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Roberta Venturella, Fulvio Zullo, Errico Zupi & Costantino Di Carlo

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Effect of salpingectomy on ovarian response to hyperstimulation during *in vitro* fertilization: does it really matter?

Until the end of the twentieth century, the medical community has considered salpingectomy as a trivial appendix of more complex gynecological surgeries or as an “emergency” option to solve life-threatening conditions such as ruptured ectopic tubal pregnancies. In the last 20 years, however, something has changed. Salpingectomy “*per se*” achieved increasing consensus as a procedure which (1) can reduce the risk of serous ovarian carcinoma, (2) can improve IVF pregnancy rate in patients with hydrosalpinx, and (3) represents an effective method of permanent sterilization [1].

The “Kurman theory” that considers the distal Fallopian tube as the site of origin for ovarian and peritoneal serous cancers [2] is achieving increasing consensus, leading many national societies to recommend consideration of prophylactic salpingectomy during surgery for benign conditions in women who accomplished their reproductive desire [3].

On the other side, the Practice Committee of the American Society for Reproductive Medicine (ASRM) published in 2008 a Committee opinion supporting the practice of salpingectomy prior to *in vitro* fertilization (IVF) in patients with hydrosalpinx, with the aim of improving pregnancy rates [4]; the recommendation was reiterated in 2015 in a Committee opinion on the role of tubal surgery in the era of assisted reproductive technology [5].

Hydrosalpinx adversely affect IVF outcomes, by reducing the implantation rate and increasing the risk of miscarriage [4,5]. Among the pathogenic mechanisms proposed, embryo-toxic effects, mechanical flushing and changes in endometrial receptivity are considered the most probable by reproductive gynecologists. According to these pathogenic theories, the rationale behind surgical treatment of hydrosalpinx prior to IVF is to eliminate the negative effect of the hydrosalpingeal fluid either by aspirating it (ultrasound-guided aspiration) or by removing the entire fallopian tubes (salpingectomy) or by isolating them from the uterine cavity (laparoscopic or hysteroscopic proximal occlusion).

Therefore, in tubal factor infertility, when the cause is irreparable hydrosalpinx, IVF is now considered the best option rather than attempting to restore tubal function [4,5] and tubal surgery is recommended only to exclude the tubal content from the endometrial cavity before an embryo try to implant inside.

Thanks to these procedures, the hydrosalpinx fluid can no longer reach the uterine cavity and exert its toxic effect on implantation, the most delicate phase of pregnancy. According to this view, everybody will agree that the correct method to verify the effectiveness of surgical treatments of hydrosalpinx (as salpingectomy or tubal occlusion) compared with no intervention prior to IVF is to evaluate the live birth rate or, at least, the clinical pregnancy rate as the main study outcomes.

Nevertheless, in 2016, Fan and Ma [6] published their meta-analysis aimed to compare ovarian response to hyperstimulation during IVF between patients who underwent salpingectomy for hydrosalpinx or for ectopic pregnancy and controls. Of the 25 studies included in the final analysis, 12 were in English and 13

in Chinese. Moreover, as correctly reported by authors, 21 studies were retrospective, and four were prospective. More relevant is the fact that the IVF protocols were not homogeneous. Indeed, 18 studies used long protocols, three used short protocols, three used other not-specified protocols and in one case the protocol used was not clearly stated. This most likely reduces the value of the total dose of gonadotropins and the duration of hyperstimulation as outcomes. Finally, the basal FSH value, which is another outcome evaluated, is currently considered the most indirect marker of ovarian reserve, given its recognized inter and intra-cycles variability.

The meta-analysis demonstrated that the number of oocytes retrieved in patients who underwent salpingectomy is not significantly different from that of the control group (IV -0.09 [95% CI $-0.20, 0.03$]; $p=.15$) and shows substantial evidence of heterogeneity ($I^2=65\%$). Conversely, statistical significance could be found when bilateral and unilateral salpingectomies are split into two groups and each group is compared to controls. Unfortunately, of the 25 studies included, the two negatively influencing the results of these comparisons are articles published in Chinese, for which only the abstract is available [6]. All the other studies report not significant differences among groups for this outcome. Therefore, the conclusion made by the Authors that “the present study indicated that salpingectomy may impair ovarian response” seems rather extreme.

Conversely, in 2017, another systematic review by Kotlyar et al. [7] collected and evaluated 48 studies on women treated by salpingectomy for any indication, in order to evaluate its effects on ovarian function and also on pregnancy rates. According to this review, for most indications for salpingectomy, ovarian reserve is not affected; moreover, salpingectomy does not cause substantial decrease in conception rates in patients attempting to conceive naturally after the procedure and outcomes are markedly improved when salpingectomy is performed for hydrosalpinx in the context of planned IVF [7].

These findings are consistent with those of two previous meta-analysis on the effects of salpingectomy before IVF in women affected by hydrosalpinx [8,9]. The two studies reported an increased ongoing and clinical pregnancy rates with salpingectomy versus no intervention (OR 2.14, 95% CI 1.23–3.73 and OR 2.31, 95% CI 1.48–3.62, respectively), an increase in clinical pregnancy rate with occlusion versus no intervention (OR 4.66, 95% CI 2.47–10.01) [8] and no difference in the clinical pregnancy rates between salpingectomy and tubal occlusion [9].

Given all these premises, it is not clear which is the rationale of evaluating the effect of salpingectomy exclusively on ovarian response to hyperstimulation during IVF. We find it is important to again underline that the detrimental effect of hydrosalpinx is exerted on the implantation stage, as is clearly confirmed by the two-folds increased odd ratio for pregnancy in women in which the affected tube is removed. Therefore, the real parameter which should be evaluated is pregnancy rate.

Nevertheless, even if clear and irrefutable evidence that salpingectomy significantly reduces the ovarian response to FSH

stimulation will be inferred, this could not lead reproductive gynecologists to advice against surgery, but to recommend to their patients with hydrosalpinx candidate to IVF a two-stage approach. The first stage should entail ovarian hyperstimulation, egg collection, mature oocyte *in vitro* fertilization and embryo/blastocysts freezing; the second stage would consist in salpingectomy followed by thawed embryo transfer. Obviously, such an approach could be offered only in IVF centers equipped with modern and qualified laboratories able to ensure high success rates in cycles with thawed blastocysts.

In the next years, all efforts should be focused on rigorous and objective studies on long-term consequences of salpingectomy, both in terms of live birth rates after IVF than in terms of general health. In this regard, the evaluation of age at menopause of patients treated with salpingectomy compared with controls would be the conclusive proof of the safety of the technique.

Meanwhile, considering the recommendations of many national societies on the opportunity to prevent ovarian cancers through the prophylactic removal of Fallopian tubes during surgeries for benign pathologies [3], and considering that also in those countries where the professional societies have not taken an official position the available evidence and recommendations from other countries have already changed [10–13], caution is required in reporting any indirect and not certain negative effects of salpingectomy.

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Roberta Venturella, Fulvio Zullo
*Unit of Obstetrics and Gynaecology, Department of
 Experimental and Clinical Medicine, 'Magna Graecia'
 University, Catanzaro, Italy*
 rovefa@libero.it

Errico Zupi
*Department of Biomedicine and Prevention, University of Tor
 Vergata, Rome, Italy*

Costantino Di Carlo
*Unit of Obstetrics and Gynaecology, Department of
 Experimental and Clinical Medicine, 'Magna Graecia'
 University, Catanzaro, Italy*

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