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Conversion from assisted reproductive technology to intrauterine insemination in low responders: is it advantageous?

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Abstract

Objective—To examine cycle outcomes among patients demonstrating an attenuated ovarian response that proceeded to oocyte retrieval to those converted to IUI.

Design—Retrospective cohort study.

Setting—Large private fertility center.

Patients—First, autologous ART cycles among women demonstrating a poor ovarian response to hyperstimulation (≤ 4 follicles ≥ 14 mm, peak $E_2 < 1000$ IU/L at hCG administration).

Interventions—Oocyte retrieval or IUI conversion.

Main outcome measures—Live birth and clinical pregnancy.

Results—269 IUI conversions and 167 oocyte retrievals followed a poor ovarian response to gonadotropins among first planned ART cycles. Follicles ≥ 14 mm (2.3 vs. 3.5, $p < 0.0001$) and peak E_2 (555 vs. 743 pg/mL, $p < 0.0001$) were lower for IUI conversions compared to those proceeding to ART. Peak E_2 was similar between groups after adjusting for follicle number (IUI: 611 pg/mL, 652 pg/mL; $p = 0.14$). Stimulation response was comparable between treatment groups with equivalent follicle numbers. Undergoing oocyte retrieval was associated with significantly improved pregnancy (OR: 3.6; 95% CI: 1.8, 7.4) and live birth outcome (OR: 3.5; 95% CI: 1.7, 8.0) after adjusting for age and follicle number.

Conclusions—Among women demonstrating a poor ovarian response to gonadotropins, proceeding with planned ART resulted in significantly higher pregnancy rates than converting these cycles to IUI.

Keywords

ART; oocyte retrieval; intrauterine insemination; poor response

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Introduction

Assisted reproductive technology (ART) has improved dramatically in the past 20 years (1). Nevertheless, many patients undergoing ART respond poorly to gonadotropins and continue to yield limited overall success (1–6). Consequently, many treatment cycles are cancelled due to poor ovarian response. While cycle cancellation is the least invasive option in the setting of poor ovarian response, it offers no opportunity for pregnancy (7,8). Another strategy is conversion of the cycle to a less invasive therapy, such as intrauterine insemination (IUI). Proceeding with oocyte retrieval constitutes a third treatment strategy, but involves minimal, albeit real, surgical and anesthesia-related risks associated with oocyte aspiration and increased financial costs. The diagnoses of tubal disease or severe male infertility constrain this choice due to the poor chance of success with conversion to IUI. To justify either intervention, evidence of improved pregnancy outcomes in this patient population is needed.

To date, there are few reports evaluating the outcome of cycles demonstrating a poor response to COH converted to IUI (9–12) (Table 1). Furthermore, limited data exist directly comparing cycle outcomes of poor responding patients undergoing oocyte retrieval to those converted to IUI (10,12). Given the limited available data, this study was designed to test the hypothesis that the live birth and clinical pregnancy rates among poor responders that proceed to oocyte retrieval differ from those converting to IUI.

Materials and Methods

Cycle data from the Shady Grove Fertility Reproductive Science Center from January 1, 2004 to March 1, 2008 were evaluated to identify cases of poor response to gonadotropins during a planned ART cycle. Institutional Review Board approval for this retrospective study was obtained from Schulman Associates IRB. To be included in the cohort, patients had to receive gonadotropins as part of their first planned autologous ART cycle and demonstrate 4 or fewer follicles measuring at ≥ 14 mm in average diameter with an estradiol (E_2) $< 1,000$ pg/mL at the time of human chorionic gonadotropin (hCG) trigger (Novarel®, Ferring Pharmaceuticals, Parsippany, NJ or Ovidrel®, EMD Serono, Rockland, MA). Patients converted from ART to IUI had at least 1 patent Fallopian tube and were inseminated with a post-wash total motile sperm count of ≥ 5 million. The same pool of physicians performed both the oocyte retrievals and embryo transfers of ART patients, and the inseminations of IUI patients.

Patients underwent standardized stimulation protocols that used a combination of purified or recombinant FSH and hMG with either leuprolide acetate (Lupron; Abbott Laboratories, Abbott Park, IL) or a GnRH antagonist (Ganirelix Acetate; Scherring-Plough Corporation, Kenilworth, NJ) as described previously (13). For patients undergoing oocyte retrieval for ART, oocytes were retrieved 36 hours after hCG administration when at least one follicle measured a mean diameter of 18mm using a standard transvaginal ultrasound. Conventional insemination or intracytoplasmic sperm injection were utilized as indicated. Embryos were cultured using a commercially available sequential culture media system. Fertilization assessment was performed 16–18 hours postinsemination or injection. Cleavage-stage embryos were assessed and selected based on morphologic criteria. If adequate numbers of high quality cleavage-stage embryos were present on day 3, embryos were transferred to blastocyst media and cultured through day 5 or 6. Embryo transfer occurred at the cleavage-stage in all but two patients (blastocyst transfers) using either the Tucker Embryo Catheter (Fertility Technology Resources, Inc., Marietta, GA) or the Wallace Embryo Replacement Catheter (Irvine Scientific, Santa Ana, CA) under direct ultrasound guidance. Luteal support was with 50 mg progesterone in oil IM daily.

For patients converted to IUI, the insemination occurred 36 hours following hCG administration. Sperm preparations were performed using a 90% gradient with a single wash. Inseminations were accomplished using a standard soft-tipped insemination catheter. Luteal support was likewise provided using progesterone in oil at the same dose as for ART cycles.

Data Collection and Analysis

Data were collected by reviewing electronic patient records. Age, baseline day 3 FSH, number of follicles ≥ 14 mm on the day of hCG administration, and peak serum E_2 levels were compared between treatment groups by t-test. Overall infertility diagnoses were compared between treatment groups by chi-square analysis, followed by post hoc chi-square comparisons of each individual diagnosis between the two treatment groups using the Holm-Bonferroni correction for multiple comparisons. Clinical pregnancy (defined by ultrasound identification of a gestational sac) and live birth rates were compared between treatment groups using chi-square analysis as well as multivariate logistic regression models adjusting for confounding variables (JMP; Cary, NC). Secondary outcomes including ectopic pregnancy, multiple pregnancy, spontaneous abortion, preterm birth, and low birth weight were compared between treatment groups by chi-square analysis. Yates' correction was used for chi-square comparisons in which the expected frequency in one or more cells was less than five.

Results

A total of 269 IUI conversions and 167 oocyte retrieval procedures following a poor response to stimulation were identified among first ART attempts during the study period. Age was similar between the two treatment groups, but there was a slightly lower baseline FSH for the IUI conversions compared to the ART group (IUI: 10.2 IU/L, ART: 12.2 IU/L; $p=0.0003$) (Table 2). The overall distribution of infertility diagnoses differed significantly between the IUI conversions and ART groups ($p<0.0001$). As expected, tubal factor infertility was much less common among cycles converted to IUI compared to those that underwent oocyte retrieval (IUI: 5%, ART: 19%; $p<0.0001$). With the Holm-Bonferroni adjustment for multiple comparisons, none of the other diagnoses were significantly different between the treatment groups (for each, $p>\text{adjusted } \alpha = 0.05/7 = 0.007$).

Both the number of follicles ≥ 14 mm (IUI: 2.3, ART: 3.5; $p<0.0001$) and peak E_2 concentrations (IUI: 555 pg/mL, ART: 743 pg/mL; $p<0.0001$) were lower for the IUI converted group compared to the ART cycles. However, analysis of covariance (ANCOVA) indicated that after correcting for follicle number, peak E_2 concentrations were similar between the IUI conversion and the ART cycles (IUI: 611 pg/mL, ART: 652 pg/mL; $p=0.14$ (least squares means)). Therefore, the estradiol levels were comparable between treatment groups with an equivalent number of follicles.

In patients who proceeded with ART, the mean number of oocytes retrieved was approximately one greater than the number of follicles ≥ 14 mm present on the day of hCG trigger, while the number of mature (MII) oocytes retrieved was very similar to these follicle numbers (Table 3). In only four cases (2.4%) did an attempted retrieval fail to obtain any oocytes. The mean number of fertilized (2pn) embryos was less than 1.5 among cycles with fewer than three follicles, but greater than 2 among cycles with three or four follicles. Transfers were cancelled (due to lack of any viable embryos) for more than one-quarter of cycles with fewer than three follicles, but for only 6% of cycles with three or four follicles. In addition to fresh transfers, 6% of cycles with three or four follicles also had additional high quality embryos suitable for cryopreservation and transfer in a later cycle.

Both clinical pregnancy rates (IUI: 5%, ART: 26%; $p < 0.0001$) and live birth rates (IUI: 4%, ART: 20%; $p < 0.0001$) were significantly higher for cycles that proceeded with oocyte retrieval compared to IUI converted cycles. In a multiple logistic regression model predicting clinical pregnancy (model $R^2 = 0.17$; $p < 0.0001$), patient age, number of follicles, and cycle type all contributed significantly ($p = 0.013$, 0.0003 , and 0.0003 respectively). Diagnosis (i.e. tubal factor or not, $p = 0.48$), baseline FSH ($p = 0.56$) and peak E_2 ($p = 0.28$) did not significantly predict clinical pregnancy rates after adjusting for age and follicle number. The odds of pregnancy, adjusting for patient age and number of follicles, were more than three times greater among those undergoing ART compared to those converted to IUI (OR: 3.6; 95% CI: 1.8, 7.4). Results of multiple logistic regression analysis of live birth were essentially the same, yielding a similar adjusted odds ratio for live birth (OR: 3.5; 95% CI: 1.7, 8.0). There were no significant interactions between follicle number and treatment group for either clinical pregnancy ($p = 0.48$) or live birth ($p = 0.62$) outcomes, demonstrating that the improved outcomes with ART versus IUI were consistent across the range of follicle numbers (1–4) examined in the study. Stratifying outcomes by the number of follicles (Figure 1) revealed progressive improvement in live birth across both treatment strategies.

Secondary treatment outcomes, including ectopic pregnancy, multiple pregnancy, spontaneous abortion, preterm birth, and low birth weight rates did not differ significantly between the two treatment strategies (Table 2).

Discussion

The decision to proceed to oocyte retrieval in the setting of poor ovarian response during ART cycles remains a difficult one, especially when considering the limited and conflicting available data. To evaluate treatment strategies, we compared the cycle outcomes of those women who responded poorly to gonadotropin stimulation that went on to oocyte retrieval to those who were converted to IUI. Among women with 4 or fewer total follicles measuring ≥ 14 mm and maximum peak E_2 levels of $\leq 1,000$ pg/mL, our study demonstrates that proceeding with ART yields significantly improved clinical pregnancy and live birth rates compared to those who underwent IUI conversion. The nearly five-fold difference in the unadjusted pregnancy and birth rates is not a valid comparison of the relative efficacy of the two treatment strategies, as the average response to stimulation tended to be poorer among the IUI conversion cycles. The approximately three-fold difference in pregnancy and birth rates after adjusting for confounding variables including age and follicle number (adjusted OR: 3.6 and 3.5, respectively) more accurately reflects the true treatment effect..

Our findings contrast with the results of two previous studies that also directly compared IUI conversion to ART in low responding patients. Wood *et al.* found no difference in clinical pregnancy rates between converting to IUI or progressing to ART (12% ($n = 48$) vs 8% ($n = 79$)) (10). More recently, Shahine *et al.* also reported no difference in clinical pregnancy rates between conversion to IUI or proceeding with ART as planned (8% ($n = 50$) vs 10% ($n = 170$)) (12). Interestingly, when greater numbers of follicles were present in their low responding cohorts, similar to the present study, the live birth rate was higher in those proceeded to oocyte retrieval than to those converted to IUI (12). Sample sizes used in both of these earlier studies were very limited, with no more than 50 cases of IUI conversion in either compared to the 269 cases of IUI conversion that we report. As a result, estimates of IUI outcomes from these previous studies are likely to be much less accurate than ours, and their power to detect outcome differences compared to ART treatment was much more limited. Neither of these studies adjusted for patient age and follicle number, the two variables most likely to confound results, in multivariate analyses as we did. In addition, unlike we did, neither of these earlier studies limited inclusion to only one cycle per patient

or to patients' first planned ART cycles, thus introducing additional potential sources of error and bias that could complicate comparisons.

Interestingly, our IVF results are similar to Ng *et al.*, who reported clinical pregnancy rates among low responding patients with 1, 2, or 3 follicles aspirated of 6.3% (1 of 16), 18.4% (9 of 49), and 24.7% (18 of 73) respectively (14). Overall the clinical IVF pregnancy rates that we report are also similar to those published by Lashen *et al.* and Biljan *et al.* in similar populations (Table 1) (7,15). Compared to our overall ART population who underwent oocyte retrieval during the same time period, poor responding patients had a significantly lower clinical pregnancy rate (26% (44 of 167) versus 44% (5730 of 13,024)).

Since the number of oocytes that will be retrieved remains unknown prior to the decision to convert to an IUI or proceed with retrieval, total follicle number is a more clinically relevant criterion for the question at hand. In this study, in patients who proceeded to oocyte retrieval, more than one oocyte was retrieved per 14 mm follicle on the day of hCG trigger (mean 4.4 oocytes, SD 2.6) with a corresponding maturity rate of 79% (mean 3.5 MII oocytes, SD 2.0). This increased retrieved oocyte to follicle ≥ 14 mm ratio was present at each follicle group (Table 3). Only 4 of 167 (2.4%) patients going to retrieval did not have an oocyte retrieved similar to other reports (14,15). Further, a small percentage of patients did not proceed to embryo transfer; this was more likely in patients with 1 or 2 follicles 14 mm or greater on the day of hCG trigger (5 of 18 or 28%) than in those with 3 or 4 follicles (9 of 149 or 6%) ($p=0.002$). While most patients underwent double embryo transfer (60%), some were able to freeze additional high quality embryos for a future cycle (9 of 167 or 5%).

An important finding of this study was that there were no pregnancies resulting from either therapy among those with a solitary follicle at the time of hCG, although our sample of ART cycles with only one follicle was extremely limited. Moreover, this study demonstrated a remarkably low probability of live birth among those women demonstrating 2 follicles who underwent IUI (2%). This finding is similar to that of Abusheikha *et al.* (2.4%) (9). Proceeding with oocyte retrieval in this population resulted in a 3-fold increase (6%), resulting in an estimated number needed to treat (NNT) of 25 to achieve one live birth. However, when examining patients demonstrating 3 or 4 follicles ≥ 14 mm at the time of retrieval, it was clear that there was both a statistically and clinically significant improvement in live births by proceeding with ART (absolute increase: 13% and 10%, respectively; NNT ~ 10).

The limitations of this study include its retrospective nature. We attempted to account for this in the study design and analysis. To avoid potential bias on estimates due to prior cycle information, we restricted our cohort to only those undergoing their first planned ART cycle. Moreover, treatment assignment was non-random and there were statistically significant differences between groups regarding day 3 FSH, diagnosis, number of follicles measuring ≥ 14 mm, and peak E₂. As anticipated, there was a propensity to include those with tubal factor infertility and higher follicle number in the ART group and to exclude them from the IUI group. As these factors might have influenced cycle outcomes, these imbalances represent potential confounders. To address and adjust for these discrepancies, these factors were included as terms in multivariate regression models. Even after adjusting for these confounders, there remained a statistically significant and substantial difference in success rates in favour of ART treatment.

In conclusion, our comparison of IUI conversion versus ART treatment in low responders to stimulation for planned ART is, to date, the largest and best controlled examination of this issue yet reported. Proceeding to oocyte retrieval in patients with 4 or fewer total follicles

≥ 14 mm resulted in more than a 3-fold improvement in the odds of clinical pregnancy and live birth when compared to converting these cycles to IUI. The improvement in live birth rates was especially significant in those who had either 3 or 4 follicles ≥ 14 mm. When choosing a course of treatment, this difference in clinical efficacy must be weighed against financial considerations including the differences in treatment costs, which will generally be considerably higher for ART compared to IUI conversion, and the availability of insurance coverage. Those with a solitary follicle had such poor results, that we cannot advocate any intervention other than cancellation or timed intercourse alone (although this was not evaluated in this study). Conversely, with increasing follicle numbers, significant improvements in clinical pregnancy and live birth were noted with ART. Based on these results, it is warranted to proceed with oocyte retrieval rather than conversion to IUI among patients with 3 to 4 follicles ≥ 14 mm on day of hCG trigger.

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Figure 1.

Live birth rates in 1st IVF cycles that resulted in either an IVF to IUI conversion or oocyte retrieval with 1, 2, 3, or 4 follicles ≥ 14 mm on the day of hCG trigger. n=number of patients, mean patient age, E₂=peak estradiol level, and %=live birth rate.

Table 1

Summary of published studies examining IVF to IUI conversions and low responding patients who proceeded to oocyte retrieval (7,9–12,14–16).

	Study Period	Clinical Pregnancy Rate [IUI Conversions] ^a	Clinical Pregnancy Rate [IUI Reference]	Clinical Pregnancy Rate [ART] ^a	Clinical Pregnancy Rate [ART Reference]
Lashen <i>et al.</i> , (1999)	4 years	NR	NR	21.2% (14/66)	22.0% (31/142) ^b
Biljan <i>et al.</i> , (2000)	28 months	NR	NR	14.2% (5/42) ^c	33.0% (252/763) ^d
Abusheikha <i>et al.</i> , (2001)	4 years	2.4% (1/42) ^e	12.9% (34 of 264)	NR	NR
Bahceci <i>et al.</i> , (2003)	3 years	NR	NR	8.1% (17/208)	37.3% (47/126)
Matorras <i>et al.</i> , (2003)	6 years	14% (8/57) ^f	17.3% (240 of 1389) ^g	NR	NR
Wood <i>et al.</i> , (2003)	20 months	12.5% (6/48) ^h	12.5% (1 of 8) ⁱ	7.6% (6/79)	NR
Ng <i>et al.</i> , (2006)	3 years	NR	NR	20.2% (28/138)	23.3% (176 of 756)
Shahine <i>et al.</i> , (2009)	18 months	8% (4/50)	NR	10% (17/170)	NR

NR=not reported.

^a at least one follicle ≥ 16 mm.

^b patients who had 5 to 6 follicles present.

^c <3 follicles present on day 12 of COH with at least 1 follicle > 18 mm on day of hCG.

^d >3 follicles present on day 12 of COH with at least 1 follicle > 18 mm on day of hCG.

^e at least one follicle ≥ 18 mm, all others >14 mm.

^f 2–4 follicles ≥ 14 mm & at least 2 >18 mm.

^g General IUI population with at least 2 follicles >18 mm; cancelled if >6 follicles >16 mm or when estradiol levels were >2000 pg/ml.

^h at least one follicle >16 mm.

ⁱ restricted to patients who underwent superovulation IUI patients with ovulatory disorders.

Table 2

Patient and cycle characteristics compared between cycles that were converted to IUI and cycles that proceeded to oocyte retrieval and ART as originally planned.

	IUI conversion	ART	p-value
Number of patients	269	167	
Age (years)	37.0 ± 3.8	36.9 ± 4.1	0.78
Baseline FSH (IU/L)	10.2 ± 4.6	12.2 ± 5.8	0.0003
Diagnosis (%)			<0.0001
Male factor	45 (16.7)	39 (23.4%)	0.09
Tubal factor	14 (5.2)	31 (18.6)	<0.0001
DOR	96 (35.7)	55 (32.9)	0.56
Anovulation/PCOS	14 (5.2)	4 (2.4)	0.14
Endometriosis	22 (8.2)	26 (15.6)	0.018
Uterine factor	14 (5.2)	6 (3.6)	0.43
Unexplained	85 (31.6)	39 (23.4)	0.06
Other Diagnosis	15 (5.6)	7 (4.2)	0.52
Follicles number (≥14 mm)	2.3 ± 1.1	3.5 ± 0.7	<0.0001
Peak E ₂ (pg/mL)	555 ± 311	743 ± 177	<0.0001
Ectopic pregnancy (%)	0	2 (1.2)	0.28
Clinical pregnancy (%)	14 (5.2)	43 (25.7)	<0.0001
Multiple pregnancy (%)	3 (21.4)	15 (38.9)	0.54
Spontaneous abortion (%)	3 (21.4)	10 (23.4)	0.99
Live birth (%)	11 (4.1)	33 (19.8)	<0.0001
Preterm birth (%)	1 (9.1)	9 (27.3)	0.41
Low birth weight (%)	2/12 (16.7)	12/43 (27.9)	0.68

Table 3

Cycle characteristics among IVF cycles according to the number of follicles greater than or equal to 14 mm on the day of hCG trigger injection.

	Number of follicles $\geq$ 14mm on day of hCG			
	One	Two	Three	Four
Cycles	2	16	40	109
Oocytes	2.0 ± 1.4	2.3 ± 1.9	3.7 ± 1.6	5.0 ± 2.8
MII oocytes	2.0 ± 1.4	2.2 ± 0.9	2.8 ± 1.5	4.0 ± 2.1
2pn embryos	1.5 ± 2.1	1.3 ± 0.9	2.2 ± 1.2	2.7 ± 1.7
ET	1 (50%)	12 (75%)	38 (95%)	102 (94%)
Embryos/ET	3	1.6 ± 0.7	1.8 ± 0.6	2.0 ± 0.7
Embryo cryo	0	0	3 (8%)	6 (6%)

MII = metaphase II. 2pn = 2 pronucleii. ET = embryo transfer. Embryo cryo = embryos cryopreserved.