	14	9
Parity		
0	62	41
1	43	28
2-3	39	25
4	9	6
Mode of admission	108	70.6
Going directly from home to the final management center		
Referred from another lower category health center	45	29.4
Gestational age on admission (weeks)		
No identified amenorrhea	4	2.6
< 9	135	88.2
[9-16]	13	8.5
≥16	1	0.7
Symptoms		
Amenorrhea	149	97.4
Pelvic pain	124	81
Metrorrhagia	96	62.7
Gestational sac tubal position		
Right tube	96	62.7
Left tube	57	37.3

The mean age was 28.4 ± 4.9 years (minimum 18 and maximum 45 years). The age group [25-30] was the most frequent and [20-35] represented 87.7% of the sample. Amenorrhea was present, but pain and menorrhagia were absent on 18 and 36.3% respectively. Two third were single, gestivity 2-3 represented 45%, parity 0 and 1, 69%, 71% chose at first intention university teaching hospital, 88.2% were admitted at a gestational age <9 completed weeks, 97.4% had amenorrhea and the right tube was the mostly affected (62.7%).

Table 3. Management and outcome of UTP.

Modalities	n=153	Frequency (%)
Management		
Expectant management	4	2.6
Medical treatment by MTX	149	97.4
Evolution of UTP		
Success of treatment	125	81.7
Rupture of UTP	28	18.3

Medical treatment by MTX was indicated in 97.4% of cases with a success rate of 81.7%.

Table 4. UTP outcome according to MTX protocol.

MTX protocol	Single-dose n (%)	Multi-dose (≥2) n (%)
Success of treatment	59 (79.7)	62 (82.7)
Rupture of UTP	15 (20.3)	13 (17.3)
Total P=0.87	74 (100)	75 (100)

There was no statistically significant difference between single (success rate 79.9%) and multi-dose (success rate 82.7%) p=0.87.

Table 5. UTP outcome according to initial β-hCG value.

β-hCG mUI/ml	< 1000 n (%)	[1000-5000] n (%)	[5000-10000] n (%)	≥10000 n (%)
Success of treatment	34 (97.1)	54 (80.6)	18 (85.7)	19 (63.3)
Rupture of UTP	1 (2.1)	13 (19.4)	3 (14.3)	11 (36.7)
Total	35 (100)	67 (100)	21 (100)	30 (100)
X ²	7.23	0.097	3.318	8.419
P	0.07	0.756	0.069	0.004

The rate of success decreased as initial β-hCG value increased, and the success rate was 63.3% even when initial β-hCG was >10000 mIU/ml (p=0.004)

Table 6. UTP outcome according to Fernandez score on admission.

FERNANDEZ SCORE	< 9 n (%)	9-12 n (%)	≥13 n (%)
Success of treatment	1 (100)	103 (81.1)	21 (84)
Rupture of UTP	0	24 (18.9)	4 (16)
X ²	0.225	0.178	0.106
P	0.635	0.673	0.745
Total	1	127	25

The success rate was decreasing as Fernandez score was increasing. A Fernandez score recommending surgical management of UTP still had a successful rate of 84% after medical treatment by MTX.

Table 7. UTP outcome according to MTX protocol and β-hCG value on admission.

Taux de (β-hCG mUI/ml)	< 1000 n (%)	[1000-5000] n (%)	[5000-10000] n (%)	≥10000 n (%)
MTX 1				
Success of treatment	24 (96)	24 (75)	8 (80)	3 (43)
Rupture of UTP	1 (4)	8 (25)	2 (20)	4 (57)
Total	25 (100)	32 (100)	10 (100)	7 (100)
MTX 2				
Success of treatment	8 (100)	28 (85)	10 (91)	16 (69.6)
Rupture of UTP	0	5 (15)	1 (9)	7 (30.4)
Total	8 (100)	33 (100)	11 (100)	23 (100)

MTX1: Single-dose protocol

MTX2: Multi-dose protocol

The overall success rate when β-hCG was ≥10000miu/mL was 63.3% (19/30).

Table 8. UTP outcome according ultrasonographic findings.

Evolution n=153	Cardiac activity present	Hydrosalpinx	Pyosalpinx	Salpingitis
Success of treatment	3 (43%)	5	1	1
Rupture of UTP	4 (57%)	0	0	0
X ²	7.402			
P	0.007			
Frequency (%)	4.6	3.3	0.7	0.7

Cardiac activity was present in 7/153 cases (4.6%) all treated by multidose, and the success rate of 43% was statistically significant

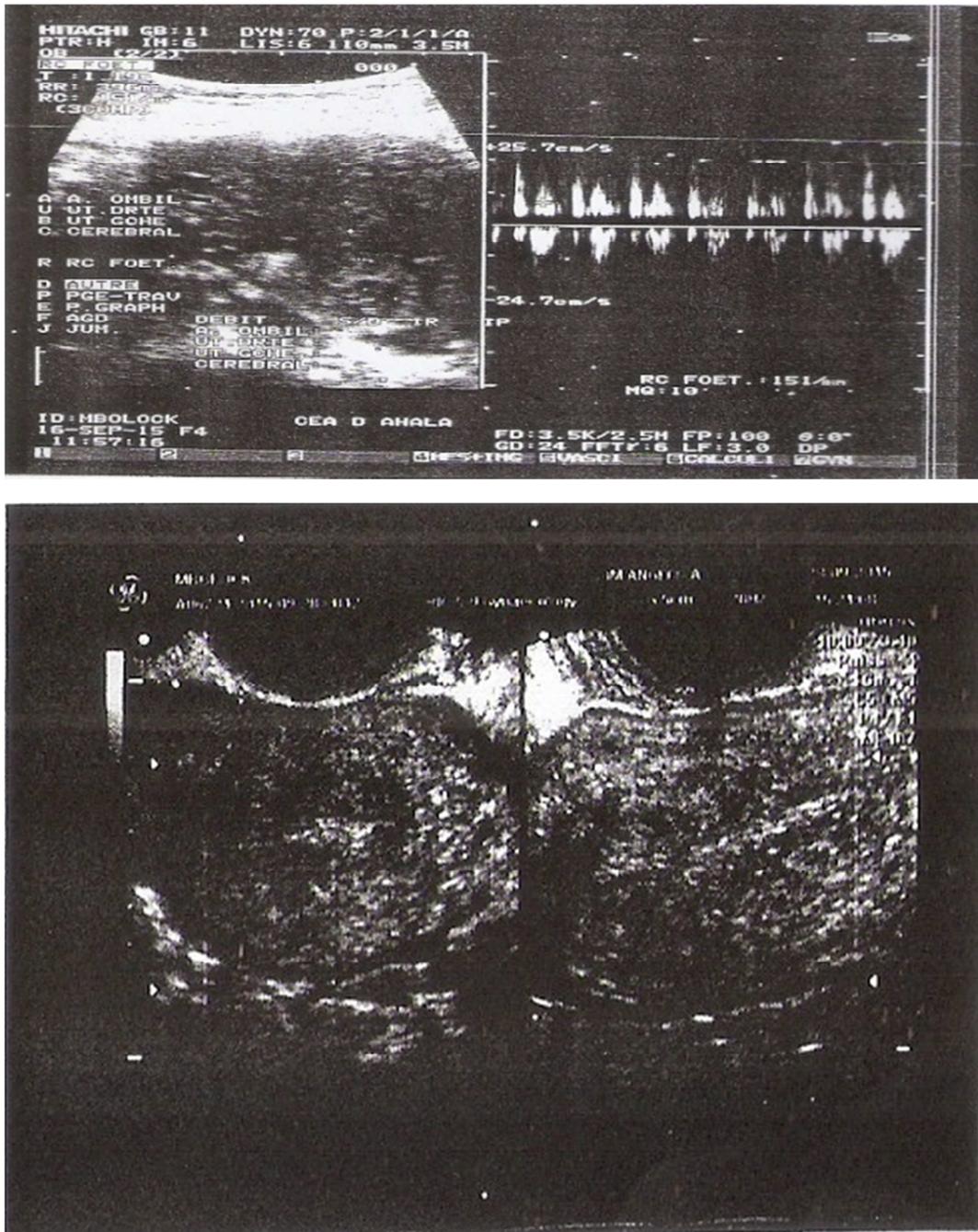


Figure 1. One of the cases of successful treatment with cardiac activity.

4. Discussion

4.1. Incidence of UTP

The incidence of ectopic pregnancy is approximately 1.5 to 2% of all pregnancies [14]. The incidence in the western world ranges between 1–3% of all pregnancies [15], and was 4.2% in a Cameroonian study conducted in the same city [16]. The incidence of UTP ranged from 0.1 to 0.8 from one hospital to another and the average was 0.46% in this study over a ten-year period (Table 1). The incidence of UTP on admission is poorly assessed in the recent literature. That

incidence was one tenth ($1/10^{\text{th}}$) of the frequency of all EP found in the Cameroonian study mentioned above [16]. Only one out of 10 cases of all ectopic pregnancies are admitted before tubal rupture. This shows the magnitude of sensitization to be implemented, in order to improve the awareness of early consultation in case of amenorrhea, and increase the proportion of EP admitted before rupture, so that EP patients can be given the opportunity of fertility preserving conservative management, since infertility is a well-known underlying risk factor, and to reduce the mortality related to this leading cause of maternal mortality in the first trimester [3]

4.2. Socio-Demographic and Clinical Data

the majority of patients were represented by the [20-35] age range (Table 2), like found in other publications [17], probably due to the fact that it is the age of maximum pregnancy rate even in intra uterine pregnancies studies [18]. Up to 29.4% didn't chose an appropriate health facility, and were referred from another health facility, adding another delay in the management (Table 3). This was probably due to the low setting environment and ignorance, as almost all of them (97.4%) consulted at a rather late gestational age (≥ 9 weeks), reducing the proportion of expectant management adopted in this study to 2.6% (4/153) of cases. (Table 3). Studies conducted in western world has shown indeed an earlier average gestational age at the moment of consultation. It was 7 weeks ± 11 days in France for example. [19]

4.3. Success Rate After MTX Protocol

The overall success rate of this study was high (81.3% 125/153) and success rate after MTX management was 81.2% (121/149) (Table 3) as found in many studies [20, 21], but it was not statistically correlated to MTX mono or multi-dose protocol (Table 4; $p=0.87$), although multi-dose success rate was higher than mono-dose, and this was obvious when β -hCG was > 10000 IU/L with a success rate of 16/23 when mono-dose succeeded only on 3/7 cases (Table 6). The success rate of MTX management of UTP varies from 72 to 95% [22-23]. A 100% success rate has already been reported [24]. The choice of the most appropriate MTX protocol is still debated. Mergenthal *et al.*, in a prospective multicenter cohort study, among UTP cases with similar initial β -hCG levels found that, the mean rate of decline of β -hCG from day 0 to day 7 was significantly more rapid in women who received the single-dose protocol compared to 2-dose protocol with no difference in success rate or time to successful resolution [25]. In a prospective randomized trial comparing the success of single-dose MTX treatment versus multiple-dose MTX in patients with unruptured EP, no difference was found between the two MTX treatment regimens [26]. A recent systematic review of randomized controlled trials between 1974 and 2016 has also concluded that, the overall success rate of multiple-dose protocol was similar to the single-dose protocol and the incidence of side-effects of multiple dose protocol was significantly higher than single-dose protocol, concluding that the double-dose regimen was an efficient alternative to the single-dose protocol [27]. But some studies based on β -hCG variation has shown a better reduction with multi-dose protocol. Inal *et al.* in a recent study found that serial β -hCG values on Day 0, 4 and 7 were statistically different between expectant management, single dose, multi-dose and the surgical intervention group [28].

The success of single-dose MTX therapy can be affected by the patient's serum β -hCG levels, positive fetal cardiac activity, the presence of a yolk sac, and the size of the ectopic mass [29]. The relation between the occurrence of rupture and β -hCG value is unknown. According to Barnhart, tubal rupture can happen at any time if β -hCG values are between

10 to 189720 UI/L [30], and Saxon added that, there was no anamnestic, clinical, biological or ultrasonic means which could permit to identify EP cases to rupture [31]. Concerning predictive factors of rupture, and according to Shaamash, a cut-off "percentage of fall" in β -hCG serum levels on D1–D7 of 33% had the best sensitivity (96%) and specificity (85%) for predicting a successful outcome and this was outperforming any cut-off on days 1–4 and was comparable to the standard D4–D7 protocol [32]. According to Pooja, pretreatment β -hCG level of < 6000 mIU/ml, adnexal mass size < 3 cms, amenorrhoea < 6 weeks and absence of free fluid in the pelvis are predictors of a successful treatment with MTX [33].

Bonin analyzing 314 UTP rather concluded that, the main factors associated with methotrexate failure included day (D) 0, D4 and D7 hCG levels, pretherapeutic blood progesterone, hematosalpinx on D0 and pain on D7 [34].

This study considered clinical acute abdomen as the only indication of surgical management take-over, since all the UTP cases were hospitalized in close hemodynamic monitoring. From our results, not focusing on the recommended "successful "falling rate" but rather on the onset or not of clinical acute abdomen as the only event recommending surgical management probably gave a chance to cases whom might have gone through surgical management without acute abdomen, and, this might explain the success rate of 63.3% even when initial β -hCG was > 10000 mIU/ml (Table 5; $p=0.004$), the unexpected success rate of 84% (21/25) in cases where the Fernandez score was > 13 and the absence of statistical correlation between Fernandez score/management/outcome ($p=0.74$; Table 6), including three successful treatment out of seven (3/7) UTP with cardiac activity (Table 7 $P=0.07$; Figure 1). This is a specific finding of this study, challenging what has been recommended so far, as long as the recommendations of Fernandez score are concerned. Whether or not considering the occurring of acute abdomen during MTX treatment of UTP as the only indication of surgical take over should be generalized still need further analytical studies.

The majority of ectopic pregnancies are admitted after rupture [35], and yet, the mortality rate is relatively low, between 2 and 4/1000 [36]. Acute abdomen occurring during hospitalization under close monitoring while administrating MTX should easily and promptly be taken care of in university teaching hospitals where this study was conducted. This leaves a ground for more daring attitude and patience in order to give optimum chance to each case as nothing can predict the occurrence or not nor the moment of rupture.

5. Conclusion

The incidence of UTP on admission was relatively low approximately $1/10^{\text{th}}$ of the incidence of all EP, the overall success rate of medical management of UTP by MTX was high even in low settings management, but was not related to MTX protocol. Some UTP patients should be given MTX treatment opportunity even when Fernandez score

recommends surgical management. Analytical studies considering the occurrence of clinical acute abdomen as the sole signal of UTP medical treatment failure should be conducted to reassess the full potential of medical management of UTP by MTX

Contribution of Authors

MVE KOH Valère did the study design and wrote the article, Dang Atanga Danielle collected the data, Felix Essiben, Essome Henri and Mbu Robinson reviewed and provided critical comments and suggestions for the manuscript.

Limitations

This study didn't analyze specifically each EP clinical data and adopted protocol

Competing Interests

All the authors do not have any possible conflicts of interest and declare that they have no competing interests; this work was not sponsored by any organization and was self-financed.

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