Nonsurgical Medical Management of Ectopic Pregnancy by Methotrexate

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Summary

The objective is to explore the effectiveness of conservative medical treatment of ectopic pregnancy (EP), using systemic intramuscular injection of methotrexate (MTX). A prospective study was made in 19 subjects of Eps, 15 treated by single dose MTX alone and 4 by multi-dose protocol with leucovorin rescue. All subjects were diagnosed by pregnancy test and transvaginal sonography (TVS) or transvaginal colour doppler imaging (TVCDI) without the aid of laparoscopy. A close controlled follow up was made with serial quantitative assays of circulatory β-hCG under guidance of serial pelvic sonography to note the progress of the disease. Out of 15 cases receiving single dose, 10 (66.6%) resolved spontaneously in 2-5 weeks and an additional 2 required second dose for successful treatment. Three cases however required surgical intervention. Of the 4 receiving multidose therapy, 3 were cured, 1 opted for surgical intervention. None complained of any significant side effects. The combined success rate for medical management using single or multidose protocol was 78.9% (15 cases). Five (62.5%) out of 8 subjects revealed patency in the affected tube when HSG was performed 3-5 months after successful treatment. The result is comparable to the patency of 8 out of 12 cases (66.6%) found after salpingostomy. We conclude that conservative treatment with single dose MTX provides an alternative line of management in carefully selected cases. We emphasize the value of early diagnosis of EPs before tubal damage and feel that medical treatment with systemic intramuscular methotrexate is simple, cost effective outpatient procedure with minimum hospital stay and may help to conserve tubal reproductive potential.

Introduction

More than any other new diagnostic modalities, transvaginal ultrasound (TVS) and sensitive pregnancy testing has made a significant improvement in the early diagnosis of ectopic pregnancy (EP), changed the face of its modern management dramatically from a radical to conservative surgery and to nonsurgical medical management. The focus is on awareness to detect EPs at an early unruptured stage.

The present work contains our ongoing experience in this exciting field particularly using Inj. MTX intramuscularly and applying transvaginal color doppler sonographic imaging (TVCDI).

Materials and Methods

From April 91 to December 98, a total 101 cases of EP were diagnosed; some forms of nonconventional treatment were planned in 44 subjects; 17 by salpingostomy, 2 by local intratubal MTX injection, 6 by expectant management. Systemic intramuscular injection of MTX was administered in 19 women. We highlight our experience in these 19 cases (Table I). In the beginning we diagnosed EPs presumptively by pregnancy testing and high resolution TVS (Das et al. 1993). Having diagnosed the disease by non invasive tools, we tried to offer prognostic status by measuring serum β-hCG levels.

Table I
Distribution of total 101 ectopic cases
(From April 1991-Dec. 1998)

	Clin. Susp.	Ect. Preg.	Conservative treatment
Total	221	101	44*

* 44 Cases treated conservatively

Treatment	No.
Salpingostomy	17
Treated expectantly	6
Intra tubal inj. MTX	2
I.M. MTX single dose	15
I.M. Multi Dose	4
Total	44*

Subsequently the condition was confirmed and treated surgically (Das and Mitra, 1995). With the expansion of our experience with pelvic scans today we are more confident of diagnosing EPs without the aid of laparoscopy (Fig. 1).

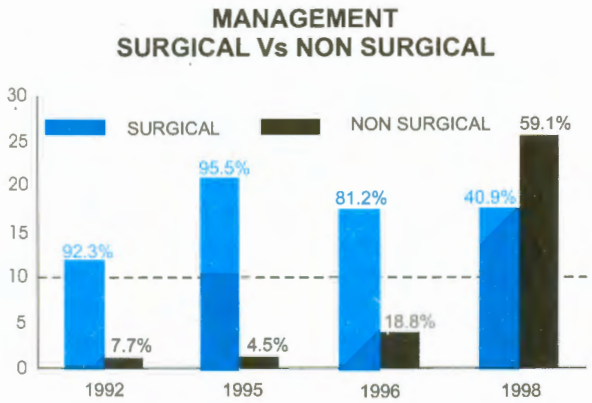

FIG. 1 - THE ABOVE GRAPH SHOWS OUR LEARNING CURVE TILL 1995. MAJORITY OF PRESUMPTIVELY DIAGNOSED EP WERE CONFIRMED AND TREATED BY SURGERY. AS OUR EXPERIENCE EXPANDED WE STARTED SELECTING MORE CASES FOR NONSURGICAL TREATMENT

For indeterminate sonographic findings in suspected failed intrauterine pregnancies (spontaneous abortions) chorionic villi were detected or excluded by bed side test. A simple naked eye examination of endometrial curretings floating in normal saline is a routine at our center (Das et al 1997). Since November 1997, 10 EPs were diagnosed and assessed by trans-vaginal pulsed wave color doppler sonographic imaging (TVCDI) (Aloka SSD 1700 Dynaview). The adnexal regions were mapped for color signal superimposed on high resolution gray scale picture to quantify the increased vascularity of peritrophoblastic areas with RI values obtained from the Doppler waveform.

Criteria for selection and follow up

Fifteen selected patients were managed with a single intramuscular injection of MTX 50-75 mg (1mg/kg of body weight), all displaying complex tubal mass, empty uterus and minimum or no fluid in peritoneal cavity. The pretreatment β-hCG titer ranged from 370 to 2246 (<2500 miu/ml). We further included 3 cases reporting higher initial β-hCG concentration at 5056, 4954 and 3702 miu/ml, for multi dose protocol as suggested by Stovall et al (1991). Inj. MTX 50-75 mg IM was given on alternate days and Inj. Leucovorin 5-7 mg IM (0.1mg/kg) on interventing days (total 4 doses). Another patient displayed tubal gestational sac of 15 X 26 mm and fetal pole (CRL 7 mm) without cardiac flicker discerning significant extra ovarian peritrophoblastic color flow signal (RI value ranging from 0.319 – 0.549) with no evidence of haemoperitoneum. Her pretreatment circulatory β-hCG concentration report was 7504 miu/ml. She was treated by intramuscular MTX injection with leucovorin rescue every week under control of weekly serum β-hCG assay till the β-hCG dropped below 25 miu/ml on day 31. All subjects selected for MTX therapy were haemodynamically stable and displayed empty uterus, no signs of tubal rupture or active bleeding. The tubal distention or the adnexal mass was not more than 3.5 cm. No patient had renal or hepatic diseases. During the week following administration of MTX the patient underwent strict follow up with daily or alternate days monitoring for pelvic scan. Serum β-hCG concentration was monitored again between day 5-7. All of them were counseled and advised to report to the hospital immediately, if the symptoms worsened. Cross matched blood was kept ready. Majority were treated as outpatients. However cases displaying gestational sac and high titer of hormone level or those complaining of moderate to severe pain were admitted initially for 2-3 days. Once the disease started resolving, the follow up interval was longer till the β-hCG became negative and tubal mass disappeared. Assessment of RBC, WBC, platelet count and liver and renal function tests were done before treatment and repeated between day 5-7.

Observation & Discussions

Out of 15 cases receiving single dose, 10(66.6%) resolved spontaneously. The pain and tenderness subsided within 4-5 days although a sharp increase of pain was reported within few hours of MTX administration in 3 cases which could be attributed to tubal spasm. TVS displayed gradual change in echo texture and size of adnexal mass which resolved in 2-7 weeks time (mean 35 days). Hormone level declined within the first 7 days and became negative within 10 to 35 days (mean 24 days).

Criteria for abandoning medical management

Three women required surgical intervention (laparoscopic salpingostomy) because the signs and symptoms started worsening along with a fall of haematocrit level and an increase in intraperitoneal bleeding. None had violent tubal rupture and we could preplan the surgical procedure. Rajan (1995) recommended combined approach of routine preoperative parenteral injection of 50-75 mg MTX following sonographic diagnosis to protect against imminent rupture and to buy time to perform easy surgery. After 5-7 days of follow up, another 2 cases experienced moderately intense abdominal pain, increasing tubal mass but no significant internal haemorrhage. Second sample of serum β-hCG concentration on day 5-7 did not indicate any significant fall (more than 66% of pretreatment value). We treated both of them with another dose of methotrexate; the pain and the mass subsided slowly. Of the 4 cases that received multi dose MTX therapy, 3 resolved spontaneously while 1 opted for laparoscopic salpingostomy on day 8 and we removed an organized tubal mole.

Results of color Doppler imaging (TVCDI)

Color signals were evident in 8, Seven of them reported hormone level above 1000 miu/ml where as 1 subject displayed color at 655 miu/ml concentration. Two cases did not display any color and reported low β-hCG concentration of 370 and 864 miu/ml. Kurjak (1994) observed similar findings and suggested that higher the concentration of circulatory hormone, more color flow and lower RI value. RI values in our series were variable ranging from 0.31 to 0.54. Ater MTX administration, quick decline of vascularity was evident as the trophoblastic tissue started degenerating; color signal disappeared within 4-28 days with slowly changing echo texture of adnexal mass.

Methotrexate the drug

In 1982 Tanaka and co-workers first reported successful resolution of an unruptured interstitial gestation using 15 days course of intramuscular MTX. Several studies have been reported using MTX either intravenously, intramuscularly or orally employing different regimens using folinic acid rescue and claiming success rate of around 70-90% (Goldenberg et al 1993).

Multi-dose protocol and adverse effects

Multidose protocol using systemic MTX by IM route as primary treatment of EPs found effective in 75-96% of cases (Ory et al 1986, Stovall et al 1991a). We treated 4 cases in our series, one complained of mild stomatitis and mucus membrane ulceration. However, the side effects were transient and disappeared within 48 hours after termination of therapy.

Other workers reported adverse effects like mild bone marrow suppression, stomatitis, impairment of liver function in 15-50% subjects.

Single dose protocol

Recently successful use of single dose of MTX has been advocated without the leucovorin rescue. Stovall and Ling (1993) reported successful resolution in 113 (94.2%) subjects in a prospective study of 120 women displaying EP with single dose intramuscular injection of MTX (50 mg/m2). We studied 15 subjects with single IM injection of MTX, none had side effects. Ten (66.6%) of them resolved completely. Another 2 cases required second dose of MTX injection for successful treatment giving an overall success rate of 80.0%.

Long term follow up:

After 3-5 spontaneous menstrual cycles following successful medical treatment, HSG displayed patent tube on the affected side in 5 (62.5%) out of 8 cases. This compared well with our salpingostomy series in which 8 out of 12 (66.6%) women reported patent ipsilateral tube after salpingostomy (Fig. II).

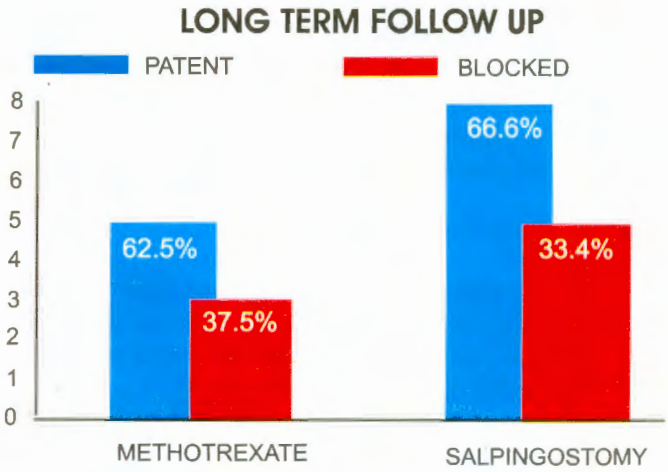

FIG. II. TUBAL PATENCY FOUND IN THE AFFECTED TUBE AFTER SALPINGOSTOMY AND MEDICAL TREATMENT WITH MTX

The single dose protocol offers many advantages like minimal hospital stay, outpatient treatment, and earlier resumption of normal activity. It is remarkably cost effective with a success rate of around 70-90% in selected cases (Piserka et al 1998). The key to the success however, is the ability to diagnose EPs without the aid of laparoscopy and a proper selection of cases.

Contraindications for medical treatment.

The presence of gestational sac displaying cardiac flicker is considered as a most ominous sign and viewed by most researchers as absolute contraindication to systemic MTX therapy (Ory et al 1986, Sauer et al 1987). Others observed that subjects having serum β-hCG level greater than 15000 miu/ml have more protracted course and likely to experience complication. Ory in 1991 observed that those who had tubal rupture following MTX therapy had initial serum β-hCG level 15000 miu/ml or above. Barring one, all 18 cases in our series displayed hormone concentration less than 5000 miu/ml.

Transvaginal color Doppler sonography

The recent introduction of TVCDI has added yet another tool in the hands of a modern clinician. Taylor et al (1989) first observed increase of high velocity low impedance blood flow from the intra or extra uterine placentation sites. As the trophoblasts invade the maternal tissue, increased blood flow was evident.

With TVCDI we could discern the areas of increased vascularity randomly dispersed in the adnexal complex mass and assess the trophoblastic activities which corelate well with the β-hCG titer in our studies. The addition of color in the same trans vaginal probe helped in early detection of extra uterine gestation and allowed better visualization of a tubal pregnancy, improved differentiation of nonviable intra-uterine pregnancy (incomplete and missed abortions) from pseudo gestational sac. The new modality offers increased accuracy and immediate results in the early detection of EPs and can predict its invasiveness.

Key Points for Clinicians

1. The aim of modern approach is nonsurgical medical management but key to success is our ability to diagnose early and offer prognosis and select the cases without the aid of laparoscopy.
2. Selection of different therapeutic options however, does not always depend on the clinician himself but on the individual case and her natural history.
3. Selected cases should be without active bleeding, serum β-hCG concentration should be below 10,000 miu/ml, without displaying cardiac activity.
4. Medical treatment is mainly based on the use of MTX. MTX treatment has its limit. The response to MTX is not uniform. While some are easily amenable to treatment others proved fairly resistant.
5. With careful selection and follow up, surgery can be avoided in significant number of cases in ambulatory patients with single dose of MTX,

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