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Effects of laparoscopic salpingectomy *versus* proximal tubal separation on ovarian reserve in management of hydrosalpinx in females undergoing intracytoplasmic sperm injection (ICSI) cycle: a comparative study

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ABSTRACT

Background. Females presented with hydrosalpinx have lower rates of pregnancy by artificial reproductive techniques. There are variable management strategies for hydrosalpinx as: salpingostomy, salpingectomy, proximal tubal ligation and trans-vaginal aspiration; but recent management techniques which proved effective in improving outcome of intracytoplasmic sperm injection (ICSI) are laparoscopic tubal ligation and salpingectomy.
Aim of the present study was to compare the ovarian reserve and ICSI outcomes after performing either laparoscopic tubal separation or laparoscopic salpingectomy in females with hydrosalpinx.
Patients and methods. The study was performed in Department of Gynecology and Obstetrics, School of Medicine, Zagazig University in about 3 years. Patients who fulfilled the inclusion criteria were divided into two groups. Group A included 60 patients that underwent bilateral Laparoscopic proximal tubal separation and group B included 60 patients that underwent bilateral laparoscopic salpingectomy before ICSI. The outcome evaluated parameters of the study were; rates of clinical pregnancy and live births in addition to changes in parameters of ovarian reserve, changes of rate of fertilization, rate of cleavage, rates of implantation and rates of miscarriage.
Results. In the salpingectomy group after surgery we found a significant increase in the serum FSH and serum estradiol levels, a significant reduction in the post-surgery AFC and a significant reduction of levels of serum AMH than the other group ($p < 0.001$). We showed that patients who underwent salpingectomy needed more stimulation days, lower rates of fertilization and higher doses of gonadotropins than patients with bilateral tubal separation ($p < 0.001$).

SOMMARIO

Contesto. Le donne presentate con idrosalpinge mostrano tassi di gravidanza inferiori mediante tecniche riproduttive artificiali. Esistono strategie di gestione variabili per l'idrosalpinge come: salpingostomia, salpingectomia, legatura delle tube prossimali e aspirazione transvaginale; ma recenti tecniche di gestione che si sono dimostrate efficaci nel migliorare l'esito dell'iniezione intracitoplasmatica di spermatozoi (ICSI) sono la legatura delle tube laparoscopica e la salpingectomia.Lo scopo del presente studio era di confrontare la riserva ovarica e gli esiti ICSI dopo aver eseguito la separazione tubarica laparoscopica o la salpingectomia laparoscopica nelle donne con idrosalpinge.
Pazienti e metodi. Lo studio è stato condotto presso il Dipartimento di Ginecologia e Ostetricia, Facoltà di Medicina, Università di Zagazig in circa 3 anni. Le pazienti che soddisfacevano i criteri di inclusione sono state divise in due gruppi. Il gruppo A includeva 60 pazienti sottoposte a separazione tubarica prossimale laparoscopica bilaterale e il gruppo B comprendeva 60 pazienti sottoposte a salpingectomia laparoscopica bilaterale prima di ICSI. I parametri valutati per l'esito dello studio erano: tassi di gravidanza clinica e nati vivi oltre a cambiamenti nei parametri della riserva ovarica, cambiamenti del tasso di fecondazione, tasso di scissione, tassi di impianto e tassi di aborto spontaneo.
Risultati. Nel gruppo salpingectomia dopo l'intervento chirurgico abbiamo riscontrato un aumento significativo dei livelli sierici di FSH e di estradiolo, una significativa riduzione dell'AFC post-operatorio e una significativa riduzione dei livelli sierici di AMH rispetto all'altro gruppo ($p < 0,001$). Abbiamo dimostrato che le pazienti sottoposte a salpingectomia avevano bisogno di più giorni di stimolazione, tassi di fecondazione inferiori e dosi più elevate di gonadotropine rispetto alle pazienti con separazione tubarica bilaterale ($p < 0,001$).

Conclusions. Our study demonstrated the benefits of laparoscopically tubal separation over salpingectomy in patients with hydrosalpinx regarding preventing reduction in ovarian reserve particularly in women underwent ICSI.

Conclusioni. Il nostro studio ha dimostrato i benefici della separazione tubarica per via laparoscopica rispetto alla salpingectomia in pazienti con idrosalpinge per quanto riguarda la prevenzione della riduzione della riserva ovarica, in particolare nelle donne sottoposte a ICSI.

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Key words
Hydrosalpinx; salpingectomy; tubal separation; ovarian reserve.

INTRODUCTION

Infertility due to pathological tubal causes forms about 25-35% of causes of females infertility and it was considered an important indication of artificial reproductive techniques (1). Hydrosalpinx is the most severe manifestation of tubal disease. Females presented with hydrosalpinx have lower rates of pregnancy by *in vitro* fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI) (2). There are variable management strategies for hydrosalpinx as: salpingostomy, salpingectomy, proximal tubal ligation and trans-vaginal aspiration, but the most recent management techniques which proved effective in improving outcome of ICSI are laparoscopic tubal ligation and salpingectomy (3). It was found that the blood supply of the ovary might be interrupted after laparoscopic surgery as the blood vessels supplying the ovary and the oviduct are close to each other that reduced ovarian reserve (4, 5).
The quantitative evaluation of ovarian reserve is very important in patients needing ICSI. Salpingectomy is an easily performed surgical procedure that when performed by an efficient surgeon could reduce injuries to tubal and ovarian blood vessel.
So it will be important to evaluate the benefits and drawbacks of laparoscopic tubal separation or salpingectomy to ovarian reserve before performing ICSI in female patients with hydrosalpinx (6).
Aim of the present study was to compare the ovarian reserve and ICSI outcomes after performing either laparoscopic tubal separation or laparoscopic salpingectomy in females with hydrosalpinx.

PATIENTS AND METHODS

The study was performed in Department of Gynecology and Obstetrics, School of Medicine, Zagazig University in about 3 years from March 2016 to May 2019. An approval was taken from the local ethical committee of School of Medicine, Zagazig University and a written informed consent was acquired from all included participants.

Inclusion criteria

We included female patients with a sure diagnosis of bilateral hydrosalpinx of more than 0.3 cm by ultrasound or by hysterosalpingography (HSG) aged less than 38 years having normal cavity of the uterus and seeking for ICSI.

Exclusion criteria

We excluded female patients having endometriosis, adenomyosis, thin endometrium, uterine synechiae, patients with polycystic ovary syndrome, patients with previous surgery on the ovary and patients with contraindications to laparoscopic surgery.
Several reports found an AMH decline after endometriomas removal and a progressive subsequent recovery of AMH levels after surgery (7, 8), We excluded patients with any ovarian cysts, polycystic ovary syndrome and patients with endometriomas to avoid this findings. Male factor of infertility was excluded.
Patients who fulfilled the inclusion criteria were randomly divided by computer generated randomization into two groups. Group A included 60 patients that underwent bilateral laparoscop-

ic proximal tubal cutting and separation and and group B included 60 patients that underwent bilateral laparoscopic salpingectomy before ICSI. Intracytoplasmic sperm injection (ICSI) is the most recent technique used nowadays.

We assessed all parameters of ovarian reserve to all included patients before surgery as: serum AMH, FSH and antral follicle counts in days 2-5 of the menstrual cycle then repeated in the same phase about eight weeks after performing all surgeries.

The outcome evaluated parameters of the study were: rates of clinical pregnancy and live births in addition to changes in parameters of ovarian reserve, changes of rate of fertilization, rate of cleavage, rates of implantation and rates of miscarriage. We defined pregnancy rate as the presence of a gestational sac containing a fetal pole and cardiac activity during transvaginal ultrasound examination at 6 weeks.

Live birth rate was the percentage of cycles which lead to live birth. Implantation rate was the gestational sacs number determined by ultrasound in comparison with number of transferred embryos. Miscarriage rate was number of losses in pregnancy less than 20 weeks of gestation.

We have performed bilateral salpingectomies and bilateral tubal separation operations laparoscopically for all included patients using bipolar diathermy.

All patients were subjected to standard protocol of pituitary down-regulation on day 21 of the previous cycle using GnRH-a 0.5 mg. confirmation of pituitary desensitization was diagnosed 14 days later by finding serum estradiol levels of < 50 pg/ml, serum LH < 3 IU/l, no follicles > 10 mm in size and thickness of the endometrium was < 5 mm during ultrasound examination.

Later on administration of Gonadotropin 150-300 IU/day was done according to patients' age, BMI and serum AMH. We tracked the follicles serially for assessment of ovarian response to stimulation and doses of gonadotropin were modified accordingly. Trigering all patients with recombinant hCG (250 mcg) if there were a minimal 3 follicles ≥ 18 mm. We performed transvaginal sonar-guided retrieval of the oocyte about 36 hours after trigger. Insemination of retrieved oocytes was done by conventional ICSI. After performing insemination we checked for fertilization about 16-18 hours.

We assessed further cleavage and graded embryos so as to transfer up to 2 embryos with a good quality on Day 3 or 5 under sonar guidance using a soft embryo transfer catheter. We give intramuscular progesterone 100 mg daily for luteal support.

We checked serum β hCG 16 days after transferring embryos and patients with a positive β hCG were confirmed to have clinical pregnancy by ultrasound 4 weeks after embryo transfer.

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were compared using Chi square test and Fisher exact test when appropriate. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. Mann whitney test (for not-normally distributed data) was used to compare medians of two groups. Independent sample t test (for normally distributed data) was used to compare means of two groups. Percent change was calculated by subtracting postoperative value from preoperative value then divided it by preoperative value*100. Pearson correlation coefficient was used to assess strength and direction of a linear relationship between two variables. Binary logistic regression was used to predict the odds of being a case based on the values of the independent variables (predictors). Linear stepwise regression analysis was used to determine the extent to which there is a linear relationship between a dependent variable and one or more independent variables. The level statistical significance was set at 5% ($P < 0.05$).

RESULTS

During the study period of 3 years a total of 60 patients having bilateral tubal hydrosalpinx were laparoscopically managed by salpingectomy or proximal tubal separation.

Both included groups have no significant differences in demographic or clinical baseline criteria as age, BMI, type or duration of infertility, 2 days serum FSH, serum Estradiol or serum AMH (**table I**).

Post-surgery Serum FSH on day 2 increased in both groups to 6.79 U/L and 6.957 U/L for tubal separation and salpingectomy groups respectively. Post-surgery Serum EH on day 2 increased to 44.4 U/L and 44.5 U/L for tubal separation and salpingectomy groups respectively.

Post-surgery serum AMH decreased significantly in both groups to 3.663 ng/mL and 2.697 ng/mL for tubal separation and salpingectomy groups

Table I. *Comparison between the studied groups regarding baseline data.*

Parameters	Surgical procedures		Test	
	Tubal occlusion	Salpingectomy	χ^2/t	p
	N = 30 (%)	N = 30 (%)		
Age:				
Mean ± SD	27.7 ± 2.961	28 ± 3.434	Fisher	0.731
Range	23-35	23-35		
BMI (kg/m²):				
Mean ± SD	23.9 ± 1.125	24.07 ± 1.112	0.278	0.598
Range	22-26	22-26		
Infertility duration:				
Mean ± SD	4.73 ± 1.337	4.43 ± 1.331	0.287	0.592
Range	2-7	2-7		
Infertility:				
Primary	24 (80)	26 (86.7)	Fisher	0.731
Secondary	6 (20)	4 (13.3)		

χ^2: chi square test; t: independent sample t test.

respectively. In the salpingectomy group after surgery we found: a slight increase in the serum FSH (p value = 0.015), serum EH (p = 0.022) and a significant reduction of levels of serum AMH (p value < 0.001) than in group of patients underwent bilateral tubal separation (**figures 1, 2**).

Days of stimulation within group of tubal separation ranged from 8 to 10 days with mean 9.233 while within salpingectomy group, it ranged from 10 to 12 days with mean 11.033. Total gonadotropin within group of tubal separation ranged from 2800 to 3700 with mean 3187.33 while within salpingectomy group, it ranged from 3500 to 4200 with mean 3793.33. We showed that patients who underwent salpingectomy needed more stimulation days and higher doses of gonadotropins than patients with bilateral tubal separation (p < 0.001) (**table II**).

We found that the rates of fertilization rate in salpingectomy group were lower than tubal separation group (p value = 0.049).

We found no significant differences between both included groups regarding: rates of implantation, rates of clinical pregnancy, live birth or miscarriage rates.

DISCUSSION

Hydrosalpinx was incriminated in reduction of rates of clinical pregnancy and increasing rates of ectopic pregnancy and abortion (9). Moreover it inversely affected IVF, ICSI success rates by unsure mechanisms. There are several suggested mechanism explain how hydrosalpinx inversely affected the fertility; the accumulated fluid of hydrosalpinx might return to cavity of the uterus, negatively affects receptivity of the endometrium, has embryotoxic effects, interfering with implantation or even simply wash out the embryos (10). So treatment of hydrosalpinx either by salpingectomy of by tubal separation before

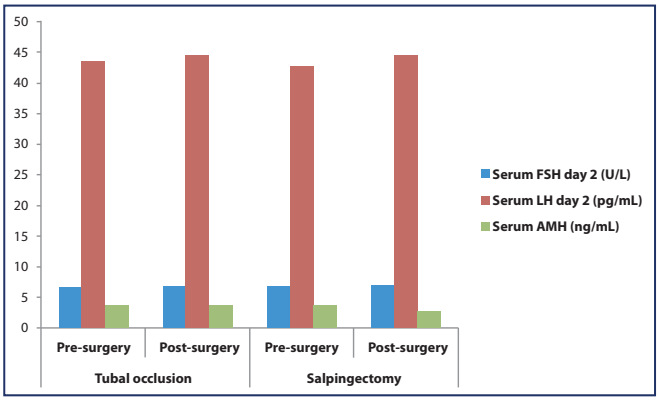

Figure 1. *Multiple bar chart showing hormonal profile among the studied groups before and after surgery.*

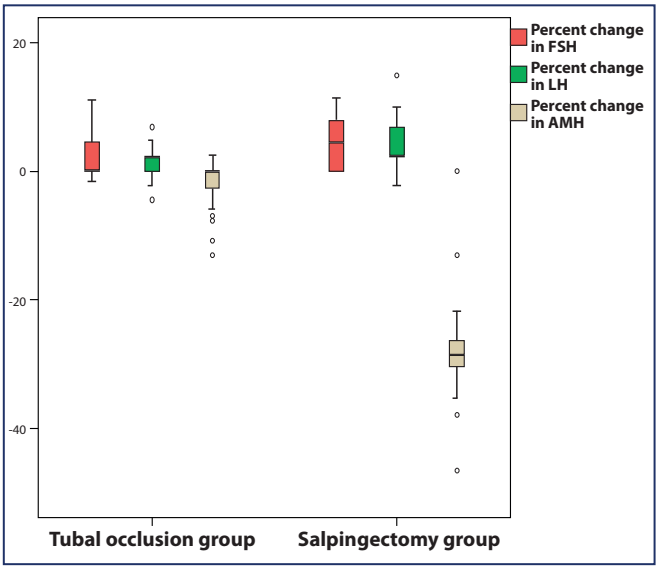

Figure 2. *Boxplot showing percent change in hormonal profile among the studied patients.*

Table II. *Comparison between the studied groups regarding days of stimulation and total dose of gonadotropins.*

Parameters	Surgical procedures		Test	
	Tubal occlusion	Salpingectomy	t	p
	N = 30 (%)	N = 30 (%)		
Days of stimulation:				
Mean ± SD	9.233 ± 0.679	11.033 ± 0.765	- 9.64	< 0.001**
Range	8-10	10-12		
Gonadotropin total dose:				
Mean ± SD	3187.33 ± 369.66	3793.33 ± 206.67	- 7.387	< 0.001**
Range	2800-3700	3500-4200		

t: independent sample t test; **p ≤ 0.001 is statistically highly significant.

starting IVF.ICSI program is needed to increase the rates of success (11). In the current study, we found no significant differences in levels of FSH in the laparoscopic salpingectomy and laparoscopic bilateral tubal separation. We showed that higher AMH levels were found in the tubal separation group than the salpingectomy group similarly Vignarajan *et al*. (12). Salpingectomy as a surgical management strategy for hydrosalpinx was found to inversely affect ovarian vascularity which might decrease ovarian reserve (6). Johnson *et al*. (13) found that salpingectomy might damage ovarian vascular supply while tubal obstruction by ligation has no effect on vascular supply.

Tubal excision may damage the arch of the artery, while tubal ligation at the proximal end and distal salpingostomy may cause less damage to the mesangium (13). A study which assessed salpingectomy effects on the ovarian reserve in patients with tubal disease showed near results to ours that there is marked reduction in levels of ovarian reserve and AMH levels in the salpingectomy group (14). Similarly previous reports showed that proximal tubal occlusion could preserve ovarian reserve more than salpingectomy (15-17). Salpingectomy was found to impair blood supply of the ovary shortly after operation, but the long-term performance was not proved yet (18).

Xu *et al*. (19) metaanalysis showed that patients underwent proximal tubal occlusion has significantly higher AMH levels than salpingectomy but there were no differences between both groups in rates of: clinical pregnancy, implantation or live birth. Their results showed that salpingectomy leads to damage to ovarian reserve than tubal occlusion.

Additionally Vignarajan *et al.* (12) showed that salpingectomy causes more harm to the ovaries than tubal occlusion (**tables III, IV**). Regarding the benefits of salpingectomy over tubal occlusion it was found that salpingectomy leads to removal of any inflammation source, prevents releasing pro-inflammatory cytokines in addition to decreasing incidence of ovarian and tubal malignancies. So salpingectomy is still considered in management of any patients with tubal disease regardless the ovarian reserve (6) (**tables V, VI**).

Although many studies agreed with our results, but other reports who confirmed a regular ovarian function after salpingectomy are found (20, 21), which specify that this problem is not universally proven yet.

CONCLUSIONS

Our study demonstrated the benefits of laparoscopically tubal separation over salpingectomy in patients with hydrosalpinx regarding preventing reduction in ovarian reserve particularly in women underwent ICSI. So proximal tubal separation as suggested as a better surgical management option or treatment of hydrosalpinx in patients undergoing ICSI due to preservation of ovarian reserve. But due to different results of previous studies regarding advantages of tubal separation or salpingectomy, further researches on large number of patients were needed to explore the long term outcomes of surgery on ovarian reserve and ICSI outcome.

Limitations of the study: few number of patients were included aditionally endometriomas were excluded, AMH evaluation was carried out 8 weeks after surgery and no AMH evaluation was carried out later to asses a long term AMH increase as found after surgical treatment of endometrioma which might impair the result of the study, so there is the lack of long term results assessment.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

Table III. *Comparison between the studied groups regarding hormonal profile before and after surgery.*

Parameters	Surgical procedures		Test	
	Tubal occlusion	Salpingectomy	t	p
	N = 30 (%)	N = 30 (%)		
Pre surgery Serum FSH D2 (U/L):				
Mean ± SD	6.643 ± 0.374	6.65 ± 0.365	- 0.07	0.945
Range	6.1-7.2	6.2-7.2		
Post-surgery Serum FSH D2 (U/L):				
Mean ± SD	6.79 ± 0.339	6.957 ± 0.376	- 1.805	0.076
Range	6.2-7.4	6.2-7.9		
P¥	0.001**	< 0.001**		
Pre surgery Serum E D2 (pg/L):				
Mean ± SD	43.5 ± 1.28	42.7 ± 1.44	2.273	0.027*
Range	41-45	40-45		
Post-surgery Serum E D2 (pg/L):				
Mean ± SD	44.4 ± 1.275	44.5 ± 1.28	- 0.303	0.763
Range	42-46	42-46		
P¥	< 0.001**	< 0.001**		
Pre surgery AMH:				
Mean ± SD	3.743 ± 0.353	3.743 ± 0.355	- 0.004	0.997
Range	3.3-4.6	3.3-4.6		
Post-surgery AMH:				
Mean ± SD	3.663 ± 0.329	2.697 ± 0.461	9.35	< 0.001**
Range	3.2-4.6	2.2 – 4		
P¥	0.012*	< 0.001**		

t: independent sample t test; *p < 0.05 is statistically significant; **p ≤ 0.001 is statistically highly significant; ¥paired sample t test.

Table IV. *Comparison between the studied groups regarding percent change in hormonal profile after surgery.*

Percent change	Surgical procedures		Test	
	Tubal occlusion	Salpingectomy	t	p
	N = 30 (%)	N = 30 (%)		
Serum FSH D2:				
Median	0%	4.39%	- 2.443	0.015*
Range	- 1.587, 11.115	0, 11.429%		
Serum LH D2:				
Median	2.27%	2.325%	- 2.284	0.022*
Range	- 44.4, 6.977%	-2.22, 15%		
AMH:				
Median	0%	- 28.57%	- 6.526	< 0.001**
Range	- 13.043, 2.564	0, 46.512%		

Z: Mann Whitney test; *p < 0.05 is statistically significant; **p ≤ 0.001 is statistically highly significant.

Table V. *Comparison between the studied groups regarding outcome.*

Parameter	Surgical procedures		Test	
	Tubal occlusion	Salpingectomy	χ^2/t	p
	N = 30 (%)	N = 30 (%)		
Fertilization rate:				
Mean ± SD	0.932 ± 0.088	0.777 ± 0.059	0.871	0.049
Range				
Clinical pregnancy:				
No	17 (56.7)	19 (63.3)	0.278	0.598
Yes	13 (43.3)	11 (36.7)		
Live birth:				
No	18 (60)	20 (66.7)	0.287	0.592
Yes	12 (40)	10 (33.3)		
Miscarriage:				
No	12 (92.3)	11 (91.7)	Fisher	> 0.999
Yes	1 (7.7)	1 (8.3)		

χ^2: chi square test; t: independent sample t test.

Table VI. *Univariate analysis of parameters associated with ovarian reserve.*

Parameters	Univariate analysis		
	Yes N = 24 (%)	No N = 36 (%)	p
Procedure			
Tubal occlusion	16 (66.7)	14 (38.9)	0.035∞*
Salpingectomy	8 (33.3)	22 (61.1)	
Infertility			
Primary	19 (79.2)	31 (86.1)	0.48∞
Secondary	5 (20.8)	5 (13.9)	
Age	28.38 ± 3.1	27.5 ± 3.23	0.301¥
BMI	24.13 ± 0.85	23.89 ± 1.26	0.425¥
Duration of infertility	4.63 ± 1.35	4.56 ± 1.34	0.845¥
Preop serum FSH D2	6.57 ± 0.38	6.7 ± 0.37	0.17¥
Postop serum FSH D2	6.82 ± 0.36	6.91 ± 0.37	0.33¥
Preop serum LH D2	43.17 ± 1.66	43.06 ± 1.24	0.768¥
Postop serum LH D2	44.5 ± 1.44	44.42 ± 1.16	0.805¥
Preop serum AMH	3.66 ± 0.31	3.8 ± 0.37	0.126¥
Postop serum AMH	3.33 ± 0.66	3.08 ± 0.6	0.146¥
Total gonadotropin used	3344.2 ± 472.96	3587.78 ± 366.86	0.039¥*
Days in stimulation	9.83 ± 1.09	10.33 ± 1.17	0.101¥

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