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Use of ICSI in IVF cycles in women with tubal ligation does not improve pregnancy or live birth rates

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STUDY QUESTION: Does ICSI improve outcomes in ART cycles without male factor, specifically in couples with a history of tubal ligation as their infertility diagnosis?

SUMMARY ANSWER: The use of ICSI showed no significant improvement in fertilization rate and resulted in lower pregnancy and live birth (LB) rates for women with the diagnosis of tubal ligation and no male factor.

WHAT IS KNOWN ALREADY: Prior studies have suggested that ICSI use does not improve fertilization, pregnancy or LB rates in couples with non-male factor infertility. However, it is unknown whether couples with tubal ligation only diagnosis and therefore iatrogenic infertility could benefit from the use of ICSI during their ART cycles.

STUDY DESIGN, SIZE, DURATION: Longitudinal cohort of nationally reported cycles in the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System (SART CORS) of ART cycles performed in the USA between 2004 and 2012.

PARTICIPANTS/MATERIALS, SETTING, METHODS: There was a total of 8102 first autologous fresh ART cycles from women with the diagnosis of tubal ligation only and no reported male factor in the SART database. Of these, 957 were canceled cycles and were excluded from the final analysis. The remaining cycles were categorized by the use of conventional IVF (IVF, $n = 3956$ cycles) or ICSI ($n = 3189$ cycles). The odds of fertilization, clinical intrauterine gestation (CIG) and LB were calculated by logistic regression modeling, and the adjusted odds ratios (AORs) with 95% confidence intervals were calculated by adjusting for the confounders of year of treatment, maternal age, race and ethnicity, gravidity, number of oocytes retrieved, day of embryo transfer and number of embryos transferred.

MAIN RESULTS AND THE ROLE OF CHANCE: The main outcome measures of the study were odds of fertilization (2PN/total oocytes), clinical intrauterine gestation (CIG/cycle) and live birth (LB/cycle). The fertilization rate was higher in the ICSI versus IVF group (57.5% vs 49.1%); however, after adjustment this trend was no longer significant (AOR 1.14, 0.97–1.35). Interestingly, both odds of CIG (AOR 0.78, 0.70–0.86), and odds of LB were lower (AOR 0.77, 0.69–0.85) in the ICSI group. Plurality at birth, mean length of gestation and birth weight did not differ between the two groups.

LIMITATIONS, REASONS FOR CAUTION: This was a retrospective study, therefore only the available parameters could be included, with parameters of interest such as smoking status not available for inclusion. Smoking status may have led practitioners to use ICSI to improve pregnancy and LB outcomes.

WIDER IMPLICATIONS OF THE FINDINGS: Studies have shown that in the USA there is an increasing usage of ICSI for non-male factor infertility despite a lack of evidence-based benefit. Our study corroborates this increasing use over the last 8 years, specifically in the tubal ligation only patient population. Even after adjusting for multiple confounders, the patients who underwent ICSI had no statistically significant improvement in fertilization rate and actually had a lower likelihood of achieving a clinical pregnancy and LB. Therefore, our data suggest that the use of ICSI in tubal ligation patients has no overall benefit. This study contributes to the body of evidence that the use of ICSI for non-male factor diagnosis does not improve ART outcomes over conventional IVF.

STUDY FUNDING/COMPETING INTEREST(S): None.

Key words: SART / IVF / ICSI / tubal ligation / live birth / male factor

Introduction

Tubal ligation is one of the most common procedures used for contraception by married women worldwide (18%) (Clifton and Kaneda, 2013). In the USA, roughly 30% of couples use tubal ligation as a means of permanent sterilization, with up to 30% of them regretting their decision at a later date (Wilcox *et al.*, 1990; Hillis *et al.*, 1999; Fritz and Speroff, 2010; ASRM, 2012). For those who regretted the decision and sought future fertility, re-anastomosis of the fallopian tubes was historically the only means of restoring fertility. The development of IVF provided an alternative to re-anastomosis.

In 1992, ICSI was developed, where one sperm could be injected directly and mechanically into an egg *in vitro* to achieve fertilization, allowing for couples with male factor infertility to achieve the goal of having a biological child. ICSI is a more costly technique compared to conventional IVF due in part to the increase in technical expertise and time required of embryologists. As such, the medical indication for the use of this technique needs to be justified by either disease type or outcomes. The Practice Committee of the American Society for Reproductive Medicine has advised that ICSI be used for male factor infertility or for 'selected female factors including, but not limited to, morphologic anomalies of the oocyte, and anomalies of the zona pellucida'. They also stated that ICSI might be indicated if a prior conventional IVF cycle had poor fertilization or if 'pre-implantation diagnosis (PGD) is planned, especially for single gene defects' (ASRM and SART, 2012). The Center for Disease Control of the USA (CDC) (Boulet *et al.*, 2015) and ESHRE have published guidelines on the appropriate use of ICSI (ESHRE, 2008). Notwithstanding these recommendations, Boulet *et al.* (2015) have observed that from 2008 to 2012 ICSI use in the USA has increased while the incidence of male factor infertility has remained unchanged. The increase in ICSI use has also been noted in the international community, with Mansour *et al.* (2014) reporting an ICSI rate of 66%, ranging from 56% in Asia to 96% in the Middle East, and the ESHRE 2011 ART report reporting a 68% ICSI rate in Europe (Mansour *et al.*, 2014; Kupka *et al.*, 2016). Similar calls have been made from officials for improved guidelines on the appropriate use of ICSI with the Chair of the Human Fertilization and Embryology Authority in the UK criticizing the increased use of ICSI (Fleming, 2013).

The increasing use of ICSI is likely to be also occurring in couples with non-male factor indications. A recent CDC report found that ICSI was used in 65–78% of non-male factor ART cycles in the USA (CDC, 2013). A multicenter randomized control trial found that ICSI did not benefit non-male factor patients (Bhattacharya *et al.*, 2001). Subsequently, a Cochrane Review of conventional IVF versus ICSI in 2003 discussed that 'IVF gives better fertilization results than ICSI in couples with non-male subfertility' and that 'pregnancy rates after IVF and ICSI are not significantly different' (van Rumste *et al.*, 2003). However after noting that much of the research is based on observational data, it reflected that IVF versus ICSI in non-male factor patients was still an open question (van Rumste *et al.*, 2003).

Tubal ligation patients provide a means to study ART outcomes without influence by other female factors (except female age) or male factor. It also is a way to analyze cycles of women who were likely to have had previous pregnancies and thus have proven fertility. Since tubal ligation patients without male factor do not meet the criteria for ICSI, one would expect an evidence-based approach to result in most of these cycles being performed using conventional insemination. Surprisingly, ICSI was found to have been used in 50% of cases for tubal ligation-only between 2004 and 2008 in the USA (Nangia *et al.*, 2011). The reasons for this high rate remain unclear, but a concern that conventional IVF may lead to poorer outcomes in such cases may be one issue.

The aim of our study is to compare the outcomes of IVF versus ICSI cycles in the USA for patients with a diagnosis of tubal ligation with no male factor and to test the hypothesis that ICSI improves pregnancy and live birth (LB) outcome in this population.

Materials and Methods

Ethical approval

This study received Institutional Review Board exemption from Dartmouth College in New Hampshire, USA.

Population

Data from the USA Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) online database for fresh, autologous oocyte cycles performed between 2004 and 2012 were analyzed. There was a total of 8102 first autologous fresh ART cycles from women with the diagnosis of only tubal ligation and no reported male factor in the SART database. Of these, 957 were canceled cycles and excluded from the final analysis, 3956 cycles underwent conventional IVF (IVF) and 3189 cycles underwent ICSI (all oocytes in these cycles underwent ICSI). In the SART database, there is an ICSI-some category (where some oocytes underwent ICSI), these cycles (<6% of total cycles) were excluded from the analysis due to ambiguity on what proportion of oocytes underwent ICSI versus IVF and also on which of these embryos were transferred. The characteristics of the women who had a canceled cycle are as follows: they tended to be older than the women in the study population (mean age 37.1 ± 4.2 years compared to 35.3 years ± 4.0 for IVF and 35.9 ± 4.0 for ICSI; 18.7% were ≥40 years of age, compared to 7.5% and 10.3%, respectively for IVF and ICSI). They also averaged higher BMIs (mean 28.1 ± 5.6, compared to 27.2 ± 5.5 and 27.5 ± 5.6, respectively, for the IVF and ICSI groups), and fewer oocytes retrieved (5.6 ± 11.3 compared to 13.2 ± 7.9 and 12.0 ± 7.4, respectively, for the IVF and ICSI groups). The reasons for cycle cancellation included low response (75.5%), high response (5.9%), inadequate endometrium (0.8%), concurrent illness (1.3%), psychological factors (0.8%), financial (2.2%), family factors (2.3%) and other factors (11.2%).

Variables and outcome measures

The variables studied included: year of treatment; maternal age at cycle start; gravidity; BMI; ovarian hyperstimulation syndrome (OHSS); number of oocytes retrieved; day of embryo transfer; number of embryos transferred. Outcomes measured included fertilization rate [two pronuclear (2PN) embryos/total retrieved oocytes]; number of embryos cryopreserved; clinical intrauterine gestation (CIG) rate (defined as a confirmed gestational sac within the uterus: CIG/cycle); LB rate (calculated per cycle with embryo transfer, canceled cycles omitted: live birth (LB)/cycle), plurality, and length of gestation and live birth weight in singletons and twins, respectively. Failed pregnancy included biochemical, ectopic or heterotopic pregnancy. LB included gestation ≥154 days and birth weights ≥300 g.

Statistical analysis

Logistic regression was used to model the odds of fertilization, CIG and LB; the IVF group was used as the reference to the treatment group. The models were adjusted for female age, year of treatment, race and ethnicity, gravidity, number of oocytes retrieved, day of transfer and number of embryos transferred. Interaction terms were tested between the use of ICSI and maternal age and body mass index, and the IVF factors of number of oocytes retrieved, day of embryo transfer and number of embryos transferred. Results were presented as adjusted odds ratios (AORs) with 95% confidence intervals (CI). Statistical significance $P \leq 0.05$.

Results

Demographics

Of the first start cycles in the USA in patients with tubal ligation only and no other female or male factor infertility between 2004 and 2012, 3956 cycles were done with conventional IVF and 3189 cycles were performed with ICSI. Basic demographics of these cycles are reported in Table I.

Trends in use of ICSI in the USA

The use of ICSI for tubal ligation in the USA increased between 2004 and 2012. In 2004–2006, 39.7% of the cycles were performed using ICSI, which rose to 50.0% of the cycles by 2010–2012 ($P < 0.0001$, Table I).

Female age, race and weight were the other statistically significant differences in demographics between the two groups. Mean age was 35.3 years in IVF versus 35.9 years in ICSI cycles ($P < 0.0001$). Mean woman's weight was 72.0 kg in IVF versus 73.1 kg ($P = 0.05$) in ICSI cycles.

Cycle characteristics in IVF and ICSI cycles

Characteristics of IVF versus ICSI cycles are outlined in Table II. There were statistically different rates of OHSS, with higher numbers in the IVF group (moderate: 1.9 vs 1.0% in ICSI, $P < 0.05$; severe: 1.1 vs 0.2% in ICSI, $P < 0.0001$), as well as a greater number of eggs retrieved in this group (13.2 vs 12, $P < 0.0001$). A higher percentage of single embryo transfers were seen in ICSI group (10.7 vs 8.8 in IVF, $P < 0.05$). The calculated fertilization rate (2PN/oocytes) was higher in the ICSI versus IVF group (57.5% vs 49.1%, $P < 0.0001$).

Outcomes

There were higher rates of CIG (48.4% IVF, 1913/3956 cycles vs 41.6% ICSI, 1327/3189 cycles, $P < 0.0001$) and LB (39.6% IVF, 1566/3956 cycles vs 33% ICSI, 1051/3189 cycles, $P < 0.0001$) in the IVF group compared to the ICSI (Table III). LB was calculated per cycle with an embryo transfer, and within pluralities, there were no differences in length of gestation, percent of premature deliveries or birth weight.

We tested for interaction effects between the use of ICSI and maternal age and body mass index, and the IVF factors of number of oocytes retrieved, day of embryo transfer, and number of embryos transferred. None of the interactions were significant and therefore were not retained in the final models (see Table IV). Adjusted outcomes revealed a trend toward higher rates of fertilization in the ICSI group (AOR 1.14, 95% CI 0.97, 1.35) but this difference did not reach significance. However, CIG (AOR 0.78, 95% CI 0.70, 0.86) and LB rates (AOR 0.77, 95% CI 0.69, 0.85) were both statistically lower in the ICSI group compared to the reference group (Table IV).

Table I Demographics of the ART cycles.

Mode of fertilization	IVF	ICSI	*P*-value
(*N*, cycles)	(3956)	(3189)	
Year of treatment (%)			
2004–2006	60.3	39.7	<0.0001
2007–2009	54.4	45.6	
2010–2012	50.0	50.0	
Female age, mean yrs, SD	35.3 (4.0)	35.9 (4.0)	<0.0001
(%) 18–29	10.4	7.6	<0.0001
30–34	34.9	32.5	
35–37	26.8	26.8	
38–40	20.4	22.7	
41–43	6.5	8.7	
44–59	1.0	1.6	
Race/ethnicity-female			
(%) Asian	1.9	2.3	<0.0001
Black	8.4	9.4	
Hispanic	16.2	16.3	
White	44.5	43.5	
Other/mixed	1.8	3.0	
Unknown	27.2	25.5	
Gravidity (%)			
0	6.5	6.7	0.92
1	5.9	5.7	
≥2	87.6	87.6	
Height (mean meters, SD)	1.63 (0.07)	1.63 (0.07)	0.12
Weight (mean kilograms, SD)	72.0 (15.2)	73.1 (16.1)	0.05
Body mass index (mean, SD)	27.2 (5.5)	27.5 (5.6)	0.13
(%) <18.5	0.5	0.7	0.009
18.5–24.9	17.1	17.9	
25.0–29.9	15.0	16.4	
30.0–34.9	8.2	8.7	
35.0–39.9	2.6	3.8	
≥40.0	1.3	1.4	
Missing	55.3	51.1	

Table II Comparison of cycle characteristics.

Mode of fertilization	IVF	ICSI	*P*-value
(*N*, cycles)	(3956)	(3189)	
OHSS (%), Moderate	1.9	1.0	0.003
Severe	1.1	0.2	<0.0001
No. oocytes retrieved (mean, SD)	13.2 (7.9)	12.0 (7.4)	<0.0001
(%) 1–5	9.0	13.0	<0.0001
6–10	29.5	30.4	
10–15	23.8	24.4	
≥16	32.6	26.4	
Not specified	5.0	5.9	
No. 2PN embryos (mean, SD)	6.6 (6.0)	5.9 (5.6)	<0.0001
(%) 0	23.4	20.2	<0.0001
1–5	25.0	33.3	
6–10	29.1	28.8	
11–15	13.9	11.8	
≥16	8.6	5.9	
Fertilization rate (2PN/oocyte)	49.1	57.5	<0.0001
Embryos cryopreserved (mean, SD)	2.4 (3.9)	1.9 (3.4)	<0.0001
(%) 0	54.8	59.1	<0.0001
1	5.2	4.9	
2–5	24.5	24.0	
6–10	10.7	8.9	
≥11	4.9	3.0	
Day embryo transfer (%)			
Day 2	3.8	5.3	<0.0001
Day 3	53.9	51.6	
Day 4	2.6	4.3	
Day 5	38.1	37.0	
Day 6	1.6	1.8	
Embryos transferred (%)			
1	8.8	10.7	0.001
2	56.9	53.4	
3	20.6	22.5	
4	6.1	5.9	
≥5	1.4	2.1	
Not specified	6.2	5.4	

OHSS, ovarian hyperstimulation syndrome; 2PN, two pronuclear.

Table III Comparison of cycle outcomes.

	IVF	ICSI	*P*-value
(*N*, cycles)	(3956)	(3189)	
Treatment outcome (%)			
Not pregnant	46.0	51.9	<0.0001
Biochemical or heterotopic	5.6	6.5	
CIG[a] (%(*N*))	48.4 (1913)	41.6 (1327)	
Pregnancy outcome of CIG (*N*)	(1913)	(1327)	
Fetal loss or stillbirth (%)	18.2	20.8	0.049
LB (% per CIG)	81.8	79.2	
LB rate (per cycle % (*N*))	39.6 (1566)	33.0 (1051)	<0.0001
Plurality at birth (%), Singleton	66.2	67.8	<0.0001
Twins	31.3	30.3	
Triplets+	2.5	1.9	
Singleton LB[a] (*N*)	(1036)	(713)	
Length of gestation (mean days, SD)	264 (16)	264 (16)	0.56
<37 weeks(%)	22.1	22.9	0.71
Birth weight (mean grams, SD)	3184 (626)	3237 (618)	0.08
(%) <1500 g	1.6	1.7	0.82
<2500 g	10.2	9.4	0.61
Twin LB[a] (*N*)	(490)	(318)	
Length of gestation (mean days, SD)	243 (20)	245 (18)	0.16
(%) <37 weeks	83.1	80.5	0.36
Birthweight (grams, SD, mean of sibling pair)	2329 (540)	2391 (510)	0.10
(%) <1500 g	8.8	6.0	0.14
<2500 g	57.8	51.6	0.08

[a]CIG, clinical intrauterine gestation
[b]LB ≥154 days and birth weight ≥300 g.

Discussion

Our study demonstrates that ICSI does not improve clinical pregnancy or LB rates over conventional IVF when used for the treatment of patients whose only indication for IVF is tubal ligation. Our data further demonstrate that after adjusting for the potential confounders of age, year of treatment, race and IVF cycle characteristics, the patients who underwent ICSI had a significantly lower chance of achieving a LB than patients who had conventional IVF. Therefore, these data would question the benefit of choosing to use ICSI in the tubal ligation patient. Our findings support previous studies that found no advantage in using ICSI for non-male factor indications (Nangia *et al.*, 2011; Boulet *et al.*, 2015). Our data also demonstrate that this practice has been increasing in the USA over the last 8 years specifically in the tubal ligation only patient population, a relatively fertile population (in our study, 93.5% of the IVF group, and 93.3% of the ICSI group had prior documented pregnancy).

There are a number of possible reasons for this increasing trend. One is the goal of overcoming failed fertilization and providing comfort to both the provider and the couple that everything has been done to keep this from occurring. The American Society for Reproductive Medicine has recommended that ICSI can be used in cycles where prior cycles had failed fertilization (ASRM and SART, 2012). In our study, we included only the first cycle, therefore, it is unlikely that the reason for using ICSI was due to a history of failed fertilization. An additional reason for the use of ICSI may be the fee for service nature of ART treatment in the USA, where the cost of treatment increases expectations, and hopes are high for positive outcomes.

Our observation that use of ICSI resulted in lower pregnancy and LB rates in these cycles is compounded by recent concerns regarding the

Table IV Adjusted fertilization/pregnancy/LB rates.

Type of fertilization	Fertilization			CIG			LB		
	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI
IVF	49.1	1.00	Reference	48.4	1.00	Reference	39.6	1.00	Reference
ICSI	57.5	1.14	0.97, 1.35	41.6	0.78	0.70, 0.86	33.0	0.77	0.69, 0.85

Model adjusted for year of treatment, maternal age, race and ethnicity, number of oocytes retrieved, day of transfer, and number of embryos transferred. AOR; adjusted odds ratio; CIG, clinical intrauterine gestation; LB, live birth.

safety of ICSI. Although results are mixed, children born after ICSI as compared to IVF have been found to have a 3-fold increased risk of congenital heart disease (Tararbit *et al.*, 2013), a 2-fold risk of major birth defects and a 50% increased risk of minor birth defects (In't Veld *et al.*, 1995; Kurinczuk and Bower, 1997; Hansen *et al.*, 2002; Katalinic *et al.*, 2004; Yan *et al.*, 2011; Davies *et al.*, 2012; Farhi *et al.*, 2013) and an increased risk of developing autism (even in couples without male factor) (Kissin *et al.*, 2015). Nevertheless, some studies have suggested no difference (Bonduelle *et al.*, 1996; Loft *et al.*, 1999; Sutcliffe *et al.*, 1999; Bonduelle *et al.*, 2002; Lie *et al.*, 2005). Due to concerns raised about these safety issues suggest that judicious use of ICSI for indicated reasons should be exercised until we have more data about the safety of this technique in couples with non-male factor infertility.

Strengths of the study included the sample population; tubal ligation patients have usually proven their ability to bear children with a prior pregnancy and can be regarded as fertile. These couples, in general, should have no physiologic barriers to pregnancy once the sperm and oocyte are in proximity, thus allowing us to study the specific question of whether or not ICSI carries an implicit additional benefit over IVF. By selecting for these patients, we avoided other female factors as contributors (except for age), or male factor. The large sample size allowed for adequate numbers. The USA SART CORS database also provided cycle and patient characteristics, which allowed us to adjust for variables such as maternal age, race and ethnicity, number of oocytes retrieved and embryos transferred. By using the first cycle only, we were able to limit the number of ICSI cycles included in our data set due to a history of a prior cycle with failed fertilization.

This study had several limitations; in our study, the actual reasons for use of ICSI are unknown. In addition, percentage of fertilized eggs and BMI only began to be collected in the SART CORS database in the USA in 2007 and were not reported consistently, thus resulting in missing data. It is also possible that patients may have other characteristics (such as smoking) not captured in our data, which led practitioners to use ICSI to improve chances of pregnancy and LB.

Use of ICSI in tubal ligation only patients has increased from 2004 to 2012 with 50% undergoing ICSI in USA clinics. Our study suggests that ICSI in non-male factor couples does not improve fertilization rates and significantly reduces the overall odds of achieving a pregnancy and LB.

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Authors' roles

F.W.G., MD: Participated in study analysis, manuscript drafting and critical discussion; A.K.N., MD: Participated in study design, execution, analysis, manuscript drafting and critical discussion; B.L., ScD, MPH: Participated in study design, execution, analysis, manuscript drafting and critical discussion; J.E.S., PhD: Participated in study design, execution, analysis, manuscript drafting and critical discussion; W.M., MD, PhD: Participated in study design, execution, analysis, manuscript drafting and critical discussion.

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Conflict of interest

None declared.

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