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Original Research Article

Medical management of ectopic pregnancy in a low resource setting: the role of methotrexate

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ABSTRACT

Background: Medical treatment using methotrexate. However, its indications and the protocol of administration are still under discussion. Even if follow-up problems are often raised in developing countries, medical treatment of ectopic pregnancy remains a reasonable option that we practice and share our experience here.

Methods: We performed a retrospective cohort study of patients managed for an unruptured ectopic pregnancy in two university hospital facilities in Dakar: the Centre Hospitalier National de Pikine and the Centre de Santé de Philippe Maguilen Senghor. The data of this study are spread over a period of 10 years, from 2010 and 2019. We planned to evaluate maternal age, parity, gestational age, diagnosis circumstances, medical management, monitoring, and outcome. A single dose protocol was used. Data extracted from the registries were transferred to Microsoft Excel 2019, Mac version and then moved to SPSS (Statistical Package for Social Sciences, 26).

Results: Over ten years, we had registered 18 patients who had received medical treatment out of a total of 263 ectopic pregnancies treated in the two facilities, i.e., a frequency of 6.8%. The average age was 28.8 years. The average initial HCG level was 10,460 mIU/ml. Treatment succeeded in more than 6 out of 10 patients (61.1%). However, we noted 5 cases of failure that had secondarily benefited from salpingectomy by laparotomy.

Conclusions: Methotrexate is now part of the therapeutic arsenal in the management of unruptured tubal ectopic pregnancies. However, in developing countries, particularly in Senegal, there is a reluctance to use this therapeutic method, which, however, when a personalized follow-up is carried out, is achievable with a success rate comparable to other therapeutic methods.

Keywords: Dakar (Senegal), Ectopic pregnancy, Low resource, Methotrexate

INTRODUCTION

Ectopic pregnancy is the implantation and development of the egg outside the uterine cavity.¹ The inflammatory sequelae of Chlamydia trachomatis infection are among the leading causes of ectopic pregnancy.² Its diagnosis has benefited from the development of ultrasound, the particularly improved resolution with high-frequency probes, and biology with the determination of gonadotropic chorionic hormone. Formerly surgical and performed by laparotomy, the treatment of ectopic

pregnancy has been de-escalated with the advent of endoscopic surgery and medical treatment with methotrexate.^{3,4} Unruptured ectopic pregnancies, 95% of ectopic pregnancies can benefit from endoscopic management if the technical platform allows it.⁵ Based on hospital data, ruptured ectopic pregnancies still occupy the leading group, so that the simple reference to it triggers in the mind of the physician (surgeon or obstetrician) the entire cascade of management of a hemorrhagic emergency by laparotomy. However, for some patients seen early on, a more conservative

alternative should be offered, such as medical treatment. Medical treatment using methotrexate, introduced in the management of ectopic pregnancy since the 1980s, has gained ground over the years and has finally demonstrated its efficacy in unruptured forms.^{6,7} However, its indications and the administration protocol of are still under discussion.^{8,9} Its obvious advantages, relative efficacy compared to standard gold, and its safety are attracting more and more practitioners and patients. Even if problems of follow-up are often raised in developing countries, medical treatment of ectopic pregnancy remains a reasonable option that we practice and share our experience here.

METHODS

It was a retrospective cohort study of patients managed for an unruptured ectopic pregnancy in two university hospital facilities in Dakar: the Centre Hospitalier National de Pikine and the Centre de Santé de Philippe Maguilen Senghor. These two facilities record an average of 7,000 deliveries per year, including 50 to 60 ectopic pregnancies. The data of this study are spread over a period of 10 years, from 2010 and 2019.

Usual treatment of ectopic pregnancy in both hospitals

In both hospitals, the treatment of ectopic pregnancy is usually performed by laparotomy or endoscopy surgery. Whether performed by laparotomy or endoscopy, the procedure is most often radical, ie, a salpingectomy.

Inclusion criteria

We included all patients who had received medical treatment for an ectopic pregnancy during the study period at both centers.

Exclusive criteria

Patients with incomplete data in their records were not included in the study.

Variables assessed

We planned to evaluate maternal age, parity, gestational age, circumstances of diagnosis, medical management, monitoring and outcome.

Data collection method

In each of the two facilities, there is a software program for data collection, which can be recorded retrospectively and prospectively. Patient data for this study were extracted from these electronic registries.

Data analysis

Data extracted from the registries were transferred to Microsoft Excel 2019, Mac version and then moved to

SPSS (Statistical Package for Social Sciences, 26). Mean, median, and standard deviation were considered to describe continuous variables while frequencies were reported for categorical and nominal variables. Pearson correlation was computed to evaluate the association between continuous quantitative variables.

RESULTS

Socio-demographic characteristics

Over ten years, we had registered 18 patients who had received medical treatment out of a total of 263 ectopic pregnancies treated in the two facilities, i.e., a frequency of 6.8%. The average age was 28.8 years, with extremes at 20 and 36 years. A proportion of 22.2% of patients had a history of ectopic pregnancy treated surgically.

Clinical data

Metrorrhagia was present in 50% of cases, associated with pelvic pain in 16.7% of cases. Patients were asymptomatic in 38.9% of cases, the diagnosis was solely made by ultrasound. However, all patients had benefited from an ultrasound scan to confirm the diagnosis. The average initial HCG level was 10,460 mIU/ml with extremes of 162.5 and 87,110 mIU/ml. The mean gestational age was seven weeks' gestation (WG) with extremes of 5WG and 9WG+4 days. Table 1 shows the socio-demographic and clinical characteristics of the patients.

Treatment

A single dose protocol was used. It consisted of an intramuscular injection of Methotrexate at a dose of 1 mg per kilogram; a pre-therapeutic assessment was carried out beforehand, namely the level of plasma chorionic gonadotropic hormone (hCG), a blood count, liver transaminases and creatinine levels. Monitoring by weekly dosing was carried out. All patients had a physician who personally monitored their progress. A single-dose protocol was used in our patients. Additional doses were given in 16.7% of patients. All patients were hospitalized for 3 to 4 days after initiation of treatment to monitor and manage possible side effects of Methotrexate or ruptured ectopic pregnancy.

Outcome

Treatment succeeded in more than 6 out of 10 patients (61.1%), as shown in Table II. However, we noted 5 cases of failure that had secondarily benefited from salpingectomy by laparotomy. One of them was an ectopic pregnancy with a live 9WG embryo. Two patients were lost to follow-up. Success was not correlated with the initial hCG level. However, we found a moderate correlation ($r = 0.6$, $p = 0.027$) between gestational age in days and time to achieve undetectable hCG levels, as shown in Figure 1.

Table 1: Clinical characteristics of patients with ectopic pregnancy.

Case	Age	Gestity	Parity	Living Living child	History of EP	History of STIs	Treatment with progestins	Symptoms	Gestational age
1	29	1	0	0	Yes	No	No	Pelvic pain+metrorrhagia	7WG
2	20	1	0	0	No	No	No	Metrorrhagia	6WG
3	27	1	0	0	No	No	No	Ultrasound	7WG
4	29	2	1	1	No	No	No	Pelvic pain+metrorrhagia	5WG
5	31	2	1	1	No	No	No	Metrorrhagia	7WG
6	30	4	2	2	No	No	No	Pelvic pain+metrorrhagia	7WG
7	34	2	1	1	No	No	No	Metrorrhagia	5WG
8	33	1	0	0	No	No	No	Metrorrhagia	6WG
9	23	1	0	0	No	No	No	Metrorrhagia	6WG
10	29	2	2	2	No	No	No	Metrorrhagia	5WG
11	34	2	0	0	Yes	No	No	Ultrasound	7WG+3d
12	36	0	0	0	No	Yes	No	Pelvic pain+metrorrhagia	7WG+4d
13	29	0	0	0	No	No	No	Ultrasound	7WG+6d
14	26	0	0	0	No	Yes	No	Ultrasound	7WG+6d
15	25	0	0	0	No	Yes	No	Ultrasound	7WG+6d
16	26	1	1	1	No	Yes	Yes	Pelvic pain+metrorrhagia	7WG
17	28	1	1	1	No	Yes	No	Pelvic pain	9WG+4d
18	29	1	0	0	Yes	Yes	Yes	Ultrasound	9WG

EP : Ectopic pregnancy, STI : Sexually Transmitted Infection, WG : Weeks' gestation, d : day

Table 2: Patients' outcomes.

Case	Initial hCG rate (UI/L)	Outcome	Time to undetectable hCG (weeks)	Time to become pregnant (months)
1	3,491	Success	6.43	-
2	1,62.5	Lost-to-follow-up	-	-
3	6,462	Success	8.14	7.6
4	5,120	Success	3.29	-
5	1,571	Success	6	-
6	6,463	Failure	-	-
7	915	Failure	-	-
8	3,180	Success	5.3	-
9	2,970	Success	4.5	9
10	1,792.29	Success	5.28	7.8
11	-	Failure	-	6.8
12	7,859.22	Success	9.7	-
13	1,704	Lost-to-follow-up	-	-
14	1,800	Success	3.4	28
15	25,287	Success	9.5	8.6
16	10,460	Failure	-	-
17	20,082	Success	5.7	-
18	87,110	Failure (rupture)	-	-

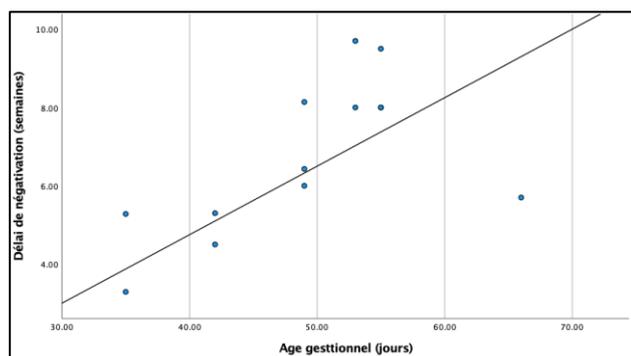


Figure 1: Correlation between time to denial and gestational age in days

Subsequently, 6 patients underwent pregnancy, 5 of which resulted in live births and one in an abortion. Only one patient had experienced methotrexate side effect (allergic vulvo-vaginitis).

DISCUSSION

Main results

Methotrexate given intramuscularly as a single dose of 50mg/m² is efficient in the treatment of ectopic pregnancy. This is moderately positively correlated with gestational age and not with baseline hCG levels.

Interpretation of the results in the light of the international literature

Methotrexate is the molecule of choice used in the medical treatment of ectopic pregnancy. Methotrexate is a folinic acid antagonist.^{10,11} It inhibits dihydrofolate reductase, an enzyme needed to convert dihydrofolic acid into tetrahydrofolic acid, thus preventing DNA synthesis and inhibiting cell multiplication.¹ It was first used by Tanaka in 1982 in the treatment of interstitial ectopic pregnancy. The success rate of methotrexate ranges from 65 to 95%.^{6,12} Other molecules have been proposed such as potassium chloride or hyperosmolar glucose but their efficacy was 60% and 80% respectively.^{13,14} Three main treatment regimens have been described in the literature:

Single-dose intramuscular methotrexate regimen, multiple-dose intramuscular methotrexate regimen and in situ injection of methotrexate. The multiple-dose regimen involves the administration of four intramuscular doses of methotrexate (1mg/kg) alternating with folinic acid (0.1mg/kg).¹⁵ The single-dose protocol involves a single administration of intramuscular methotrexate, followed by serum hCG measurement on days 4 and 7; if the hCG decrease is less than 15%, a second dose of methotrexate is required.¹⁶ This protocol was developed to reduce the incidence of side effects after multiple dosing regimens, eliminating the need for folinic acid and increasing convenience of administration.¹⁷ The double-dose protocol involves the administration of two doses of

methotrexate at D0 and D4, which was developed to combine the efficacy of multiple doses with the safety of single doses.¹⁸ In our series, without an established protocol for the medical management of ectopic pregnancies, the single-dose regimen was administered to all of our patients for its safety.

For the indications of medical treatment, certain criteria are consensual, namely an estimated hemoperitoneum of fewer than 100 ml, stable hemodynamics with normal hematocrit, a hematosalpinx size of less than 4 cm, a β hCG level of less than 5,000 IU/l and the absence of embryonic cardiac activity.¹ Fernandez has proposed a pre-therapeutic score and recommends medical treatment if it is less than 13.¹⁹ However, there is no consensus on serum hCG levels. The 2007 meta-analysis by Hajenius et al. concluded that methotrexate is a treatment option for the medical treatment of low hCG ectopic pregnancies, although hCG levels are undefined. It ranges from < 5,000 IU/L to < 10,000 IU/L depending on the studies.¹² These recommendations seem justified considering that among the failures are those patients with the highest hCG levels, above 50,000 IU/ml. A level below 25,000 IU/L seems to be a reasonable option.

Certain conditions contraindicate medical treatment, namely lack of understanding of or compliance with follow-up, unstable hemodynamic status (pulse, blood pressure), extra-pelvic effusion on ultrasound, laparoscopy necessary for a definite diagnosis, history of homolateral ectopic pregnancy, tubal ectopic pregnancy with a size of more than 4 cm in diameter, presence of an embryo with cardiac activity.^{20,21} Nevertheless, cases of successful medical treatment for an unruptured ectopic pregnancy with a live embryo have been observed, which shows the relativity of the limits in the indications for medical treatment for an unruptured ectopic pregnancy.²²

Regardless of the protocol used, rigorous clinical and biological monitoring is necessary. HCG measurement should be continued weekly until it falls below 15 IU/ml. The time required to achieve undetectable β -hCG levels is variable.¹ Persistent ectopic pregnancy occurs when the hCG level rises.²³ In our series the time to achieve undetectable β -hCG levels was 6.7 weeks. The subsequent safety of methotrexate on fertility has been proven by its use in patients with trophoblastic tumors since the 1970s.¹ In these women, there was no increased risk of miscarriage or increased risk of birth defects or cancer.⁷ In fact, 5 pregnancies were recorded in our series. The success rate of methotrexate ranged from 65-95%.¹² Several studies have shown comparable efficacy of medical treatment compared to surgical treatment in unruptured ectopic pregnancies.^{7,12,24,25} Our success rate was comparable to those found in single-dose protocols.¹

Implications for practice and research

The indications for medical treatment are still subject to discussion. Most of the reported series are of small

sample sizes, which reduces their statistical power. Multicenter studies are therefore necessary in order to establish strong criteria for the selection of patients to be included. Patient advice should also be required, as medical treatment requires longer follow-up. Regarding cost, only studies evaluating the cost of conservative treatment of ectopic pregnancy are currently available. In these studies, the overall cost of medical treatment was lower than that of conservative surgical treatment thanks to a reduction in the duration of hospitalization. This financial advantage, however, was only verified for the early discovery forms: when the initial plasma hCG level was less than 3000 mIU/L in Mol's work, and 1,500 mIU/L in Sowter's study.^{26,27} Furthermore, in terms of quality of life, a randomized study comparing treatment with methotrexate with laparoscopic salpingotomy reported poorer tolerance to medical treatment.²⁸

Strengths and limitations

A strength of our study is that it is based on a large dataset in the leading maternities in Dakar.

However, this was a retrospective study. The data was taken from our E-Perinatal databases. The main limitation was the existence of incomplete files. It happened that certain parameters were not correctly recorded, which could be the origin of a bias.

CONCLUSION

The treatment of ectopic pregnancy, which used to be exclusively surgical, has evolved with the possibility of medical treatment. Methotrexate is now part of the therapeutic arsenal in the management of unruptured tubal ectopic pregnancies. However, in developing countries, particularly in Senegal, there is a reluctance to use this therapeutic method, which, however, when a personalized follow-up is carried out, is achievable with a success rate comparable to other therapeutic methods.

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