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Randomized comparison of health-related quality of life in women with ectopic pregnancy or pregnancy of unknown location treated with systemic methotrexate or expectant management

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ABSTRACT

Objective: To study the impact on health-related quality of life (HRQoL) of treatment with systemic methotrexate (MTX) or expectant management in women with ectopic pregnancy or pregnancy of unknown location (PUL) with low and plateauing serum hCG concentrations.
Study design: HRQoL was assessed alongside a randomized clinical trial (RCT) with the use of standard self-administered psychometric measure questionnaires.
Patients and setting: All women who participated in the multicenter RCT comparing treatment with systemic MTX to expectant management in women with ectopic pregnancy or persisting PUL were eligible for the HRQoL measurements.
Main outcome measure: HRQoL measures of three standardized questionnaires (SF-36, RSCL, HADS).
Results: Data were available for 64 of 73 women (78%) randomized in the RCT. We found no difference in HRQoL between the two treatment groups. The need for additional treatment, i.e. additional MTX injections or surgical intervention, had no impact on HRQoL.
Conclusion: Women treated with MTX or expectant management for an ectopic pregnancy or persisting PUL have comparable quality of life.

Introduction

The incidence of ectopic pregnancy is approximately 1–2% of all pregnancies [1]. At the initial presentation of women with a clinical suspicion of ectopic pregnancy, sonographic findings of an ectopic ring or mass and/or free fluid in the pouch of Douglas are supportive of the diagnosis. If these sonographic findings are absent, a tentative diagnosis of pregnancy of unknown location (PUL) is made. Women with a visible ectopic pregnancy and low and plateauing serum hCG concentrations or a persisting PUL have thus far been offered medical treatment with systemic methotrexate (MTX) [2]. However, it may be that early ectopic pregnancies follow the natural course of a self-limiting process, resulting in tubal abortion or reabsorption.

We published the results of a multicenter randomized clinical trial (RCT) in which we evaluated the effect of single dose systemic MTX and expectant management in women with ectopic pregnancy or PUL and low and plateauing serum hCG concentrations, the METEX study [3]. This RCT showed no advantage of single dose systemic MTX over expectant management in reaching an uneventful serum hCG clearance (relative risk 1.3, 95% confidence interval 0.9–1.8). In fact, 60% of women after expectant management had an uneventful clinical course with steadily declining serum hCG levels without any intervention. On the other hand, 30% of women who received MTX reported side effects. Thus, systemic MTX, a potentially harmful drug, did not have a larger treatment effect than expectant management and may be withheld in asymptomatic women with an ectopic pregnancy or PUL and low and plateauing serum hCG concentrations.

Given the observed clinical equivalence of systemic MTX and expectant management, health-related quality of life (HRQoL)

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becomes an important factor for women to choose one treatment over the other leading to better treatment satisfaction. The aim of this study was therefore to examine women's HRQoL in the METEX study. We hypothesized that systemic MTX treatment would be more burdensome to women as a result of the potential side effects and the necessity for adequate contraception during three months because of the potential teratogenicity of MTX.

Materials and methods

Study population

All women who participated in our RCT with sufficient Dutch or English language skills to complete questionnaires were eligible for the HRQoL measurements. Included in the RCT were hemodynamically stable women with either an ectopic pregnancy visible on transvaginal sonography (an ectopic ring or an ectopic mass and/or fluid in the pouch of Douglas) and a plateauing serum hCG concentration <1500 IU/l or with a persisting PUL and a plateauing serum hCG concentration <2000 IU/l. A plateauing serum hCG was defined as a <50% hCG increase or decrease between day 0 (first visit for clinically suspected ectopic pregnancy) and day 4. Women with a viable ectopic pregnancy, signs of tubal rupture and/or active intra-abdominal bleeding, a contraindication for MTX or <18 years of age were not eligible.

After written informed consent had been obtained, women were randomly allocated to systemic MTX or expectant management. The trial was conducted from April 2007 to January 2012 in one academic hospital, eight teaching hospitals and two non-teaching hospitals in The Netherlands. The trial was registered as an International Standard Randomized Clinical Trial (METEX study ISRCTN 48210491, Eudract number: 2006-003003-39) and was approved by the Medical Ethical Committee of the Academic Medical Center and the boards of the individual participating hospitals. Individual or aggregate HRQoL results were not made available at any stage of the clinical study.

Clinical study design and treatment

Women allocated to systemic MTX received a single MTX injection, 1 mg/kg body weight i.m. with a maximum of 100 mg, within 24 h after randomization. Women allocated to expectant management did not receive any specific treatment. Both treatment and weekly follow up were carried out in an outpatient setting.

The primary treatment outcome was an uneventful decline of serum hCG to an undetectable level (<2 IU/l) by the initial intervention strategy. All women received instructions to contact the clinic in case of clinical symptoms related to tubal rupture. Women were advised to refrain from sexual intercourse until serum hCG was undetectable. Women receiving MTX were informed about the possible side effects and the interactions with alcohol, non-steroidal anti-inflammatory drugs, aspirin and antibiotics, and received advice on fluid intake, buccal hygiene and exposure to sunlight. They were advised to use adequate contraception during a period of three months after the last MTX injection [4]. In both groups of women, weekly serum hCG measurements (expressed in IU/l) were performed until hCG was no longer detectable. In women treated with systemic MTX, repeated doses of MTX were given if the serum hCG concentration failed to fall by at least 15% at the weekly follow up visit, with a maximum of three additional injections [5,6]. If more than four MTX injections in total were required, surgical treatment was indicated. In women allocated to expectant management, treatment with systemic MTX (single dose 1 mg/kg i.m.) was administered whenever at any of the weekly follow-up visits the serum hCG concentration had risen compared with the prior value. Expectant management was continued if the serum hCG concentration fell by >15% of the prior value. In case of a persistent plateauing serum hCG concentration the serum hCG concentration was reassessed after 48 h to ensure it was not increasing. If it did increase by >15%, treatment with systemic MTX was administered with a maximum of four injections. In case more than four MTX injections were required, surgical treatment was indicated. Whenever hemodynamic instability and/or clinical signs of tubal rupture (i.e. increasing abdominal pain in combination with a falling hemoglobin level and signs of intra-abdominal hemorrhage on transvaginal sonography) occurred, laparoscopic surgical intervention was carried out. Surgery, either via salpingotomy or salpingectomy, was done according to local protocol. Patient characteristics and clinical data were collected in a case record form filled in by the local coordinator of the trial and coded by a unique patient identification number. The case record forms were collected by the main investigator (NvM) after completion of treatment. Details of the design, follow up and results of this trial have been described earlier [3].

Health-related quality of life measures

We assessed women's HRQoL with the use of several standard self-administered psychometric measures with established reliability and validity: the Medical Outcome Study 36-Item Short Form Health Survey (SF-36), the Rotterdam Symptom Checklist (RSCL), and the Hospital Anxiety and Depression Scale (HADS). The questionnaires were administered via one single document.

Women were asked by their clinicians to fill out the questionnaire which was available in the Dutch and English language. The questionnaire was coded by the unique patient identification number. HRQoL was assessed at four time points to compare short- and long-term treatment effects on health-related quality of life. Each questionnaire was identical and took 10–15 min to complete. The first questionnaire was completed before randomization and thus before women were informed about their treatment allocation (baseline, T0). The second questionnaire was given to women to complete at their first follow up visit after one week (T1). Women received the next questionnaires to complete at home at four weeks (T2), and 12 weeks (T3) after randomization. These questionnaires were filled in and returned in a sealed pre-paid envelope to the main investigator.

The SF-36 is a generic questionnaire with eight health-status subscales: physical functioning, role limitations due to physical health problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional health, and general mental health. The scores on the subscales are aggregated into the standardized summary scores Physical (PCS) and Mental Component Score (MCS). Scores were transformed into a 0–100 scale, a standardized score of mean = 50 and SD = 10 represents the Dutch population average [7].

The RSCL is a standard questionnaire with established validity and reliability [8]. This questionnaire was developed to measure symptoms, originally to assess the HRQoL of patients with cancer. It comprises four sub-scales: physical symptoms, psychological distress, activity level and a single item measuring overall quality of life. For this study we only used the subscale physical symptoms. The physical symptom scale consists of a list of symptoms that may be experienced by patients in general, and we added a few items on MTX specific side effects. Subscale scores were transformed into a 0–100 scale, with higher scores indicating more symptoms and a lower quality of life.

The HADS is a self-report instrument that exists of two 7-item scales: one for anxiety and one for depression each with a score range of 0–21; a lower score indicating less anxiety or depression, a score of 9–12 is indicative of a depressive period [9].