Impaired ovarian blood flow and reduced antral follicle count following laparoscopic salpingectomy for ectopic pregnancy

C.C.W.Chan\textsuperscript{1}, E.H.Y.Ng, C.F.Li and P.C.Ho

Department of Obstetrics & Gynaecology, The University of Hong Kong, 102 Pokfulam Road, Hong Kong SAR, China

\textsuperscript{1}To whom correspondence should be addressed. E-mail: cwcchan@graduate.hku.hk

BACKGROUND: Whether salpingectomy affects ovarian function is controversial. In this study, ovarian function was assessed by antral follicle count, ovarian volume and ovarian stromal blood flow measured by three-dimensional (3D) power Doppler ultrasonography. The objectives of the study were to compare the ovarian function of the operated side with the non-operated side after unilateral salpingectomy performed through laparoscopy or laparotomy for ectopic pregnancy. METHODS: Thirty-two patients with unilateral salpingectomy performed for ectopic pregnancy were recruited: 18 through laparoscopy and 14 through laparotomy. Ultrasound scans were performed in the early follicular phase. RESULTS: Ovarian volume, antral follicle count and 3D power Doppler indices were comparable between the operated and the non-operated sides in the whole group and in the laparotomy group. The antral follicle count and 3D power Doppler indices were significantly reduced on the operated side in the laparoscopy group. CONCLUSIONS: Ovarian function seems to be impaired after laparoscopic unilateral salpingectomy at short-term assessment.

Key words: antral follicle count/ovarian function/salpingectomy/three-dimensional power Doppler ultrasonography

Introduction

Salpingectomy is indicated in patients with ectopic pregnancy and with hydrosalpinx proceeding to IVF treatment. For treatment of ectopic pregnancy, salpingectomy is in general preferred to salpingotomy because the subsequent intrauterine pregnancy rate was found to be comparable whether the previous ectopic pregnancy was treated with salpingectomy or salpingotomy in two meta-analyses (Clausen, 1996; Yao and Tulandi, 1997), but the recurrent ectopic pregnancy rate was higher after salpingotomy than after salpingectomy (Clausen, 1996). Furthermore, failure to completely remove the ectopic pregnancy was also higher with salpingotomy (Pouly et al., 1986; Maymon et al., 1995; Dubuisson et al., 1996; Dwarakanath et al., 1996). The presence of hydrosalpinx impairs the outcome of IVF (Strandell et al., 1994; Zeyneloglu et al., 1998; Camus et al., 1999). A large-scale multicentre study showed that prophylactic bilateral salpingectomy in the sub-group of patients with ultrasound-visible bilateral hydrosalpinges improved the IVF outcome (Strandell et al., 1999). Recently, a meta-analysis of three randomized trials confirmed that the odds of pregnancy, ongoing pregnancy and live birth were increased with laparoscopic salpingectomy for hydrosalpinges prior to IVF (Johnson et al., 2002). One of the concerns against salpingectomy is the possibility of impairing the ovarian function after the procedure. The most important blood supply to the Fallopian tube is the medial tubal artery, which originates at the same point as the median ovarian artery. If the salpingectomy procedure is not properly performed close to the tube, it may disrupt the normal blood flow to the ovary. Various studies have attempted to evaluate the impact of salpingectomy on ovarian function. All these studies used the ovarian response after ovarian stimulation for IVF as the study model (Verhulst et al., 1994; Lass et al., 1998; Dar et al., 2000; Strandell et al., 2001; Tal et al., 2002), but the results were not consistent. Some of these operations were performed via laparoscopy (Dar et al., 2000; Strandell et al., 2001), others were either not specified (Verhulst et al., 1994; Lass et al., 1998) or mixed (Tal et al., 2002). Furthermore, additional procedures including either contralateral salpingectomy or tubal cauterezation were performed in some (Dar et al., 2000; Strandell et al., 2001) or all patients (Verhulst et al., 1994); and some had pelvic adhesions or hydrosalpinx in the contralateral tube (Tal et al., 2002). With the exception of the studies by Lass et al. (1998) and Dar et al. (2000) who compared the ovarian response of the operated and the non-operated sides after unilateral salpingectomy, all other studies reported the overall ovarian response in patients with unilateral or bilateral salpingectomy, or before and after salpingectomy.

Ovarian volume (Syrop et al., 1995; Lass et al., 1997; Sharara et al., 1999; Syrop et al., 1999), antral follicle count (Tomáš et al., 1997; Chang et al., 1998; Sharara et al., 1999; Ng et al., 2000) and ovarian stromal blood flow (Zaidi et al.,...
1996; Bassil et al., 1997; Engmann et al., 1999; Kupesic and Kurjak, 2002; Kupesic et al., 2003) have been extensively used to predict ovarian response prior to stimulation for IVF. In particular, three-dimensional (3D) ultrasound power Doppler imaging has been shown to be well correlated with ovarian response and subsequent IVF outcome (Kupesic and Kurjak, 2002). Since ovarian function cannot be measured directly, ovarian response to gonadotrophin stimulation can be considered as a surrogate measurement for ovarian function. In this study, these markers were used to assess the ovarian function. The objectives of the study were to compare ovarian function between the operated and the non-operated sides in the same individual who had unilateral salpingectomy for ectopic pregnancy through laparoscopy or laparotomy. The hypothesis was that ovarian function was impaired after salpingectomy.

**Materials and methods**

This study was approved by the Institutional Review Board of the hospital. Patients with a history of salpingectomy for treatment of ectopic pregnancy who presented to the subfertility clinic in a teaching
hospital for investigation or treatment between July 2002 and December 2002 were recruited. All these patients met the following criteria: unilateral salpingectomy at least 3 months ago, no history of ovarian or other tubal surgery, no extensive pelvic adhesion found during the operation, no ovarian cyst on pelvic ultrasound scan examinations, and no hormonal treatment for the preceding 3 months.

Patients were asked to attend the clinic on the second day of the menstrual cycle, at around 08:00 to 10:00. All 3D ultrasound scan examinations were performed by C.C.W.C. using Voluson 730® (Kretz, Austria), after the patients had emptied the bladder. The assessor was blinded to the treatment the patients received. The antral follicle count was obtained using the same machine in the two-dimensional (2D) mode during the ultrasound examinations. Both ovaries were scanned with the power Doppler mode. The setting condition for this study was: Frequency: Mid, Dynamic set: 2; Balance: G>140; Smooth: 5/5; Ensemble: 12; Line Density: 7; power Doppler Map: 5; and the setting condition for the sub-power Doppler mode was: Gain: –6.0; Balance: 140; Quality: normal; Wall Motion Filter: low1; Velocity range: 0.9 kHz. The 3D ultrasound images were stored for later analysis by C.C.W.C., who was blinded as to what the operation the patient had had and which side was operated on.

The built-in Vocal® (virtual organ computer-aided analysis) Imaging Program for the 3D power Doppler histogram analysis was used for analysis with computer algorithms to form indices of blood flow and vascularization and the ovarian volume. The vascularization index (VI) indicated the proportion of the volume showing a flow signal in the total volume of the ovary. The flow index (FI) was an average of the intensity of flow signal inside the ovary. The vascularization flow index (VFI) was a combination of the presence of vessel and the amount of flow made by multiplying the FI and VI (Pairleitner et al., 1999). During the analysis and calculation, the manual mode of the Vocal® Contour Editor was used to cover the whole 3D volume of the ovary with a 15° rotation step. Hence, 12 contour planes were analysed for each ovary to cover 180°. A completely reconstituted 3D view of the ovary is shown in Figure 1A. The VI, FI and VFI of this ovary are shown in the grey box in Figure 1B.

To determine the intraobserver error, another 14 healthy women underwent similar 3D ultrasound examinations with the same Doppler setting as in the study. These 28 3D images were stored and later evaluated by the same investigator (C.C.W.C.) on two separate occasions. The intraobserver variations for VI, FI and VFI were 6.6, 0.5 and 4.9% respectively. The readings of the two independent assessments by the same investigator were highly correlated, with the Pearson’s correlation coefficients for VI, FI and VFI being 0.92, 0.98 and 0.97 respectively.

**Statistical analysis**

Distributions of the variables were given as median (interquartile range). Continuous variables were compared using Mann–Whitney U-test, whereas categorical variables were compared using χ²-test. In this study, ovarian function was assessed by the antral follicle count, the ovarian volume and the ovarian stromal blood flow indices including VI, FI and VFI. These parameters of the operated and the non-operated sides were compared using Wilson signed ranks test. Possible confounding factors included age of the patient, smoking and the interval from operation to ultrasound examination. \( P < 0.05 \) was considered significant. For the purpose of sample size calculation, FI was used as the primary outcome parameter. The FI of 64 fertile subjects was 28.26 ± 7.42 (mean ± SD) (unpublished data). The sample size of 14 patients should be able to detect a 20% reduction in FI of the operated side after salpingectomy as compared to the non-operated side with a power of 80% and \( P = 0.05 \). This reduction in FI was arbitrarily chosen and its clinical significance was undetermined.

**Results**

A total of 32 patients with a history of unilateral salpingectomy was recruited. Eighteen underwent laparoscopic while 14 underwent laparotomy approach. The median age for all of the patients was 34 (interquartile range 31–40) years. The median duration between the operation and the ultrasound scan examination was 17 (7–40) months. The median total antral follicle count per patient was 10.5 (7.0–16.0), and the median total ovarian volume was 13.79 (10.98–16.32) cm³. The median VI, FI and VFI were 0.80 (0.11±1.42), 26.77 (22.77–26.70) and 0.23 (0.03–0.39) respectively.

There were no significant differences in the antral follicle count, the ovarian volume, and 3D ovarian stromal indices (VI, FI and VFI) between the operated and the non-operated sides in the whole group (data not shown) and in the laparotomy group (Table I). However, when the analysis was restricted to those in the laparoscopy group, the antral follicle count and 3D ovarian stromal indices of the operated side were significantly reduced when compared to the non-operated side. The ovarian volume was not affected (Table II).

The baseline characteristics of the patients including the age and smoking status were similar between the two groups except that patients with salpingectomy by laparotomy had a longer interval between the date of operation and the ultrasound scan assessment (Table III). This was understandable, as most cases of ectopic pregnancies would have been operated via the laparoscopic approach in recent years unless there was haemodynamic instability at the time of presentation.
Discussion

Whether salpingectomy affects ovarian function remains a controversial issue. Theoretically, since the median ovarian artery is very close to the medial tubal artery at their origins, an injudicious surgery to this area can undoubtedly jeopardize ovarian arterial supply which can in turn disrupt normal steroid production and follicular development. An early study using 2D Doppler ultrasonography demonstrated an increase in the pulsatility index (PI) of the ovarian artery 3 months after Filshie clip sterilization but the increase was not detected at 2 days (Sumiala et al., 1995). Hence it was not surprising that a later study involving patients who underwent laparotomy for tubal ligation by Pomeroy technique showed no difference in ovarian blood flow when the ultrasound scan examination was performed 1 month after the surgery (Geber and Caetano, 1996). Furthermore, 2D frequency-dependent Doppler ultrasonography was limited by the subjective selection of the plane of measurement, low sensitivity, angle-dependency and susceptibility to aliasing (Rubin et al., 1994; Meyerowitz et al., 1996). With the recent advent of 3D power Doppler ultrasonography, the quantification of the total blood flow of the ovaries becomes feasible.

In this study, we evaluated ovarian stromal blood flow using 3D power Doppler ultrasonography in patients who had had unilateral salpingectomy for ≥3 months. Two other markers of ovarian function, the antral follicle count and the ovarian volume, were evaluated at the same time. There was no difference in all these markers on the ipsilateral side of salpingectomy when compared to the non-operated side. However, when only those with laparoscopic salpingectomy were analysed, the antral follicle count and the ovarian blood flow were significantly reduced. Our findings were in fact similar to those of Sumiala et al. (1995). If the mechanism of reduced ovarian blood flow after sterilization is due to the interruption of blood supply, the same mechanism applies in salpingectomy which involves more extensive surgery than sterilization. Furthermore, the decreased antral follicle count was further evidence that vascular supply was jeopardized. In fact, Lass et al. (1998) reported a reduction in the ovarian response after gonadotrophin stimulation during IVF treatment on the side with salpingectomy performed while the ovarian volume remained unchanged. Ovarian volume is generally viewed as an insensitive marker in this respect, as it may require years for such a difference to be clinically evident.

It is interesting to find that such a reduction in antral follicle count and ovarian blood flow were not seen in those in the laparotomy group. We are cautious about the difference between the laparotomy and laparoscopy groups, which may be related to uneven distribution of patients as this was not a randomized study. However, it is possible that during open surgery, it was easy to place the surgical clamp very close to the mesenteric border of the affected Fallopian tube and hence limit any damage to blood vessels in the mesosalpinx. In contrast, during laparoscopic salpingectomy, bipolar diathermy was the method employed in cauterizing the mesosalpinx in our hospital. This procedure was sometimes made difficult by the angle of access. Moreover, the heat damage could be more extensive with diathermy as the depth of damage was not limited to the excision site. It is therefore imperative that meticulous surgical skills be employed and surgical excision of the Fallopian tube be performed as close to the tube as possible. Since the laparotomy group had significantly longer interval between the date of the operation and the ultrasound scan assessment than the laparoscopy group, the differences in these ovarian markers could be accounted for in terms of this different interval rather than the mode of surgery. If the impaired ovarian blood flow was related to a disruption in blood supply, it was possible that the effect might be short term only as no such reduction in ovarian blood flow could be observed in the laparotomy group after a longer gap between operation and the assessment. Further long-term follow-up studies will be necessary to address this issue.

Ovarian response to gonadotrophin during IVF treatment is commonly used to evaluate ovarian function after salpingectomy. In two retrospective case-controlled studies (Verhulst et al., 1994; Tal et al., 2002), no difference in ovarian response after gonadotrophin stimulation during IVF treatment could be found between patients with and without salpingectomy. In order to limit bias introduced by the control group, Dar et al. (2000) and Strandell et al. (2001) used the patients themselves as the controls, and compared the ovarian response to gonadotrophin during IVF treatment before and after salpingectomy. There was again no difference demonstrated. However, Lass et al. (1998) showed a reduction in the number of follicles >10 mm in mean diameter on the day of the hCG administration and the number of oocytes recovered from the operated side compared with the non-operated side. When the

### Table III. Comparison between the laparoscopy and laparotomy groups: baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Laparoscopy (n = 18)</th>
<th>Laparotomy (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34 (31–38)</td>
<td>36 (33–44)</td>
<td>0.251</td>
</tr>
<tr>
<td>Median body weight (kg)</td>
<td>53.0 (47.9–61.8)</td>
<td>52.1 (50.0–61.4)</td>
<td>0.750</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159 (155–164)</td>
<td>156 (154–157)</td>
<td>0.138</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>22</td>
<td>36</td>
<td>0.400</td>
</tr>
<tr>
<td>Interval from operation to ultrasound examination (months)</td>
<td>7 (6–71)</td>
<td>38 (17–86)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Values are median (interquartile range).

*Mann–Whitney U-test.

*K-test.
ovarian response was compared between patients with and without salpingectomy, the difference was not evident.

These controversial findings probably indicated that the difference in ovarian response after gonadotrophin stimulation was modest, even if it was present. Such observations did not contradict with our findings in this study because the models employed were different. We believe that if ovarian function is affected by salpingectomy through disruption of arterial blood supply, the ovarian blood flow is the first parameter to be affected. The use of 3D power Doppler ultrasonography is therefore the best method to study such a subtle and early change. The antral follicle count may also be affected early by disrupted blood supply to the ovaries. Ovarian response after gonadotrophin stimulation, like ovarian volume, is a late phenomenon and can only be shown years after salpingectomy. Any subtle reduction in ovarian blood flow and antral follicle count may be overcome by the hyperstimulation induced by high dose gonadotrophin given during IVF treatment. This postulation helps to explain the observation that ovarian response was not altered even after bilateral salpingectomy (Strandell et al., 2001). However, the long-term implication of impaired ovarian function cannot be overlooked. Not addressed in this study is the possibility of early menopause as a result of these changes especially if the procedure is performed on both sides. Furthermore, the effect on ovarian function may differ with the initial indication for salpingectomy. While these parameters were impaired after laparoscopic salpingectomy for ectopic pregnancy, such observations might not present after laparoscopic salpingectomy for hydrosalpinx. In conclusion, we have demonstrated impaired ovarian blood flow and reduced antral follicle count on the operated side shortly after laparoscopic unilateral salpingectomy. This may imply an adverse sub-clinical short-term effect on the ovary after salpingectomy. Whether such an effect persists in the long term will need further evaluation. However, during the operation, care should be undertaken not to disrupt the blood vessels in the mesosalpinx as far as possible.

Acknowledgements

The three-dimensional ultrasound machine used in this study was funded by the Hong Kong Research Grant Council (HKU 7280/01M).

References


Tal, J., Palitzie, Y., Korobotchka, R., Ziskind, G., Eibschitz, I. and Ohel, G., 2179


Submitted on April 1, 2003; resubmitted on May 13, 2003; accepted on June 26, 2003