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## Methotrexate versus hyperosmolar glucose in the treatment of extrauterine pregnancy

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**Abstract** The aim of this prospective, randomized, double blind study was to compare the efficacy of methotrexate and hyperosmolar glucose injected directly into the extra-uterine gestational sac under laparoscopic vision. The study included twenty women with ectopic pregnancy. Inclusion criteria were intact tubal pregnancy, not exceeding 4 cm in diameter, rising or plateauing  $\beta hCG$  levels, and no evidence of intra-abdominal bleeding. The patients were treated by laparoscopically guided injection of 3 mL fluid into the area containing the tubal pregnancy. The fluid contained either 25 mg methotrexate ( $n=9$ ) or 50% glucose ( $n=9$ ). Daily decrease in  $\beta hCG$  levels was faster in patients treated by methotrexate (median 8.7%) than in those treated by hyperosmolar glucose (median 4.8%),  $p=0.17$ . The study was discontinued due to a higher failure rate in the group treated by hyperosmolar glucose. In conclusion, local injection of methotrexate is superior to hyperosmolar glucose. It can be used as an alternative to salpingostomy or salpingotomy whenever laparoscopy is performed for the diagnosis and treatment of extra-uterine pregnancy.

**Keywords** Methotrexate · Hyperosmolar glucose · Ectopic pregnancy

### Introduction

Non-surgical management of extra-uterine pregnancy includes expectant management, systemic and local administration of a variety of drugs under different protocols, including methotrexate and hyperosmolar glucose.

Methotrexate is an anti-metabolite acting by inhibiting the action of dihydrofolate reductase. Hyperosmolar glucose causes local necrobiosis.

In the present study we have evaluated the efficacy of methotrexate and hyperosmolar glucose injected directly into the extra-uterine gestational sac under laparoscopic vision.

### Materials and Methods

This randomized double blind study included twenty women with sonographically confirmed diagnosis of extra-uterine pregnancy. Inclusion criteria were the presence of an intact tubal sac not exceeding four cm in diameter, rising or plateauing  $\beta hCG$  levels and no evidence of intra abdominal bleeding. All women were hemodynamically stable and wished to preserve their fertility potential.

The patients underwent laparoscopy for the confirmation of the diagnosis and were then randomized to be treated by either methotrexate (group 1) or 50% glucose (group 2). Eleven women were treated by laparoscopically guided injection of 25 mg methotrexate into the gestational sac, and in nine women 50% glucose was used for injection. The total volume of fluid injected into the gestational sacs was 3 mL.

Serum  $\beta hCG$  levels were measured on alternate days. Ultrasound assessment was performed daily. Originally, it had been planned to recruit a larger number of women. After interim analysis of the data on twenty patients the study was discontinued due to the results obtained.

### Results

Twenty women were enrolled. Fourteen patients completed the study. Clinical data is presented in Table 1.

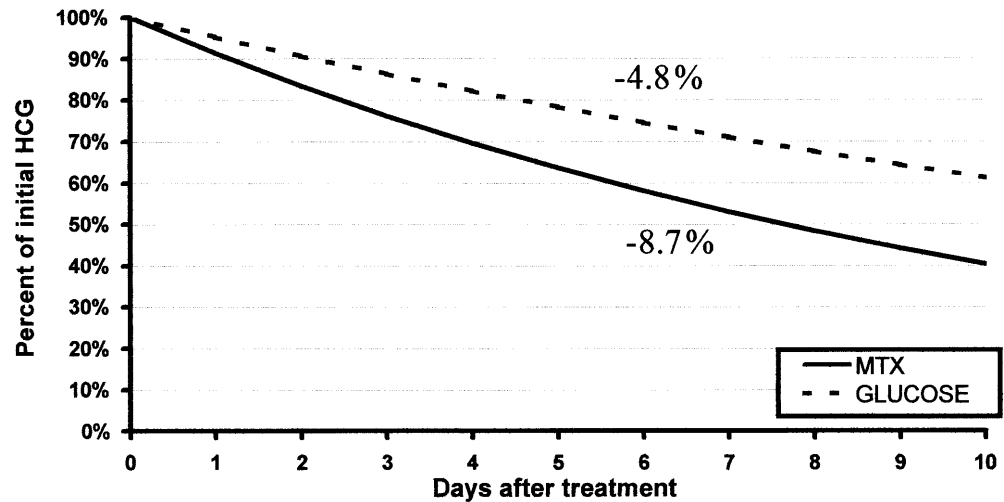
A decline of  $\beta hCG$  levels in group 1 was observed in nine of eleven patients (82%) after a mean of 3.1 d (range 2–8 d). In group 2  $\beta hCG$  levels decreased in five of nine patients (56%) after 5.2 d (range 2–12 d),  $p=0.34$ . Daily decrease in  $\beta hCG$  levels was faster in patients treated by methotrexate than in those treated by hyperosmolar glucose (median daily decrease of 8.7% and 4.8% respectively,  $p=0.17$ , Fig. 1. The mean hospital stay was shorter in patients receiving methotrexate than in patients treated with hyperosmolar glucose.

More failures were observed in patients treated by hyperosmolar glucose than in those treated by methotrex-

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**Table 1** Clinical data

Variable	Methotrexate <sup>a</sup> (Group 1; n=11)	Hyperosmolar <sup>a</sup> glucose (Group 2; n=9)	t-test p
Age [years]	27±5.1	31±5.9	0.138
Size of pregnancy [mm]	28±0.87	25±0.85	0.489
βhCG level on admission [mIU/mL]	3,238±4271.7	1,394±1165.4	0.196
Days until βhCG started to decrease	3.1±1.66	5.2±1.87	0.346
Hospitalization [d]	8±4.38	10±4.38	0.449

<sup>a</sup>Mean±S.D.**Fig. 1** Median daily decrease of βhCG levels

ate. In group 1, one woman underwent additional surgery (salpingectomy) because of persistent abdominal pains and obvious signs of peritoneal irritation. A second patient received an additional intra-muscular injection of methotrexate, because of rising βhCG levels. In group 2, two women underwent additional surgery (salpingectomy) because of ruptured extra-uterine pregnancy. Two other patients received an adjuvant of intra-muscular injection of methotrexate because of rising βhCG levels.

## Discussion

Methotrexate is a folic acid antagonist. It inhibits de novo synthesis of purines and pyrimidines, interfering with DNA synthesis and cell division. Actively proliferating trophoblast tissues are vulnerable to methotrexate [1]. Hyperosmolar glucose acts by an osmotic effect causing trophoblast cell dehydration.

High doses of methotrexate can cause bone marrow suppression, acute and chronic hepatotoxicity, stomatitis, pulmonary fibrosis, alopecia, and photosensitivity [4]. These side effects are infrequent in shorter treatment schedules, as used in ectopic pregnancy, and can be attenuated by the administration of leucovorin (citrovorum factor), [7]. Local therapy, i.e. direct injection into the ectopic gestational sac, resulted in fewer side effects probably due to reduced systemic distribution [4]. The advantage of hyperosmolar glucose is the virtual lack of toxicity and the absence of systemic side effects.

Direct injection delivers methotrexate to the site of implantation at a higher concentration that could be

achieved with systemic administration. Methotrexate was originally applied locally into an extra-uterine tubal pregnancy, by the vaginal route and under sonographic guidance [2]. In 1989 we reported our experience with a combined approach, namely direct injection of methotrexate into the gestational sac under laparoscopic vision followed by a course of intra-muscular methotrexate including folinic acid rescue [11]. In prospective studies [9], the reported success rate in the treatment of tubal pregnancy using local injection of methotrexate under laparoscopic vision was 79% (range 43–100%), and by ultrasound guidance 81% (range 70–95%). The success rate of a single intra-muscular injection of methotrexate was 92% (range 86–94%). Tzafettas et al. [8] reported on local administration of high dose methotrexate (100 mg), in advanced extra – uterine pregnancy which proved safe and effective (89%). The success rate of hyperosmolar glucose therapy was 74.4% (range 51–92%) by laparoscopic guidance [5, 6] and 84.2% (range 74–94%) when directed by ultrasound [3, 10].

In the present study methotrexate proved to be more effective than hyperosmolar glucose in treating extra-uterine pregnancy. βhCG levels started to decline earlier in patients treated by methotrexate than in those treated by hyperosmolar glucose. The daily decrease in βhCG levels was faster in patients receiving methotrexate than in those treated by hyperosmolar glucose (Figure 1). Results between both treatment groups were not statistically different, probably due to the small number of patients involved. Methotrexate therapy was associated with fewer requirements for supplementation of medical treatment as well as surgical intervention than treatment with

hyperosmolar glucose. The study was discontinued due to a higher failure rate in the group treated by hyperosmolar glucose.

Should we continue to treat patients with extra-uterine pregnancy by local injection of methotrexate or hyperosmolar glucose?

The success rate with systemic methotrexate treatment is high, and is now regarded as treatment of choice in the asymptomatic patient with unruptured ectopic pregnancy [9]. If laparoscopy is used in the management of EUP, most gynecologists would probably choose salpingostomy if the Fallopian tube needs to be preserved, although some may prefer local treatment. Moreover, some patients may request to refrain from surgical treatment of their oviduct and prefer other medical options. If under those circumstances local treatment is chosen, then we feel that local injection of methotrexate is superior to hyperosmolar glucose.

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