In Vtro Maturation Outcomes of hCG-primed Unstimulated Cycles in Patients with Polycystic Ovarian Syndrome: a Single-center Experience

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Abstract

Background: IVM has emerged as a safe and promising alternative procedure to conventional in vitro fertilization (IVF) for minimizing the risk of ovarian hyperstimulation syndrome (OHSS) in patients with PCOS. Despite the comparable obstetric and perinatal outcomes, there are no definite factors known to affect the outcomes of IVM.

Methods: Retrospective analysis of a total of 313 women with PCOS undergoing 427 hCG-primed IVM cycles between January 2010 and February 2016 at the Fertility Center of CHA Gangnam Medical Center, Seoul, Korea. The number of retrieved oocytes and maturation, fertilization, and implantation rates were analyzed.

Results: After transferring a mean of 2.4 ± 0.5 fresh embryos, the clinical pregnancy rate was 39.1% ($n = 167$), and the live birth rate was 30.7% ($n = 131$) with the implantation rate of 20.9%. The numbers of retrieved (18.1 ± 9.7 vs. 15.6 ± 8.7 , $p = 0.014$), fertilized (8.6 ± 5.2 vs. 6.6 ± 3.8 , $p < 0.001$) oocytes; good-quality embryos (1.3 ± 0.9 vs. 1.0 ± 0.9 , $p = 0.001$); and blastocyst transfer cycles (22 vs. 15, $p < 0.001$) were significantly higher in the live birth group than in the no live birth group. Among the factors associated with live births, retrieved oocytes had a slightly positive effect on live birth (RR = 1.03; 95% CI, 1.00, 1.06; $p = 0.021$).

Conclusions: It seems that the number of retrieved oocytes has a favorable effect in increasing the clinical pregnancy rate and live birth rate during hCG-primed IVM procedure in women with PCOS. Physicians' skills and cautious efforts may be required to retrieve a higher number of oocytes in IVM procedures.

Background

Subfertility occurs in 15-20% of couples trying to conceive, and ovulatory factor account for up to 30-40% of all cases of female subfertility. Polycystic ovarian syndrome (PCOS) affects 4-7% of all women of reproductive age and 50% of those presenting with subfertility [1]. A certain proportion of women with PCOS require assisted reproductive technology (ART). Occasionally, controlled ovarian hyperstimulation in women with PCOS is associated with risks of complications such as ovarian hyperstimulation syndrome (OHSS), resulting in cycle cancellation or freeze-all strategies.

In vitro maturation (IVM) has emerged as a safe alternative procedure to conventional in vitro fertilization (IVF) for minimizing the risk of OHSS in patients with PCOS. Cha et al. reported the first successful pregnancy resulting from IVM of unstimulated ovaries from donors [2], and Trounson et al. initially achieved an IVM baby from the mother's autologous oocytes [3]. Since then, IVM has also been successfully used in a wide range of subfertile populations, especially in women with PCOS. So far, more than 5,000–6,000 IVM babies have been born worldwide [4]. The American Society for Reproductive Medicine (ASRM) Committee announced that the IVM procedure should be performed only as an experimental procedure evaluating both efficacy and safety in carefully selected patients in 2013 [5].

However, a recent meta-analysis found that the clinical pregnancy rate was higher with the IVM procedure than with conventional IVF although with very low-quality evidence, investigating randomized controlled trials in patients with PCOS [1]. More recently, Yu et al. reported no significant increased risk in obstetric, neonatal, and childhood development associated with IVM after a mean follow-up of 7.5 years compared with conventional IVF in women with PCOS in a retrospective case–control study [6].

Several researchers have developed and used different kinds of protocols for IVM procedures: IVM with FSH priming, which is a short course usage of gonadotropins to increase oocyte yield, or IVM with hCG priming to facilitate the resumption of meiosis in vivo before full oocyte maturation [7]. According to some studies, hCG priming increased the maturation, fertilization, and pregnancy rates from 69% to 84%, 45% to 80%, and 31% to 51.9%, respectively, while FSH priming increased the pregnancy rate by up to 29% [8, 9].

Although IVM is considered a promising alternative procedure in women with PCOS, most studies have focused on the efficacy and safety, especially compared with conventional IVF. Several studies have tried to investigate the potential factors to improve IVM procedures, such as the size of follicles before oocyte retrieval, use of either FSH or hCG priming, optimal timing for hCG injection in hCG-primed cycles, and components in culture media [10, 11]. However, currently, there is no definite factor that has been proven to improve IVM outcomes.

The aim of this study was to investigate the factors that are related to successful IVM outcomes in women with PCOS during hCG-primed unstimulated cycles.

Methods

Study population

This retrospective study investigated the parameters from medical charts of 313 patients with PCOS who underwent IVM cycles between January 2010 and February 2016 at the Fertility Center of CHA Gangnam Medical Center, Seoul, Korea. A total of 427 IVM cycles were included in this study. PCOS was diagnosed based on the consensus meeting of the European Society of Human Reproduction and Embryology (ESHRE) and ASRM [12]; if patients had other etiologies such as congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, or neoplastic disease, they were excluded. This study was approved by the Institutional Review Board of CHA Gangnam Medical Center (GCI 2020-03-006).

IVM protocol, oocyte retrieval, and culture procedure

All patients underwent unstimulated cycles with hCG priming. Oocyte retrieval was performed between menstrual cycle days 9 and 33, based on the patient's cycle length after serial checking of antral follicle count (AFC) and endometrial thickness by transvaginal ultrasonography. The patients were subcutaneously injected with recombinant hCG (choriogonadotropin- α , 250 μ g, Ovidrel, Merck Serono,

Germany) 35–36 h before oocyte retrieval. The immature oocytes were retrieved with a transvaginal ultrasound guide using a 17-gauge double-lumen aspiration needle (Cook, Australia) with a suction pressure of 160 mmHg.

All oocytes were isolated from the follicular fluid by filtration (70 µm Cell Strainer, Falcon, USA) and washed 3–4 times in washing medium (Sage, Cooper Surgical). Immature oocytes were then transferred into IVM medium (G2 medium; Vitrolife) supplemented with 20% human follicular fluid, 75 mIU/mL of recombinant FSH, 0.5 IU/mL of hCG, 1 µg/mL of E2, and 10 µg/mL of melatonin for maturation.

IVM procedures were performed at 37°C, 5% CO₂, and 5% O₂ in the incubator. After the oocytes were cultured for 24–48 h, they were denuded with hyaluronidase solution (ICSI Cumulase; Origio). The maturity of the oocytes was microscopically determined by the presence of the first polar body. Mature oocytes were inseminated by ICSI to initiate fertilization and embryonic development. At 66–120 h after ICSI, one to three embryos were selected according to the number and quality of embryos and transferred into the patient's uterus. Supernumerary embryos were cultured and frozen when they reached the blastocyst stage. A good-quality embryo at the cleavage stage was defined as a 4-cell embryo on day 2 and a 7- or 8-cell embryo on day 3, contained <20% anucleate fragments, and exhibited no apparent morphological abnormalities. As for blastocyst-stage embryos, a good-quality embryo was defined according to the Gardner and Schoolcraft criteria [13].

For endometrial preparation, patients were given oral estradiol valerate (Progynova, Schering Pharmaceuticals) with a daily oral dose of 4 mg, starting from the day of oocyte retrieval. Luteal support was also provided by both progesterone injection (daily, 50 mg, Watson Pharmaceuticals) and transvaginal progesterone (daily, 600 mg of Utrogestan, Piette International Laboratories; 300 mg of Lutinus, Ferring Pharmaceuticals; or 300 mg of Endometrin, Ferring Pharmaceuticals) starting from the day of fertilization until 8 weeks of gestation, if a patient was pregnant. Serum β-hCG concentrations were measured 11–12 days after embryo transfer (ET). Clinical pregnancy refers to the identification of a pregnancy sac in the uterus at 6 weeks of gestation. After the confirmation of clinical pregnancy, women were followed up for pregnancy outcomes.

Measurement of demographic and clinical outcomes

All data were collected using electronic medical records, including baseline characteristics (age, body mass index (BMI), AFC, and duration of infertility) and basal hormone levels (anti-Müllerian hormone (AMH), FSH, LH, and estradiol). Parameters related to IVM cycles were also investigated, such as the number of retrieved oocytes and maturation, fertilization, implantation, and clinical pregnancy rates.

Statistics

Data were analyzed using SPSS 26.0 (IBM, USA). Statistical analysis was performed using the chi-square test, Student t-test, and multivariate regression analyses. Differences were considered significant when the *P* value was less than 0.05.

Results

Baseline patient characteristics are summarized in TABLE 1. The mean age at undergoing IVM was 33.1 ± 3.4 years, having the mean duration of infertility of 3.7 ± 2.4 years. All of 313 women in this study had PCOS with the mean AMH of 10.9 ± 5.6 ng/mL, having the mean AFC of 30.4 ± 15.0 on hCG day.

TABLE 1

Baseline characteristics of patients

Variables	mean $\pm$ SD
Age (y, range 23-44)	33.1 ± 3.4
Duration of infertility (y, 0-14)	3.7 ± 2.4
BMI (kg/m ²)	21.7 ± 2.4
AMH (ng/mL)	10.9 ± 5.6
Basal FSH (mIU/mL)	8.6 ± 4.2
Basal LH (mIU/mL)	8.2 ± 5.5
Basal Estradiol (pg/mL)	43.8 ± 27.0

Abbreviations: BMI, body mass index; AMH, anti-Müllerian hormone

Among a total of 427 cycles of IVM procedures, the mean number of retrieved oocytes was 16.4 ± 9.1 oocytes per cycle. Each patient was transferred a mean number of 2.4 ± 0.5 fresh embryos, and the mean endometrial thickness on hCG day was 6.9 ± 0.2 mm. The clinical pregnancy rate was 39.1% ($n = 167$), with the singleton, twin, and triple pregnancy rates of 30.0% ($n = 128$), 7.5% ($n = 32$), and 1.4% ($n = 6$), respectively, per cycle. There was only one quadruple pregnancy after transferring two embryos (0.2%). The implantation rate was 20.9% per embryo, and the live birth rate was 30.7% ($n = 131$).

The ART outcomes according to the patient group with or without live birth and ET with or without blastocyst are shown in TABLE 2. There was no statistically significant difference in terms of AMH, AFC, size of leading follicle and endometrial thickness on hCG day, and number of transferred embryos between the live birth and no live birth groups. The numbers of retrieved (18.1 ± 9.7 vs. 15.6 ± 8.7 , $p = 0.014$; range, 2–60 in all cycles) and matured (10.8 ± 6.4 vs. 8.4 ± 4.7 , $p < 0.001$) oocytes were significantly higher in the live birth group. The number of fertilized oocytes was significantly higher in the live birth group (8.6 ± 5.2 vs. 6.6 ± 3.8 , $p < 0.001$) although the fertilization rate was not significantly different between the groups (82.2 ± 9.1 vs. 80.2 ± 20.4 , $p = 0.337$). Although the number of transferred

embryos was not different between the groups (2.3 ± 0.5 vs. 2.4 ± 0.6 , $p = 0.365$), the day of ET after oocyte retrieval (4.4 ± 0.8 vs. 4.2 ± 0.7 , $p = 0.042$) and the numbers of good quality embryos (1.3 ± 0.9 vs. 1.0 ± 0.9 , $p < 0.001$) and blastocyst transfer cycles (22 vs. 15, $p < 0.001$) were significantly higher in the live birth group.

TABLE 2

Characteristics of patient in IVM cycles

Variables	Live births (n = 167) mean ± SD	No Live birth (n = 260) mean ± SD	<i>P</i> value	ET with blastocyst (n = 37) mean ± SD	ET without blastocyst (n = 390) mean ± SD	<i>P</i> value
Age (y)	33.6 ± 3.4	33.3 ± 3.3	0.059	32.4 ± 3.3	33.2 ± 3.4	0.180
Duration of infertility (y)	3.6 ± 2.3	3.7 ± 2.4	0.545	3.0 ± 1.7	3.8 ± 2.4	0.018
BMI (kg/m ²)	21.7 ± 3.3	21.8 ± 3.5	0.627	22.1 ± 3.5	21.8 ± 3.4	0.608
AMH (ng/mL)	11.5 ± 5.5	10.6 ± 5.6	0.387	11.5 ± 5.9	10.8 ± 5.5	0.553
Estradiol on hCG day (pg/mL)	128.2 ± 148.5	98.7 ± 148.5	0.106	257.8 ± 240.7	101.3 ± 98.5	0.070
AFC on hCG day (n)	30.1 ± 14.5	30.6 ± 15.3	0.782	37.8 ± 13.3	29.7 ± 15.0	0.002
Leading follicle diameter on hCG day (mm)	9.2 ± 3.3	9.7 ± 3.3	0.172	8.2 ± 1.9	9.7 ± 3.4	0.008
Endometrial thickness on hCG day (mm)	0.7 ± 0.2	0.7 ± 0.2	0.698	7.6 ± 1.6	6.9 ± 1.6	0.018
Retrieved oocytes (n, range 2-60)	18.1 ± 9.7	15.6 ± 8.7	0.014	22.8 ± 8.7	15.8 ± 8.9	< 0.001
Total matured oocytes (n)	10.8 ± 6.4	8.4 ± 4.7	< 0.001	13.9 ± 5.8	8.7 ± 5.2	< 0.001
Matured oocytes on retrieval day (n)	7.3 ± 4.9	5.3 ± 3.3	< 0.001	0.0 ± 0.2	0.2 ± 0.7	0.001
Matured oocytes, one day after retrieval (n)	3.4 ± 3.4	3.0 ± 3.1	0.263	9.5 ± 4.6	5.5 ± 3.7	< 0.001
Matured oocytes, two days after retrieval (n)	0.0 ± 0.0	0.0 ± 0.2	0.507	4.4 ± 3.3	3.0 ± 3.2	0.012
Maturation rate (%)	60.9 ± 16.6	56.2 ± 20.5	0.021	62.1 ± 15.7	57.2 ± 20.0	0.148
Fertilized oocytes (n)	8.6 ± 5.2	6.6 ± 3.8	< 0.001	11.2 ± 4.5	6.8 ± 4.1	< 0.001
Fertilization rate (%)	82.2 ± 19.1	80.2 ± 20.4	0.337	82.3 ± 17.2	80.7 ± 20.3	0.639
Day of embryo transfer	4.4 ±	4.2 ±	0.042	5.9 ± 0.3	4.1 ± 0.6	< 0.001

after oocyte retrieval	0.8	0.7				
Transferred embryos (n)	2.3 ± 0.5	2.4 ± 0.6	0.365	2.0 ± 0.0	2.4 ± 0.6	< 0.001
Good quality embryos (n)	1.3 ± 0.9	1.0 ± 0.9	0.001	0.9 ± 0.8	1.1 ± 0.9	0.173
Blastocyst transfer cycles (n)	22 (16.8%)	15 (5.1%)	< 0.001	37	0	
Implantation rate (%)	57.5 ± 23.3	5.6 ± 16.2	< 0.001	50.0	18.9	< 0.001
Live births (cycles, n)				22 (59.5%)	109 (27.9%)	< 0.001
<i>Abbreviations:</i> ET, embryo transfer; BMI, body mass index; AMH, anti-Müllerian hormone; AFC, antral follicle count						

In the ET with blastocyst group (n = 37), the number of retrieved oocytes was significantly higher than that in the ET without blastocyst group (n = 390) (22.8 ± 8.7 vs. 15.8 ± 8.9 , $p < 0.001$). The AFC, numbers of total matured and fertilized oocytes, and maturation and fertilization rates were also significantly higher in the ET with blastocyst group. The clinical pregnancy (67.6% vs. 36.4% , $p < 0.001$), live birth (59.5% vs. 27.9% , $p < 0.001$), and implantation (50.0% vs. 18.6% , $p < 0.001$) rates were significantly higher in the ET with blastocyst group than in the ET without blastocyst group, even though the number of transferred embryos was significantly higher in the ET without blastocyst group (2.0 ± 0.0 vs. 2.4 ± 0.6 , $p < 0.001$).

The factors associated with live births are shown in TABLE 3. Among these factors, retrieved oocytes had a slightly positive effect on live birth (RR = 1.03; 95% CI, 1.00, 1.06; $p = 0.021$).

TABLE 3

Factors associated with live births in multivariate log-binomial regression analysis

Variables	RR	95% CI	P value
Age group			
< 30 y (n=61)	Reference		
30-34 y (n=234)	0.99	0.54 – 1.83	0.977
1. y (n=118)	0.75	0.37 – 1.50	0.414
≥ 40 y (n=14)	0.97	0.26 – 3.61	0.970
BMI (kg/m ²)	0.99	0.93 – 1.04	0.624
AFC on hCG day (n)			
< 20	Reference		
20 - 29	0.55	0.30 – 1.00	0.049
30 - 39	0.77	0.40 – 1.47	0.430
≥ 40	0.098	0.27 – 1.12	0.099
Leading follicle diameter on hCG day (mm)	0.96	0.89 – 1.04	0.295
Retrieved oocytes (n)	1.03	1.00 – 1.06	0.021
Maturation rate (%)	2.31	0.07 – 76.01	0.638
Fertilization rate (%)	1.88	0.54 – 6.61	0.324
<i>Abbreviations:</i> BMI, body mass index; AFC, antral follicle count; CI, confidence interval; RR, relative risk			

Discussion

This study found that the numbers of retrieved, total matured, and fertilized oocytes and day of ET after oocyte retrieval were significantly higher in favor of live births during hCG-primed IVM cycles in women with PCOS.

The overall clinical pregnancy (39.1%) and live birth (30.7%) rates in this study were comparable to previous reports of 20.4% and 68.5% of the clinical pregnancy rate and 18.8%–33.7% of the live birth rate [8, 14, 1, 4]. The ET with blastocyst group showed a significantly higher clinical pregnancy rate (67.6%) than the ET without blastocyst group after transferring a mean number of 2.0 blastocysts. In a previous study of hCG-primed IVM in women with PCOS in 2007, the clinical pregnancy rate of blastocyst ET was also higher than that of cleavage ET (51.9% vs. 28.4%), following the transfer of a mean number of 2.95 blastocysts [15]. Therefore, the results of the present study imply more evolved and promising aspects of IVM procedures via recent developments in ART departments.

The present study suggests a positive effect of the number of retrieved oocytes in terms of clinical pregnancy and live births. Tan et al. previously reported that the pregnancy rates after IVM were correlated with the number of immature oocytes retrieved, assessing 189 IVM cycles with hCG priming in 146 women, among whom 73 had PCOS [16]. Guzman et al. reported in a recent retrospective study of 124 patients with PCOS an association of the retrieval of ≥ 8 oocytes with higher clinical pregnancy rates (30.4% vs. 11%) when compared with patients with a lower oocyte yield [17]. Tannus et al. also found that the number of retrieved oocytes was an important predictive factor for live birth after transferring cleavage-stage embryos during IVM cycles with FSH and hCG priming in 159 women with PCOS [18]. These studies indicated that AFC was a significant predictor of the number of oocytes retrieved. The present study did not show a significant difference in the AFC on hCG day between the live birth and no live birth groups. However, the number of retrieved oocytes and AFC on hCG day were significantly higher in the ET with blastocyst group than in the ET without blastocyst group.

Considering the findings of the present study, it may be important to try to retrieve more oocytes for higher pregnancy rates as well as higher blastocyst formation. For this, it is worrisome about patients' pain, intraperitoneal bleeding, and other possible complications. Seyhan et al. recently reported that oocyte retrieval was well tolerated and did not seem to be associated with more complications than IVF although IVM required more punctures per ovary [19]. The number of retrieved oocytes was much smaller than that of AFC on hCG day in the present study. Therefore, physicians' skills and cautious efforts are needed to retrieve a higher number of oocytes in IVM as well as in IVF.

To increase the clinical pregnancy rate, some authors in previous studies have insisted that IVM should be scheduled when the follicles are larger than 12 mm in diameter for better oocyte competence [10], whereas other researchers have suggested retrieving the leading follicles sized <12 or <14 mm in IVM cycles [20, 9, 21, 22]. However, the diameter of the leading follicles on hCG did not differ between the live birth and no live birth groups in this study, with a mean diameter under 10 mm in both groups.

Endometrial thickness is also an important parameter in ART, but there are only a few studies that have analyzed the effect of endometrial thickness in IVM procedures. The present study showed no significant difference between the live birth and no live birth groups in terms of endometrial thickness (overall mean thickness, 7.0 mm). It is known that endometrial development may be suboptimal in IVM compared with that in natural or stimulated cycles [8]. In this regard, Ortega-Hrepich et al. suggested successful pregnancy after warming vitrified embryos in FSH-primed IVM cycles without hCG priming, adopting hormone replacement ET cycle [23]. The present study used hCG priming and endometrial preparation with sufficient hormone therapy. Several researchers have suggested that hCG priming is beneficial in terms of endometrial synchronization with the developing embryo as well as oocyte yield and maturational competence [24]. The patients in this study were prescribed hormonal medications for endometrial preparation, including oral estradiol with vaginal and intramural progesterone, whereas most studies used oral estradiol and vaginal progesterone [24]. Therefore, it is possible to suggest that hCG priming combined with sufficient luteal supplement is beneficial for relatively thinner endometrium in women in fresh IVM cycles.

This study has a few limitations. This was a retrospective study with a relatively small number of patients. However, to our knowledge, this is the largest study analyzing the factors associated with hCG-primed unstimulated IVM outcomes. Further prospective studies with larger numbers of patients are needed to confirm the results of this study.

Conclusion

It seems that the number of retrieved oocytes has a favorable effect in increasing the clinical pregnancy rate and live birth rate during hCG-primed IVM procedure in women with PCOS. In conclusion, it seems that the number of retrieved oocytes has a favorable effect on the live birth rate during hCG-primed IVM procedures in women with PCOS.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of CHA Gangnam Medical Center (GCI 2020-03-006).

Consent for publication

Not applicable.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Myung Joo Kim performed the data collection and statistical analysis and wrote the manuscript; You Shin Kim developed the ideas and reviewed the manuscript; Seung-Ah Choe checked and interpreted the statistical analysis; Eun A Park drafted the methods in the manuscript; Ran Kim corrected the manuscript.

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