Surgical management of tubal pregnancy
Mol, Femke

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Salpingotomy or salpingectomy in tubal ectopic pregnancy: What do women prefer?

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ABSTRACT

There is an ongoing debate whether tubal ectopic pregnancy should be treated by salpingotomy or salpingectomy. It is unknown which treatment women prefer in view of the potentially better fertility outcome but disadvantages of salpingotomy. 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: intrauterine pregnancy (IUP) chance, 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 IUP rate. For all women, the risk of persistent trophoblast was acceptable if compensated by a small rise in the spontaneous IUP rate. The conclusion was that women preferred avoiding a repeat ectopic pregnancy to a higher probability of a spontaneous IUP in the surgical treatment of tubal ectopic pregnancy.
INTRODUCTION

In the majority of women with tubal ectopic pregnancy, laparoscopic surgery is the treatment of first choice (1). So far, no consensus has been reached whether salpingotomy or salpingectomy leads to better fertility outcome. A few non-randomized studies using life table analysis suggested that intrauterine pregnancy (IUP) rates are higher and time to subsequent IUP is shorter after salpingotomy compared with salpingectomy (2-4). Especially in women with a history of bilateral tubal pathology, salpingotomy offered better IUP rates, whereas in women without a history of tubal pathology this benefit could not be demonstrated. Not unexpectedly, these studies found that the risk of persistent trophoblast, necessitating additional treatment with systemic methotrexate (MTX), and repeat ectopic pregnancy after salpingotomy was increased (3, 4).

Apart from clinical outcomes, patients’ preferences are also of importance in clinical decision making. In the field of surgical treatment of ectopic pregnancy, patients’ preferences are not known. The question is whether patients feel that a possibly better fertility outcome after salpingotomy as compared with salpingectomy outweighs the risk of persistent trophoblast and repeat ectopic pregnancy. Discrete choice experiments (DCE) have increasingly been used in health care as an approach to elicit patient preferences (5-7). The current study therefore Investigated the preference of women of reproductive age regarding salpingotomy relative to salpingectomy by means of a DCE.

MATERIALS AND METHODS

Participants

Women were Included who had been treated for tubal ectopic pregnancy in The Netherlands as part of The European Surgery in Ectopic Pregnancy (ESEP) trial (ISRCTN37002267). The ESEP trial is an ongoing international multicenter randomized controlled trial that compares salpingotomy and salpingectomy for tubal ectopic pregnancy to study the impact on future fertility. Only women with a tubal ectopic pregnancy amenable to both treatment interventions and a healthy contralateral tube at surgery are included in this trial. Women pregnant after IVF and/or with known documented tubal pathology are excluded, as well as women with no desire for future pregnancy. Further details of the ESEP protocol are described elsewhere (8). Women were invited to participate in the present study at least 3 months after undergoing surgery. They were contacted by telephone by the Dutch ESEP coordinators and were informed about this study. As these women had experienced either salpingotomy or salpingectomy, their preferences could have been biased by the treatment they had received (9). This study therefore also included consecutive patients first visiting the Centre for Reproductive Medicine in the Academic Medical Centre and the infertility clinic in the Onze Lieve Vrouwe Gasthuis in Amsterdam from March until June 2008. These women
CHAPTER 7

were considered to be representative for those who might experience an ectopic pregnancy in the future, and thus could face this dilemma, yet were naive to both salpingotomy and salpingectomy. These women were invited through an Information leaflet explaining the study, handed out by the consulting doctor of the infertility clinic. Women with a history of surgically treated ectopic pregnancy and those referred for IVF were excluded for obvious reasons.

Interview procedure

All women were sent a web-based questionnaire. Women with unopened or incomplete questionnaires were contacted by phone as a reminder and were offered additional instructions if required. A paper version of the questionnaire was sent to women without an internet connection and/or e-mail address. The questionnaire contained general information about tubal ectopic pregnancy, followed by a thorough description of salpingotomy and salpingectomy and the pros and cons of both treatment interventions. After reading the general Information, but before starting the actual questionnaire, women were asked about their preference if they were to be confronted with the choice between salpingotomy and salpingectomy in case of a tubal ectopic pregnancy (a-priori preference).

Discrete choice experiment

Preferences for salpingotomy relative to salpingectomy were studied by means of a DCE. A DCE assumes that a given treatment intervention can be described by its characteristics or ‘attributes’ and that women’s preferences for an intervention are determined by the levels of these attributes (5, 7, 10, 11). The relative importance of the attributes is assessed by offering a choice between several sets of treatment alternatives with systematically varying combinations of attribute levels (6). A DCE was designed to determine the trade-offs that women make between a hypothetically improved spontaneous IUP rate against the burden of additional treatment with systemic MTX for persistent trophoblast together with the increased risk of a repeat ectopic pregnancy after salpingotomy.

<table>
<thead>
<tr>
<th>Table 1. Chosen attributes and given attribute levels (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous IUP rate within 1 year (81)</td>
</tr>
<tr>
<td>Salpingotomy</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>Salpingotomy</td>
</tr>
</tbody>
</table>

EP = Ectopic Pregnancy; IUP = intra uterine pregnancy; MTX = methotrexate.
Attributes and attribute levels

The selection of attributes was based on data from the literature, expert panel opinion and personal views of women eligible for the ESEP study. The attributes were defined as: (i) spontaneous IUP rate within 1 year after surgical treatment; (ii) the risk of additional treatment with systemic MTX for persistent trophoblast; and (iii) the risk of a repeat ectopic pregnancy in the same tube. The attribute levels for spontaneous IUP were 20-50%, for persistent trophoblast 5-20% and for repeat ectopic pregnancy 5-15%. IUP and ectopic pregnancy rates were derived from previous non-randomized studies using life table analysis (3, 12). Persistent trophoblast rates were derived from data of randomized controlled trials varying from 8% to 20% (1). The current study also included some hypothetical frequency rates within a clinically realistic range to emphasize the trade off within certain scenarios. Each attribute was composed of four levels (Table 1).

Development of the choice sets

The questionnaire consisted of choice sets. Each choice set was built up by two alternatives representing hypothetical scenarios of salpingotomy (treatment option A and treatment option B) and a similar ‘opt out’ alternative representing salpingectomy (treatment option C). An example of a choice set is shown in Figure 1.

The combination of three attributes with four levels each, provided 64 (43) hypothetical scenarios for salpingotomy. For practical reasons, not all of these could be used in a questionnaire. Therefore, a fractional factorial design was used to generate a functional sample of these 64 scenarios. The fractional factorial method systematically selects this sample according to an orthogonal design. Orthogonality guarantees an optimal balance of the levels and attributes with minimal correlation (13). The orthogonal design was generated by Orthoplan (Statistical Package for Social Sciences version 14.0; SPSS, USA) and a set of 16 profiles was selected for treatment option A. Second, to ensure minimal overlap of attribute levels, a set of profiles for treatment option B was created by means of a cycle fold over technique based on the profiles of treatment option A (6). As a result, 16 choice sets of treatment option A and B were sufficient to estimate all main effects representing the relative importance of each attribute.

In each choice set, treatment option C (salpingectomy) had identical levels of the attributes, being an opt-out scenario (Table 1). In this scenario, the levels for a spontaneous IUP within 1 year were set at 20%, for the risk of persistent trophoblast at 0% and for repeat ectopic pregnancy in the same tube at 0% (3).

Two dominant questions were introduced as a rationality test to select valid responses for further analysis. Dominant questions were questions in which one of the scenarios had all favourable attribute levels, so that it was logically preferable. Data from women who failed this rationality test were excluded from further analyses.

Finally, a pilot study was performed with 10 subfertile women desiring future pregnancy to ensure the understanding of the questionnaire. An interesting additional factor that
some DCE include is financial costs. The pilot study introduced a willingness to pay (WTP) question. A WTP question requires the respondent to specify a monetary amount that she would be willing to pay for a certain advantage, benefit or other attractive attribute. Money is then simply used as a unit to quantify relative personal value. However, women found it difficult to understand the principle behind this question and subsequently had trouble estimating their willingness to pay. Therefore, it was decided to focus on clinical outcomes only, which implies that this study cannot answer issues as financial costs and success rates of subsequent IVF treatment or health insurance coverage.

Statistical analyses

The DCE was analysed by taking each choice among the three treatment alternatives (two scenarios salpingotomy and the opt-out salpingectomy) as an observation and then analysed by a multinomial logistic regression model. Assuming that all attributes have an independent effect on a woman’s preference, the following model was estimated (6, 13, 14): 

$$ V = \beta_0 + (\beta_1 \text{IUP within 1 year}) + (\beta_2 \text{treatment for persistent trophoblast}) + (\beta_3 \text{repeat ectopic pregnancy}) $$

where $V$ is the observed value and represents the utility (i.e. satisfaction or happiness) for the treatment, as derived from the observed choice behaviour, $\beta_0$ is the constant term reflecting the respondents’ preference for salpingotomy relative to salpingectomy and $\beta_1, \beta_2$ and $\beta_3$ are the coefficients that indicate the relative importance of each attribute.
The absolute value of V has no direct interpretation, but an alternative with a higher V is preferred over an alternative with a lower V (13). The sign of a coefficient reflects whether the attribute has a positive or negative effect on the overall utility. As all attributes used a similar scale (risk percentages), the magnitude of a coefficient indicates the relative importance of the corresponding attribute. A statistically significant coefficient was interpreted as indicating that the respondent considered the attribute important.

All women were analysed by a multinomial logistic regression model. Obviously, women had different profiles based on their history of ectopic pregnancy treatment by salpingotomy or salpingectomy and their a-priori preference. Therefore, the interaction effects of these profiles were tested in the model. Results are presented for the constant term and the three attributes if significant. Whether the fit of the model improved significantly by adding interaction effects, was tested with the likelihood ratio test.

RESULTS

A total of 136 women consented to participate in the study. Of these women, 103 completed the questionnaire: 56 (79% response rate) women who had been treated for tubal ectopic pregnancy (patient group) and 47 (72% response rate) subfertile women desiring pregnancy. After performing the rationality test, 50 (89%) responses from the patient group and 43 (91%) from the group of subfertile women were available for the DCE analysis. The mean number of months between surgery and the questionnaire was 19.4 ±9.4. Baseline characteristics are summarized in Table 2.

The a-priori preference of the participants before answering the DCE is presented in Figure 2. For women who experienced salpingotomy (n = 23) the a-priori preference for salpingotomy was 78%, whereas for those who experienced salpingectomy (n = 27) the a-priori preference for salpingotomy was 46%. In the subfertile women group (n = 43) the a-priori preference for salpingotomy was 88%.

The results of the multinomial logistic regression modelling of all women together are presented in Table 3. The constant term, $\beta_0$, reflecting women’s preference for salpingotomy relative to salpingectomy was not significant ($\beta_0 = -0.40$). The impact of the attributes ($\beta_1$, $\beta_2$ and $\beta_3$) on the preference for salpingotomy relative to salpingectomy was significant ($P< 0.001$). Women’s preference for salpingotomy increased per percent rise in IUP rate ($\beta_1 = 0.11$), decreased per percent rise in the risk for persistent trophoblast ($\beta_2 = -0.03$) and decreased per percent rise in the risk of repeat ectopic pregnancy ($\beta_3 = -0.18$).

The results of the interaction effects of the profiles, i.e., type of treatment (salpingotomy or salpingectomy) and a-priori preference, are presented in Table 3. Women who had experienced salpingectomy had a significantly decreased preference towards salpingotomy ($\beta_0$ constant term + interaction effect $=-0.4-1.08=-1.48$; $P = 0.02$). Women with an a-priori preference for salpingotomy had a significantly increased preference for salpingotomy ($\beta_0$ constant term + interaction effect $= -0.4 + 1.73 = +1.33$; $P < 0.001$ ).
### Table 2. Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 50)</th>
<th>Subfertile women (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Mean no. of previous Pregnancies</td>
<td>3.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean no. of children</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean no. of previous Miscarriages</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Previously treated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of salpingotomy</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>No. of salpingectomy</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>No. with no treatment</td>
<td>0</td>
<td>43</td>
</tr>
<tr>
<td><strong>Educational level (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>27 (54%)</td>
<td>21 (49%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3 (6%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>High</td>
<td>20 (40%)</td>
<td>20 (47%)</td>
</tr>
</tbody>
</table>


### Table 3. Analysis of women’s treatment preferences in tubal ectopic pregnancy and significant interaction effects of treatment and preference.

<table>
<thead>
<tr>
<th></th>
<th>Regression coefficient (β)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salpingotomy relative to salpingectomy (n = 93)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β₀: Constant term (preference for salpingotomy)</td>
<td>-0.40</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Attributes (per percent)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β₁: Spontaneous IUP rate within 1 year</td>
<td>+0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β₂: Treatment with MTX for persistent trophoblast</td>
<td>-0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β₃: Risk of repeat EP in the same tube</td>
<td>-0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Significant interaction effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women who experienced salpingectomy with β₀</td>
<td>-1.08</td>
<td>0.02</td>
</tr>
<tr>
<td>A-priori preference for salpingotomy with β₀</td>
<td>+1.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Attributes (per percent)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women who experienced salpingotomy with β₁</td>
<td>-0.04</td>
<td>0.03</td>
</tr>
</tbody>
</table>

A total of 4461 observations: (93 respondents x 16 choices x 3 options per choice) minus 3 missing values; pseudo R² = 0.29; log pseudolikelihood = -1155.9. EP = ectopic pregnancy. IUP = intrauterine pregnancy; MTX = methotrexate; NS = not statistically significant.
Of all attributes, there was only an interaction effect on the attribute spontaneous IUP. Women who had experienced salpingotomy had a significantly lower preference for salpingotomy per percent rise in IUP rate compared with the rest of the women ($\beta$, + interaction effect = 0.11-0.04 = 0.07; $P = 0.03$)

**DISCUSSION**

Patients’ perspectives on the benefits and burden of therapy can differ from those of health professionals (15). It is generally acknowledged that patients’ preferences influence clinical decision making and it is therefore important to be aware of these preferences (16, 17).

In this study, the preference of women regarding salpingotomy relative to salpingectomy in tubal ectopic pregnancy was assessed by determining the trade off women make. In these trade offs, the study focused on the clinically relevant outcomes after salpingotomy:

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**Figure 2** Flowchart on the a-priori preference for salpingotomy or salpingectomy as stated by women before starting the questionnaire.
spontaneous IUP, persistent trophoblast and repeat ectopic pregnancy in the same tube. The relative importance of these outcomes was assessed by offering choices between salpingotomy or salpingectomy and systematically varying combinations of these outcomes within a clinically realistic range. The method of a discrete choice experiment was used.

This study shows that, in general, women valued salpingotomy and salpingectomy equally if both treatments would result in the same pregnancy rate and would have the same risk of persistent trophoblast and repeat ectopic pregnancy. However, women who had experienced salpingectomy had a preference towards salpingectomy. The a-priori preference of salpingotomy led to a stronger preference towards salpingotomy in the case where clinical outcomes were equal. The moment clinical outcomes differed; the risk of a repeat ectopic pregnancy strongly influenced the preference of women. This risk of a repeat ectopic pregnancy was only accepted if compensated by a better spontaneous IUP outcome after salpingotomy. Women who had been surgically treated for a tubal ectopic pregnancy by salpingotomy weighed the risk of a repeat ectopic pregnancy even stronger than those treated by salpingectomy or who had never been treated at all. In contrast, the risk of additional treatment with systemic MTX for persistent trophoblast was already acceptable if compensated by a minor rise in the spontaneous IUP rate.

The observed difference in general preference in women who had experienced salpingectomy can be explained by cognitive dissonance reduction which means that patients will strive for consistency between past behaviour and current cognitions because inconsistencies will lead to distress (18). Patients who had been treated by salpingectomy reduced inconsistency between their current treatment preference and their past behaviour by emphasizing the advantages of salpingectomy. In the interpretation of these data, one should realize that the patient group comprised of women who participated in an ongoing randomized controlled trial comparing salpingotomy and salpingectomy for tubal pregnancy. Therefore, these women had no strong a-priori preference for one treatment or the other as they agreed to participate in the trial, but this may have changed post-operatively as a result of one of the attributes of the experienced treatment. This may be extrapolated to the group of subfertile women who responded without any personal experience of this condition. Ideally, one would like to have included women who are about to be treated surgically for tubal ectopic pregnancy, but this type of research is impossible for obvious reasons, i.e. the acute circumstances and the considerable distress patients experience preoperatively. The best one can do, therefore, is to ask women who experienced an ectopic pregnancy what their preference would be if they were to suffer from ectopic pregnancy again and to inform those who are naive to surgical treatment about the pros and cons of both treatment strategies and then ask them what their preference would be if they were to suffer this disease. Even so, this study may have slightly underestimated the preference of women concerning surgical treatment for ectopic pregnancy.
In preference studies, there is no agreed methodology for determining the statistical power based on the sample size. According to previous published work on patients’ preferences, it was decided to include at least 40 women in each group of whom the data were available for DCE analysis (5). The obtained groups were sufficiently large to demonstrate the observed effect with sufficient statistical power.

A potential limitation is that the main effects were studied only by using a fractional factorial design. Although these main effects generally account for 70-90% of explained variance in a DCE, specific effects associated by specific combinations of attribute levels may have remained unidentified (13).

This study approached the participants by telephone and invitation cards and, once informed consent had been obtained, a web-based questionnaire was sent. Advantages of offering a web-based questionnaire compared with classic interviews are improvement in patient participation, dynamic input validation during completion, the ability to provide popup boxes with additional information, elimination of manual data entry, larger geographical reach, anonymous data entry and elimination of an interviewer bias (19). An obvious drawback is that only respondents with internet access can be included (coverage bias) and respondents with a lack in knowledge or skills for computer programs may quit the questionnaire prematurely (non-response bias) or unintentionally enter the wrong answer (measurement errors). To overcome these errors, an administration page was included in the web application to keep track of the status of the questionnaires. In case of unopened or incomplete questionnaires, respondents were contacted by phone and were offered additional instructions if required. A paper version of the questionnaire was prepared and sent to respondents without an internet connection and/or e-mail address.

Pregnancy rates are often the decisive factor in decision making among infertility patients (20). In a study assessing patients’ preferences for intrauterine insemination, patients preferred a higher IUP rate, accepting the risk of ovarian hyperstimulation syndrome up to even 10%. The risk of a multiple pregnancy rate did not influence their preference at all (21). Another preference study in the field of reproductive medicine among infertile patients regarding elective single- and doubleembryo transfer strategies, showed that women were not willing to trade-off their IUP chance to avoid a multiple pregnancy (22). In contrast to these studies, both the present study and a study on patients preference for systemic MTX versus laparoscopic salpingotomy in women with tubal ectopic pregnancy showed that elimination of current disease is more important than future fertility prospects (23). These studies all concern infertility patients, but the differences in priority might be explained by their ‘point of departure’. An infertile woman is not ill from a disease: her primary goal is pregnancy. Future complications or a multiple pregnancy have mostly not been experienced (yet) and thus more difficult to take into account in choice behaviour. In contrast to an infertile woman trying to imagine suffering from this disease, a woman having
been treated for an ectopic pregnancy (a potentially lethal disease) will want to reduce the risk of disease and therefore reduce the risk of a repeat ectopic pregnancy. For this woman, future pregnancy prospects may not be the highest ranking problem when expressing her preference for treatment. This knowledge is important in understanding women with tubal ectopic pregnancy and the choices they make for the treatment they prefer.

Acknowledgements

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REFERENCE LIST


