Surgical management of tubal pregnancy
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Summary, implications for clinical practice and future research

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SUMMARY

Ectopic pregnancy was a major cause of maternal mortality until the late 19th century. The first attempts to treat ectopic pregnancy surgically were recorded in the late 18th and early 19th century, but survival rates were low. The discoveries of general anaesthesia and the control of pain, antisepsis and the possibility of autologous or allogeneic blood transfusions allowed the transition to modern surgery in the late 19th and early 20th century, which consisted of removal of the pregnancy by laparotomy.

Over the years, surgery became ever more successful which gradually shifted the emphasis from saving the life of the mother to the preservation of her future fertility. In 1920, Beckwith Whitehouse was the first to question the policy to routinely remove the tube under all circumstances. He performed the first salpingotomy. From the 1950's onwards, this concept of preservation of the affected tube (salpingotomy) was propagated over ablative surgery (salpingectomy) in view of future reproductive capacity. Salpingotomy was widely adopted, assuming a positive effect on future reproductive outcome, while accepting the potential drawback of a repeat ectopic pregnancy in the same tube or the incomplete removal of the pregnancy, i.e. persistent trophoblast.

When we started the studies described in this thesis, it still had not been proven by randomised controlled trials whether salpingotomy indeed provided better fertility prospects than salpingectomy.

The work presented in this thesis first addresses the magnitude of the clinical problem of surgically treated tubal pregnancy in The Netherlands. Next, we studied the adherence to recommendations from the Dutch guideline on diagnosis and management of ectopic pregnancy. A systematic review and meta-analysis was performed to evaluate the effectiveness of surgery, medical treatment and expectant management in terms of treatment success (i.e. complete elimination of trophoblastic tissue), financial costs and future fertility. This systematic review confirmed the lack of knowledge on the impact on future fertility of the two surgical approaches, salpingotomy and salpingectomy. Therefore, we started an international multicentre randomised controlled trial comparing salpingotomy with salpingectomy, with future pregnancy being the outcome of interest. Finally, we investigated the impact on financial costs (cost-effectiveness analysis) and women’s preference towards salpingotomy and salpingectomy.

Chapter 1 gives an overview of the historical developments in the surgical management of ectopic pregnancy leading up to current clinical practice. An outline and description of the objectives of this thesis is given.

In chapter 2 we describe the results of a nationwide population study and report on time trends in the incidence of ectopic pregnancy and pelvic inflammatory disease. The hospital admissions from 1980 to 2005 were derived from Dutch Medical Registries and incidence
trends were calculated and analysed by joinpoint regression. The peak incidence of ectopic pregnancy in 1988 (11/1,000 live births) was preceded by a peak incidence of admissions for pelvic inflammatory disease in 1983 (0.6/1,000 women of all ages). The ectopic pregnancy rate declined towards 2005 (7.3/1,000 live births) mainly due to a decrease in ectopic pregnancy in urban regions and in older aged women (≥ 35 years). In 2005, women < 25 years and born between 1985 and 1990 were once again at an increased risk of ectopic pregnancy (12/1,000 live births). This rise was not preceded by a peak incidence of clinical admissions for pelvic inflammatory disease, but may be related to the significant increase in positive tests for genital Chlamydia trachomatis during preceding years.

Chapter 3 reports an implementation study to assess the adherence to the Dutch guideline on diagnosis and management of ectopic pregnancy. We developed 12 guideline-based quality indicators using the systematic RAND-modified Delphi method. With these indicators, patient care was assessed in 317 women in six Dutch hospitals (two university, two teaching and two non-teaching hospitals) between 2003 and 2005. The highest adherence (98%) was observed for transvaginal sonography during the diagnostic workup. The lowest adherence (21%) was observed for salpingotomy in case of contralateral tubal pathology. Wide variance in adherence (0–100%) existed between the academic, teaching and non-teaching hospitals. We concluded that the overall guideline adherence of 75% was reasonable, but with ample room for improvement in the adherence to the diagnostic algorithm and salpingotomy in those cases with contralateral tubal pathology.

Chapter 4 presents a systematic review and meta-analysis to evaluate the effectiveness of surgery, medical treatment and expectant management of tubal ectopic pregnancy in terms of treatment success (i.e. complete elimination of trophoblastic tissue), financial costs and future fertility. We searched for randomised controlled trials which described treatment interventions that have been widely adopted in clinical practice. A systemic literature search identified 15 trials on eight comparisons. The meta-analysis showed that for salpingotomy, laparoscopic surgery is the most cost-effective treatment for tubal ectopic pregnancy in comparison to conventional surgery by laparotomy. The number needed to harm with laparoscopic surgery for persistent trophoblast was 12. In other words, when 12 women are treated by laparoscopy instead of laparotomy, there is one extra case of persistent trophoblast. Whether salpingotomy or salpingectomy should be performed was not studied in randomised controlled trials yet. To prevent one case of persistent trophoblast after salpingotomy the number needed to treat with a prophylactic single shot methotrexate intramuscularly immediately postoperatively was 11. As a consequence, more than 90% of women would receive the potentially harmful dose of methotrexate without needing it. In our view, therefore, post-operative serum hCG monitoring is a better option for the timely detection and treatment of persistent trophoblast in those women who actually need it.
Comparisons with methotrexate showed that systemic methotrexate in a multiple dose regimen is a good alternative to surgery in selected women with low serum hCG concentrations. Subsequent fertility did not differ between systemic methotrexate and salpingotomy and systemic methotrexate in low or standard dosages. A comparison on expectant management was not possible due to lack of randomised controlled trials and expectant management could not be evaluated.

Chapter 5 presents the results of an international multicentre randomised controlled trial in 32 centres in The Netherlands, Sweden, the United Kingdom and the United States, that investigated whether salpingotomy offers better fertility prospects in comparison to salpingectomy. From September 2004 through November 2011, we randomly assigned women with a laparoscopically confirmed tubal pregnancy and a normal contralateral tube, to either salpingotomy or salpingectomy. A total of 450 women were enrolled, 4 were excluded owing to the inability to provide data and 446 were randomised. To assess fertility after surgery, women were contacted every six months with a time horizon of 36 months. The cumulative ongoing pregnancy rate by natural conception (the primary outcome measure) was 60.7% after salpingotomy and 56.2% after salpingectomy (Fecundity Rate Ratio 1.06; 95% CI, 0.81 to 1.4; Log rank test P value = 0.67). Persistent trophoblast occurred more frequently in the salpingotomy group than in the salpingectomy group: 14/215 (7.0%) versus 1/215 (0.4%); Rate Ratio 15; 95% CI 2.0 to 113, P value = 0.001). Repeat ectopic pregnancy occurred in 18/215 women (8.4%) in the salpingotomy group versus 12/231 (5.2%) in the salpingectomy group (Rate Ratio 1.6; 95% CI 0.80 to 3.3, P value = 0.25). From these data we conclude that in women with a tubal pregnancy and a normal contralateral tube, salpingotomy does not improve fertility prospects over salpingectomy. A meta-analysis with one other study confirmed these results.

Chapter 6 describes a cost effectiveness analysis which was performed alongside the randomised controlled trial as described in the previous chapter, i.e. in women with a tubal pregnancy treated by salpingotomy or salpingectomy in the presence of a normal contralateral tube. Although women had comparable ongoing pregnancy rates, after salpingotomy there was a higher risk of persistent trophoblast necessitating additional medical or surgical treatment. Also, repeat ectopic pregnancy occurred slightly more often after salpingostomy, as compared to salpingectomy. Both conditions imply potentially higher costs after salpingotomy. We performed the cost-effectiveness analysis from a hospital perspective and compared direct medical costs of salpingotomy and salpingectomy until an ongoing pregnancy occurred by natural conception within a time-horizon of 36 months. Direct medical costs included surgical treatment of the initial tubal pregnancy, re-admissions including re-interventions, treatment for persistent trophoblast and interventions for repeat ectopic pregnancy. Mean direct medical costs per woman in the salpingotomy group and in the salpingectomy group were €3,319 versus €2,958, respectively, with a mean difference of €361 (95% Confidence Interval €217 to €515). Salpingotomy resulted in a marginal
higher ongoing pregnancy rate by natural conception compared to salpingectomy leading to an incremental cost-effectiveness ratio €40,982 (95% CI – €130,319 to €145,491). Since salpingotomy resulted in more additional treatment for persistent trophoblast and interventions for repeat ectopic pregnancy, the incremental cost-effectiveness ratios for these outcome measures were not informative. We concluded that salpingotomy is not cost effective since the costs of salpingotomy per woman with a tubal pregnancy are higher than for salpingectomy, without additional benefit on future fertility. These results suggest that in women with tubal pregnancy in the presence of a normal contralateral tube, salpingectomy is the preferred treatment.

In chapter 7 we describe a patient preference study on salpingotomy or salpingectomy for tubal pregnancy. This study investigated women surgically treated for tubal ectopic pregnancy and subfertile women desiring pregnancy and their preferences for salpingotomy relative to salpingectomy by means of a web-based discrete choice experiment consisting of 16 choice sets. Scenarios representing salpingotomy differed in three attributes: chance of an intrauterine pregnancy, risk of persistent trophoblast and risk of repeat ectopic pregnancy. An ‘opt out’ alternative, representing salpingectomy, was similar for every choice set. A multinomial logistic regression model was used to analyse relative importance of the attributes. This study showed that the negative effect of repeat ectopic pregnancy was 1.6 times stronger on the preference of women compared with the positive effect of the spontaneous intra uterine pregnancy rate. For all women, the risk of persistent trophoblast was acceptable if compensated by a small rise in the spontaneous intra uterine pregnancy rate. We concluded that women preferred avoiding a repeat ectopic pregnancy to a higher probability of a spontaneous intra uterine pregnancy. In view of the results of our randomised controlled trial as described in Chapter 5 and 6, which were obtained after the preference study took place, our conclusion that salpingectomy is the preferred treatment in women with a normal contralateral tube, indeed is justified from a patients perspective as well.

**IMPLICATIONS FOR CLINICAL PRACTICE**

- Laparoscopy is the surgical approach of choice as it is less costly than the open surgical approach, even though there is a higher persistent trophoblast rate after salpingotomy.
- In women with tubal pregnancy and a normal contralateral tube salpingectomy should be the preferred intervention because of its favourable short term outcome in terms of primary treatment success, its lower costs, and in the absence of any significant negative effect on fertility prospects. This recommendation is supported by the results of the patient preference study that showed a strong preference of women towards salpingectomy.
- In women with tubal pregnancy and contralateral tubal pathology and a wish to
conceive again a salpingotomy is recommended. Since the chance of contralateral tubal pathology is 25% and cannot be predicted pre-operatively, both possible surgical interventions should be discussed with the patient before laparoscopy (1).

- Salpingotomy should not be combined with a prophylactic shot of systemic methotrexate to prevent persistent trophoblast since the number needed to treat is 11. Postoperative serum hCG follow up is a better option to prevent unnecessary methotrexate treatment.

IMPLICATIONS FOR FUTURE RESEARCH

We encountered several difficulties during the course of the ESEP trial. These difficulties should be explored to gain more knowledge with the purpose to effectively conduct studies in the near future.

Lessons to be learned from the ESEP trial

- Recruitment of women was slower than expected thereby delaying the implementation of the results in clinical practice. Factors associated with good and poor recruitment to multicentre trials have been reported on various levels including the patient and the clinician (2). On the level of the patient, we frequently observed a strong preference for either treatment, usually salpingotomy, as a reason for denying consent. Known barriers on the level of the clinician are time constraints, lack of staff and training, loss of professional autonomy, difficulty with the consent procedure, lack of rewards and recognition, and an insufficiently interesting question (3). For the ESEP trial, time constraints, lack of staff and lack of rewards were probably applicable. Women with tubal pregnancy were frequently ad hoc diagnosed and treated out of office hours, when availability of staff was limited and research nurses were unavailable. Moreover, the time interval between diagnosis and surgery was usually short compared to other studies, with a higher risk of missing eligible patients. In addition, a financial reward for inclusion was not available because of limited funding of the study. Apart from those barriers mentioned above, we identified another potential barrier which might have contributed to the slow recruitment: the comparison between two treatments that were already established in daily practice seems to have been a barrier as well, but to our knowledge this has not been reported previously. Whenever practice variation is present in medicine, obviously, for critical outsiders and for those with an academic mind this raises questions and implies equipoise, while this may not necessarily be the case for the busy clinician following his local protocol or daily routine by using one of the established treatments. Even if the hospital participates in the trial, recruitment remains poor if equipoise is not reflected in the local protocol and thus not felt by those who should recruit patients. For future studies it might be beneficial if, before the start of recruitment, all participating centres would agree to offer the treatment which is considered ‘the experimental treatment’ within the study only. This means that some
hospitals need to bring their local protocol into agreement with the study protocol and hence change their ‘standard treatment’. This potential barrier and others should be further investigated, for example as is done in the IMPACT study. This cohort study on a series of multicenter trials performed in a nationwide network will provide insight in barriers and facilitators for successful patient recruitment in trials (4).

- In retrospect, the timing of the planned interim analysis was in adequate. When the follow up data of 150 women were complete for the planned interim analysis (being pregnant of an ongoing pregnancy by natural conception or at 36 months after randomisation), the last women had already been recruited in the trial and the interim analysis was therefore futile. In future clinical trials with a (possible) long time interval between randomisation and primary endpoint, this aspect of timing of the interim analysis should be foreseen.

- There was a long time span between the recruitment of women and the availability and publication of the results of the trial. After recruitment had finished, while awaiting the fertility follow up time horizon of 36 months, participating centres in the ESEP study did not know how to properly counsel their patients with tubal pregnancy, and which intervention to apply. When treatments are already in widespread use, the option to continue randomising patients seems to be realistic and worthy of serious consideration. The relative advantages and disadvantages of each option should be discussed including the ethical implications (5). In the situation where the trial treatment is already widely available, the point is that patients, who participate from an altruistic view point, should have a reasonable idea of the probability of their data being used and how this might contribute to society. In future studies, the study group should give a recommendation to the participating centres before recruitment ends.

- For the sample size calculation of the ESEP study, an absolute increase of 15% in ongoing pregnancy rate by natural conception was considered to be of clinical significance (from 40% after salpingectomy to 55% after salpingotomy) in overcoming the disadvantages of salpingotomy i.e. persistent trophoblast and repeat ectopic pregnancy. Perhaps we should have taken the costs of subsequent fertility workup and treatment (ART) into account and thus have focussed on a smaller difference. In a cohort study which we performed already 16 years ago, salpingotomy became cost-effective compared to salpingectomy with subsequent IVF, if the ongoing pregnancy rate by natural conception after salpingotomy was just 2.2% higher or more (absolute risk difference) in comparison to salpingectomy (6). With a 2.2% higher pregnancy rate after salpingotomy all costs of subsequent IVF were covered. Although smaller clinically relevant differences implicate much larger study sample sizes than we are currently used to, this subject of taking IVF into account should be used for sample size calculations of future studies in this field.
SUMMARY AND IMPLICATIONS

- The last but not the least difficulty concerns the problems encountered in conducting a multicentre randomised trial with limited funding. The studies presented in this thesis were supported by personal grants from The Netherlands Organisation for Health Research and Development (www.zonmw.nl) and The Health & Medical Care Committee of the Region Västra Götaland, Sweden, but the budget was very tight. The discrepancy with every day clinical practice, where unevaluated medical treatments are carried out at the expense of the community – in case of reimbursement by the health insurance – or by patients – in case of private payments – is striking. It is our hard felt belief that reimbursing unevaluated diagnostic methods and treatments should be stopped, and the money saved should be spent on clinical trials evaluating care.

Future role for salpingotomy

In the ESEP study, presented in this thesis, women with contralateral tubal pathology were excluded as previous cohort studies indicated that these women experience better fertility prospects with conservative surgery, i.e. salpingotomy. Although we did not find a treatment benefit of salpingotomy, whether salpingotomy is beneficial in women with contralateral tubal pathology should be further investigated, probably with the exception of those women with only one remaining tube. As a proof of principle, we recently started a nationwide cohort study in The Netherlands within the Dutch Consortium to investigate whether any ongoing pregnancies by natural conception occurred after salpingotomy (www.studies-obsgyn.nl/esep2).

Recently, another randomised controlled trial on salpingotomy versus salpingectomy was published (DEMETER study) (7). This trial found a similar result on cumulative ongoing pregnancy rates as the ESEP study (HR 1.13, 95% CI 0.73–1.71). Women with contralateral tubal pathology were not excluded, but no subgroup analysis on contralateral tubal pathology was done. Such a post hoc analysis is desirable. Our conventional meta-analysis of the ESEP trial and the DEMETER trial showed no significant differences in cumulative ongoing pregnancy rates between salpingotomy and salpingectomy but we observed considerable clinical heterogeneity. An Individual patient data analysis (IPD) is desirable to study the results in more detail and overcome the differences mentioned above.

When to offer surgery, systemic methotrexate or expectant management?

In our systematic review many direct comparisons were studied, but still quite a few important comparisons are lacking for clinical practice, for example surgery versus expectant management. A new type of meta-analysis is network meta-analysis. Network meta-analysis has advantages over conventional pair wise meta-analysis, as the technique borrows strength from indirect evidence to gain certainty about all treatment comparisons and allows for estimation of comparative effects that have not been investigated head to head in randomised clinical trials (8). The possibility of such a meta-analysis should be
further explored within the treatment of tubal pregnancy. Results could provide guidance for effective design of future randomised controlled trials, or identify subgroups of those women who would benefit the most from a specific treatment option. Eventually, the best but challenging study design may be a cohort study in which all asymptomatic women diagnosed with tubal pregnancy are managed expectantly, and only to install systemic methotrexate treatment in women with persisting serum hCG concentrations after a certain period of time, and to reserve surgery for those women with clinical signs of impending or obvious tubal rupture (9).
REFERENCES


