

## **LONGITUDINAL ASSOCIATIONS OF CONVENTIONAL INSEMINATION COMPARED TO INTRACYTOPLASMIC SPERM INJECTION ON FERTILIZATION AND OTHER FERTILITY OUTCOMES AMONG INDIVIDUALS UTILIZING FROZEN DONOR SPERM**

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**Background:** Although intracytoplasmic sperm injection (ICSI) was introduced in 1992 for male-factor infertility, its use has rapidly expanded to non-male factor cases despite ASRM recommendations (1). In prior studies evaluating insemination methods for non-male factor infertility using fresh sperm samples, ICSI has been associated with decreased fertilization, implantation, clinical pregnancy, and live birth compared to conventional insemination (2-4). Currently, ICSI is generally recommended for all frozen sperm samples due to concerns for sperm survival and function post-thaw, but there are limited data evaluating outcomes between conventional insemination and ICSI in cycles using frozen sperm.

**Objective:** To investigate assisted reproductive technology (ART) and pregnancy outcomes following ICSI and conventional insemination using frozen sperm. We tested the hypothesis that conventional insemination is associated with increased fertilization and better pregnancy outcomes when using frozen sperm.

**Materials and Methods:** We conducted a retrospective cohort analysis of autologous retrieval cycles and linked subsequent fresh and frozen single blastocyst transfers utilizing frozen donor sperm in a large private practice fertility network from 2010 to 2021. Cycles that used gestational carriers, donor oocytes, frozen-thawed oocytes, donor/partner sperm split, surgically retrieved sperm, preimplantation genetic testing for indications other than aneuploidy, or rescue ICSI were excluded. Outcomes of interest were fertilization rate, complete fertilization failure, blastocyst formation rate, clinical pregnancy and live birth. Associations between fertilization method and clinical outcomes were modeled using repeated measures generalized estimating equations. Models were adjusted for maternal age at retrieval, body mass index, parity, infertility diagnosis, and smoking history.

**Results:** A total of 6,536 retrieval cycles (6,427 ICSI and 109 conventional insemination) among 4,413 unique patients were included in the analysis. At first retrieval, patients receiving conventional insemination compared to those who received ICSI had a higher percentage of non-smoking (85.71% vs 67.23%), and a higher mean (standard deviation) number of oocytes retrieved (14.29 [7.70] vs 13.58 [8.84]) and number of fertilized oocytes (8.70 [5.27] vs 7.89 [5.88]). Mean fertilization and blastocyst formation was higher in those who received conventional insemination (63% and 42%) compared to those who received ICSI (58% and 31%) (Table 1). Adjusted associations examining fertilization method and fertilization outcomes showed conventional insemination compared to ICSI was associated with increased mean blastocyst formation (Mean [95% CI]: 0.12 [0.05, 0.19]). Compared to ICSI, conventional

insemination was associated with increased odds of clinical pregnancy (OR [95% CI]: 2.13 [1.37, 3.31]) and live birth 1.67 (1.05, 2.66) (Table 1).

Conclusions: Conventional insemination was associated with increased mean blastocyst formation, and increased odds of clinical pregnancy and live birth compared to ICSI. Our findings suggest that routine use of conventional insemination in ART cycles using frozen donor sperm should be considered.

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Table 1. Unadjusted and adjusted\* longitudinal associations of conventional insemination compared to ICSI with fertilization and pregnancy outcomes.

Outcome	Unadjusted Mean (95% CI)	Adjusted Mean (95% CI)	Mean Difference
Fertilization			
ICSI	0.57 (0.56, 0.58)	0.56 (0.55, 0.58)	--
cIVF	0.61 (0.57, 0.66)	0.60 (0.55, 0.65)	0.03 (-0.01, 0.08)
Blastocyst Formation			
ICSI	<b>0.30 (0.29, 0.31)</b>	<b>0.32 (0.30, 0.35)</b>	--
cIVF	<b>0.41 (0.34, 0.48)</b>	<b>0.44 (0.37, 0.52)</b>	<b>0.12 (0.05, 0.19)</b>
Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	
Failed Fertilization			
ICSI	Reference	Reference	
cIVF	1.98 (0.68, 5.75)	2.24 (0.72, 6.98)	
Clinical Pregnancy			
ICSI	Reference	Reference	
cIVF	<b>2.24 (1.51, 3.33)</b>	<b>2.13 (1.37, 3.31)</b>	
Live Birth			
ICSI	Reference	Reference	
cIVF	<b>1.82 (1.17, 2.82)</b>	<b>1.67 (1.05, 2.66)</b>	

\*Model is adjusted for age, body mass index (BMI), parity, infertility diagnosis, and smoking status.

Note: Bolded associations are significant at  $p < 0.05$ .

Abbreviations: CI=confidence interval; cIVF=conventional in vitro fertilization; ICSI=intracytoplasmic sperm injection; OR=Odds Ratio

