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Intracytoplasmic Sperm Injection in Women with Polycystic Ovary Syndrome and Isolated Polycystic Ovary Morphology: A case-Control Study

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Abstract: ***Objective:*** ***To determine the efficacy of intracytoplasmic sperm injection (ICSI) and embryo transfer (ET) in patients with polycystic ovary syndrome (PCOS) and isolated polycystic ovarian morphology (PCOM).*** ***Methods:*** ***A case-control study was conducted in In Vitro Fertilization center, Maternity Teaching Hospital, Erbil city on total of 190 consecutive infertile women with PCOS, 50 women with isolated PCOM,versus 248 women with normal ovaries .ICSI was conducted for all of them .*** ***Results:*** ***Despite a significantly lower total follicle-stimulating hormone dose, significantly higher serum estradiol levels were attained in the PCOS and PCOM groups compared with the control group. The PCOS and PCOM groups had significantly more retrieved oocyte-cumulus complexes and metaphase II oocytes compared with the control group. Fertilization rates were similar in all three groups. The mean numbers of grade 1 embryos were significantly more in the PCOS and PCOM groups compared with the controls. The clinical pregnancy rates per cycle were significantly higher in the PCOS (34%) and PCOM (42%) groups compared with the control group (25%), and there were significantly more live births per cycle in the PCOS (28%) and PCOM (36%) groups compared with the control group (18.5%).*** ***Conclusions:*** ***Patients with PCOS and PCOM respond similarly during all stages of assisted reproduction. The availability of more fertilized oocytes and grade 1 embryos means that patients with PCOS or PCOM have higher clinical pregnancy and live birth rates per cycle compared with normal controls.***

Keywords: Antimullerian Hormone, Assisted reproductive technology, technology, Intracytoplasmic sperm injection Polycystic ovary syndrome

1. Introduction

Polycystic ovarian syndrome (PCOS) can affect 6–10% of women of childbearing age [1], but its pathogenesis remains largely unknown. Recent studies have suggested that antimüllerian hormone (AMH), which is derived from the granulosa cells of early developing preantral and antral follicles [2], may play a role in ovarian follicular status in PCOS [3, 4].

Ultrasound evidence of polycystic ovary morphology(PCOM) affects approximately 20–30% of the female population [5–7], though, only a proportion of these women are symptomatic. Although it may be considered as a normal variant, the prevalence of PCOM in women attending fertility clinics is as high as 34% [8]. Many women with PCOM but without symptoms of PCOS (regular ovulatory cycles and no hyperandrogenism) have been described as having ovulatory PCO [9]. PCOM may be detected by transvaginal ultrasonography (TVS) with no evidence of anovulation, hyperandrogenism, or hyperandrogenemia. However more recent data suggest that subtle endocrine disturbances, similar to those found in PCOS, may be uncovered in up to a third of women with PCOM [10].

Information on the outcomes of intracytoplasmic sperm injection (ICSI) in women with PCOM and PCOS is limited, compared with that for women with normal ovarian morphology. The aim of this study was to examine the clinical outcomes of ICSI treatment in these three patient groups.

2. Patients and Methods

This was a prospective, observational, case-control study conducted at the Maternity Teaching Hospital Fertility Centre, Erbil, Kurdistan Province, Iraq, over a 12-month period from April 1st 2012 to April 1st 2013.All ICSI cycles were performed at the Maternity Hospital, which was established in April 2010 and provides the main referral center for infertility in Erbil. All patients were undergoing their first ICSI cycle. A total of 488 women agreed to be enrolled in the study, 190 of whom met the Rotterdam Criteria (2003) for PCOS,and 50 who had PCOM with regular documented ovulation and no evidence of clinical or laboratory hyperandrogenism. The control group consisted of 248 women with normal ovaries who had other causes of infertility requiring assisted reproduction treatment (ART). The standard infertility investigations in our center included female medical history, clinical examination, gynecological ultrasound, and day 2–3 blood analysis for follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone, prolactin, thyroid-stimulating hormone and AMH. Serum samples were stored frozen for future analysis. AMH was measured by ultrasensitive enzyme-linked immunosorbent assay (AMH Gen II ELISA, Beckman-Coulter, Inc., CA, USA). The lowest detection limit and intra-assay and inter-assay coefficients of variation were 0.03 ng/mL, 3.4%, and 7.7%, respectively. AMH was measured in ng/mL (1 ng/mL = 7.14 pmol/L). Ovarian ultrasound scanning was performed to evaluate the numbers and sizes of antral follicles. Antral follicle counts (AFC) involved counting the resting follicles in both ovaries at the beginning of the proliferative phase of the menstrual cycle by TVS.

The diagnosis of PCOS was made on the basis of the presence of any two of the following: polycystic ovaries, oligo- or anovulation, and clinical or biochemical evidence of hyperandrogenism [11]. Polycystic ovaries were characterized by the presence of 12 or more follicles in each ovary, each measuring 2–9 mm in diameter, and/or increased ovarian volume (10 mL) at transvaginal ultrasonography [12].All scans were performed by a single operator using a GE p3 (LOGIG P3, GE Healthcare, made in USA) equipped with a 6.5 MHz endovaginal probe (probe destination 8CS/E8C).

The patients in all three groups had various causes of infertility necessitating ICSI using freshly-ejaculated spermatozoa, defined as total ejaculate sperm count of 3 million and/or 2% normal morphology of sperms by Tygerberg strict criteria. Ovarian response was monitored by frequent serum E2 measurements and TVS [13].A flexible antagonist protocol was started from day 2 or 3 of the subsequent cycle with a gonadotropin (recombinant FSH (rFSH); Gonal-F ;Serono Laboratories, Aubonne, Switzerland). Gonadotropin treatment was initiated if the follicular diameters did not exceed 10 mm and theE2 level was ≤ 50 pg/mL. Patients received a starting dose of 150–300 IU of subcutaneous rFSH daily, based on age, body mass index (BMI), basal FSH, and the numbers of basal antral follicles seen on ovarian TVS.A gonadotropin-releasing hormone (GnRH) antagonist (cetrorelix acetate; Cetrotide; Merck-Serono, Switzerland) was injected at 0.25 mg subcutaneously when the lead follicle reached a diameter of 14 mm and/or the E2 levels were >400 pg/mL. Treatment with rFSH and the GnRH antagonist was continued until the day of final oocyte maturation trigger when three or more follicles ≥18 mm were seen. The final oocyte maturation trigger was given with human chorionic gonadotropin (hCG) (Choriomon; IBSA-Institut Biochimique SA, Switzerland)(1 vial of lyophilized substance 5000 IU and 1 ampoule of solvent) when three or more follicles >17–18 mm in diameter were detected, and TVS-guided oocyte retrieval was scheduled 34–36 h later .Oocyte assessment was performed using the standard morphological criteria proposed by Lin et al (14), and nuclear maturity assessment was performed in all cases subjected to ICSI.

ICSI was performed in all cases because the center's policy was to aim to maximize the fertilization rate. This policy thus ensured uniformity of fertilization and oocyte examination techniques across the groups. Embryo transfer (ET) was performed on day 2 or 3 after oocyte retrieval. The following regimens were used for luteal support: Luteal phase support was started the day after ovum pick up by administration of progesterone pessaries Cyclogest (Actavis, UK), 400 mg daily with 10 mg oral dydrogesterone (Duphaston; Solvay Pharma Istanbul) three times a day. . Pregnancy was assessed by serum hCG assay 15 days after ET and confirmed when a gestational sac was visualized by TVS after a further 2 weeks

A serum hCG level >20 IU/L was defined as a pregnancy, and a transient increase in hCG was defined as a biochemical pregnancy. In all pregnancies, an ultrasound scan was performed 5–7 weeks after ET. Clinical pregnancy was defined by ultrasound visualization of an intrauterine gestational sac, and embryonic pole with heart beat. All pregnant women were asked to report in writing on their pregnancy and live-birth outcomes; those who failed to do so were contacted by phone. Fertilization was defined as the presence of two pro-nuclei 16–18 h post-insemination/injection. Embryos were graded on day 3 according to a 1–4 scoring system (with 1 being the best), based on fragmentation, cell symmetry, and blastomere number. Only embryos with even blastomeres and no fragmentation (grade 1, G1) were included[15]. ET was performed on day 2/3 following oocyte retrieval. Serum E2, LH and progesterone levels were measured on the day of hCG administration and compared among the three groups. Biochemical pregnancies and cases with TVS confirmation of pregnancy were included in the calculations of pregnancy and implantation rates.

This study was approved by the Research Ethics Committee of Hawler Medical University, College of Medicine. Informed consent was obtained from all participants after they had been fully informed about the study's aims, processes and confidentiality.

3. Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 19). Differences in mean values were compared between two groups using Student's t-tests. Means of three or more groups were compared by one way analysis of variance (ANOVA). A post hoc test (least significant difference) performed after ANOVA was used to determine if the differences between each two groups were significant. $\chi 2$ tests were used to compare proportions. Fisher's exact test was used if the expected count in>20% of the table cells was <5. Multiple regression analysis was used if the dependent variable was numerical. A P value of ≤ 0.05 was considered statistically significant.

4. Results

A total of 488 women met the inclusion criteria and participated in the study, including 190 PCOS, 50 PCOM and 248 control women. The patient characteristics are shown in Table 1. Women with PCOS and PCOM were younger than those with normal ovaries (control) (P< 0.001) and patients with PCOS had significantly higher BMIs than the control group (P=0.03) AMH and total testosterone were significantly higher in the PCOS and PCOM groups than in the control group (P<0.001 and P =0.001, respectively).

Despite a significantly lower total gonadotropin dose, serum E2 levels were significantly higher in both the PCOS and PCOM groups compared with the control group on the day of hCG administration (Table 2). Significantly more oocyte-cumulus complexes and metaphase II (MII) oocyte were retrieved in the PCOS and PCOM groups compared with the control group (P< 0.001) (Table 2). The PCOS and PCOM groups also had significantly more embryos and more high-quality embryos (G1) compared with the control group (P< 0.001), but these parameters were comparable in the PCOS and PCOM groups. The implantation rates were comparable among the three groups(Table 2).

As shown in Table 3, pregnancy rate, clinical pregnancy and live birth rate per cycle were significantly higher in the PCOM group compared with the PCOS and control groups (P = 0.002,0.019 and 0.007, respectively). The twin pregnancy per live birth and miscarriage rates per pregnancy were also higher in the PCOM group compared with the other groups, but the differences were not significant (P =0.40 and 0.24, respectively). The clinical pregnancy rates per cycle were significantly higher in both the PCOS (34%) and PCOM (42%) groups compared with the control group (25%) (P=0.24)(Table 3).

The age was significantly lower in women with live birth positive compared with women without live births in the control and PCOS groups. Among the control group, FSH levels were significantly lower in the live birth positive group (P<0.006). Furthermore, the numbers of oocytes, MII oocytes, number of embryos, and G1 embryos were also significantly higher in women with live birth positive in the control group. Live birth was associated with significantly higher fertilization rates in the PCOS and control groups (P<0.001), and with significantly more eggs and embryos and a higher fertilization rate in the PCOS group. Live birth positive group were associated with a significantly higher implantation rate in the PCOM group with (P= 0.05) (Table 4).

Increasing age was significant negative predictor of live birth while AMH value between 2.2-3.9 was a positive predictor of live birth as shown in (Table 5.)

Table 1: Clinical, hormonal and ultrasonographic characteristics in patients with polycystic ovary syndrome, isolated polycystic ovarian morphology, and normal ovaries

Parameter	A	B	C	*P* value
	N=190	N=50	N=248	
Age	30.99±5.19 [c]	31.08±5.53 [c]	34.77±5.85 [a,b]	<0.001
AMH	3.89±2.45 [c]	3.57±2.18 [c]	1.47±1.14 [a,b]	<0.001
AFC	22.68±8.62 [c,b]	26.28±2.78 [a,c]	6.77±3.33 [a,b]	<0.001
LH	7.44±4.57 [c]	7.74±5.01 [c]	5.32±2.98 [a,b]	<0.001
FSH	5.4±1.93 [c]	6.06±2.55	6.62±2.95 [a]	0.001
LH/FSH ratio	1.45±.94 [c]	1.53±1.42 [c]	0.89±.57 [a, b]	<0.001
Total testosterone	0.65±.39 [c,b]	0.23±.14 [a]	0.32±.26 [a]	0.001
Waist	94.2±12.60 [c]	91.6±11.60	90.91±12.08 [a]	0.018
Waist/hip ratio	0.89±.083 [c,b]	0.86±.057 [a]	0.86±.075 [a]	0.004
BMI	30.80±5.58 [c]	29.48±4.32	29.45±5.45 [a]	0.028

values are expressed as mean ± standard deviation (SD).PCOS polycystic ovary syndrome, PCOM isolated polycystic ovarian morphology, BMI body mass index, AFC antral follicular count ,AMH antimüllerian hormone ,LH Luteinizing hormone, FSH follicle stimulating hormone,S significant statistically<0.001 or <0.05,NS not significant. aSignificance of difference between PCOS and contro or PCOMl groups, bSignificance of difference between PCOM and PCOS or control groups, cSignificance of difference between control group and PCOS or PCOM groups.

Table 2: Embryological data and pregnancy outcomes in patients with polycystic ovary syndrome, isolated polycystic ovarian morphology, and normal ovaries

Parameters	A	B	C	P value
	N=190	N=50	N=248	
Total dose of gonadotropin	25.61±9.01 [c]	25.86±9.02 [c]	33.34±9.75 [a,b]	0.001
E2 at day of hCG	2082±1219 [c,b]	1714.6±1020 [a,c]	1256±822 [a,b]	0.001
Number of retrieved oocyte	10.69±6.30 [c]	10.16±4.38 [c]	6.50±4.31 [a,b]	0.001
MII (best-quality oocytes)	8.48±5.15 [c]	8.46±3.80 [c]	5.29±3.50 [a,b]	0.001
Number of embryos	6.24±4.28 [c]	5.94±3.50 [c]	3.82±3.04 [a,b]	<0.001
G1 (best-quality embryo)	3.6±2.7 [c]	3.1±1.8 [c]	2.3±1.6 [a,b]	<0.001
Fertilization rate (%)	75(0.75±0.25)	70 (0.68±0.24)	73(0.71±0.30)	0.259
Implantation rate (%)	15.6(0.42±0.1)	17.5(0.37±0.1)	13.3(0.46±0.2)	0.247

Values are expressed as mean ± SD.NS not significant ,PCOS polycystic ovary syndrome(A), PCOM isolated polycystic ovarian morphology(B) and control group (C), E2 estradiol, hCG human chorionic gonadotropin.a Significance of difference between PCOS and control or PCOM groups, b significance of difference between PCOM and PCOS or control groups, cSignificance of difference between control and PCOS or PCOMl groups

Table 3: Pregnancy rate, clinical pregnancy and live birth rate per cycle in the three groups

Parameter	PCOS n = 190 (%)	PCOM n = 50 (%)	Control n =248 (%)	*P* value
Pregnancy/cycle	74 (38)	28 (56)	76 (30)	0.002
Clinical pregnancy/cycle	65 (34.2)	21 (42)	62 (25)	0.019
Live birth/cycle	54 (28)	18 (36)	46 (18.5)	0.007
Pregnancy/ET	74 (42.8)	28 (57.1)	76 (34.1)	0.007
Clinical pregnancy/ET	65 (37.6)	21 (42.9)	62 (27.8)	0.039
Live birth/ET	54 (31.2)	18 (36.7)	46 (20.6)	0.014
Twin/live birth	11 (20.4)	5 (27.8)	6 (13)	0.4
Miscarriage/pregnancy	11 (14.9)	4 (14.3)	19 (25)	0.24

PCOS polycystic ovary syndrome, PCOM isolated polycystic ovarian morphology, ET embryo transfer

Table 4: Relationships between live birth and variables in patients with polycystic ovary syndrome, isolated polycystic ovarian morphology, and normal ovaries

Variable	PCOS		*P* value	PCOM		*P* value			*P* value
	Live birth			Live birth					
	No (*n* = 136)	Yes (*n* = 54)		No (*n* = 32)	Yes (*n* = 18)		No (*n* = 202)	Yes (*n* = 46)	
Age	31.43 ± 3.45	29.91±4.306	0.02	31.25±5.36	30.78±5.97	0.77	35.27±5.94	32.27±4.93	0.002
BMI	31.17±5.62	29.85±5.41	0.14	28.5±4.22	31.06±4.14	0.52	29.3±5.61	29.7±4.71	0.65
Waist	94.5±12.2	93.4±13.6	0.61	80.9±11.5	94.7±11.4	0.16	90.5±12.3	92.3±11.03	0.37
Waist/hip	0.89±.08	0.88±.08	0.26	.85±.06	0.88±.04	0.08	0.86±0.07	0.87±0.06	0.82
AFC	22.7±8.6	22.6±8.6	0.97	26.28±2.5	26.28±3.3	0.99	6.63±3.30	7.37±3.43	0.17
AMH	3.9±2.57	3.7±2.13	0.66	3.64±2.16	3.45±2.26	0.77	1.42±1.13	1.70±1.19	0.13
LH/FSH	1.50±.99	1.33±.82	0.24	1.74±1.58	1.15±1.04	0.16	0.89±0.59	0.92±0.47	0.67
LH	7.8±4.73	6.5±4.00	0.07	8.20±4.88	6.90±5.28	0.38	3.35±2.83	5.18±2.82	0.7
FSH	5.50±1.94	5.17±1.89	0.89	5.4±2.8	6.2±1.8	0.13	6.81±3.10	5.81±2.03	0.006
Testosterone	0.65±.39	0.63±.38	0.72	0.24±.151	0.21±.127	0.5	0.31±0.260	0.33±0.261	0.69
Total dose of gonadotropin	25.9±9.3	24.6±8.11	0.34	24.3±9.25	28±8.16	0.11	33.35±10.08	31.11±7.88	0.47
E2 at day hCG	2120±1274	1986±1071	0.49	1700±886	1738±1253	0.99	1253±858.3	1271±647.3	0.89
Number of eggs	10.03±6.02	12.33±6.72	0.03	9.7±4.38	10±4.42	0.42	6.14±4.35	8.04±3.79	0.004
MII oocytes	8.09±4.82	9.43±5.80	0.1	8.3±3.94	8.7±3.64	0.71	4.92±2.92	6.80±3.50	0.002
Number of embryos	5.66±3.97	7.67±4.71	0.01	5.56±3.3	6.61±3.7	0.31	3.46±2.92	5.39±3.05	<0.001
G1 embryos	3.45±2.65	3.94±2.88	0.27	2.81±1.59	3.72±2.19	0.11	2.19±1.73	2.73±1.38	0.033
Fertilization rate	0.72±.28	81% 0.82±.14	0	0.65±.25	75%0.73±.20	0.3	0.69±0.32	79%0.81±0.19	0.001
Implantation rate	0.41±.193	39%0.43±.19	0.08	0.20±.144	39%0.41±.181	0.05	0.38±.19	43%0.49±.25	0.117

Table 5: Logistic regression analysis of predictors of live birth in all in vitro fertilization/intracytoplasmic sperm injection cycles

Variable	B	*P*value	OR	95% CI	
				Lower	Upper
PCO groups		0.247			
PCOS	0.6	0.159	1.821	0.791	4.192
PCOM	0.916	0.097	2.499	0.846	7.377
normal (reference)			1		
AMH (ng/ml)		0.013			
< 2.2 (reference)			1		
2.2–3.9	0.573	0.033	1.773	1.047	3.002
≥ 4	-0.283	0.406	0.754	0.387	1.469
PCO ovary	-0.426	0.559	0.653	0.156	2.727
Age	-0.06	0.004	0.942	0.904	0.981
AFC	0.013	0.679	1.013	0.951	1.08
Constant	0.331	0.678	1.392		

Results are presented as odds ratios (95% confidence intervals) per year. AP value ≤ 0.05 was significant.OR odds ratio, CI confidence interval, PCO polycystic ovary, PCOS polycystic ovary syndrome, PCOMisolated polycystic ovarian morphology, AMHantimüllerian hormone,AFCantral follicular count..constant it is the point where the regression line intersect with the y axis

B is stand for each unit increase in AMH, there will be 0.57 unit increase in live birth and for each unit decrease in age there will be 0.060 increase in live birth

5. Discussion

The results of this study demonstrated that patients with PCOS or isolated PCOM had more favorable ICSI outcomes than patients without these conditions. Both PCOS and PCOM patients had more oocyte retrieved, more fertilized oocyte, and more G1 embryos transferred, resulting in a significantly higher clinical pregnancy rate per transfer compared with controls.

In accordance with previous studies, serum E2 levels were higher in the PCOS and PCOM groups compared with the control group, despite significantly lower FSH consumptions. MII oocyte quality, in terms of fertilization and embryo development, was not impaired following ICSI in either the PCOS or PCOM group. The fertilization rates were comparable among the three groups. Because significantly more oocytes were retrieved in the PCOS and PCOM groups, significantly more 2-pronucleated oocytes were subsequently available. The greater availability of embryos meant that significantly more G1 embryos were transferred in the PCOS and PCOM groups, resulting insignificantly higher clinical pregnancy rates in these groups. However, implantation rates were comparable among the three groups. We therefore conclude that PCOS and PCOM are favorable prognostic findings during counseling for ART.

PCOM is not uncommon and has been reported in 23% of 257 “normal” volunteers [14]. However, there is currently little information on the efficacy of ART in patients with ovulatory PCOM. Engmann et al. [15] compared the outcomes of a course of up to three cycles of IVF treatment in 46 women (97 cycles) with PCO but no clinical PCOS symptomatology, with the outcomes in 145 women (332 cycles) with normal ovarian morphology on ultrasound examination. On average, women with PCO produced more follicles, oocytes, and embryos than women with normal ovaries, but the fertilization, cleavage, and miscarriage rates were similar. The authors concluded that the outcomes of IVF treatment in women with PCO seen on ultrasound examination may be better than those in women with normal ovaries. In accordance with those findings, the presence of PCO was a favorable prognostic sign in the present study, associated with a significantly higher clinical pregnancy rate per ET compared with the controls The multiple pregnancy

rates per live birth in PCOS,PCOM and control were 20.4%, 27.8%, and 13%, respectively. The incidence of multiple pregnancies was two-fold higher in a similar study by Esinler et al.(16), but the difference was not significant.The miscarriage rates were similar in the PCOS and PCOM groups, in accordance with the results of Engmann et al. (15).

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The retrieval of more oocytes and higher fertilization rates in patients with PCOS and PCOM allowed greater embryo selection, and subsequently higher pregnancy rates. In our study the clinical pregnancy and live birth rates were significantly higher in the PCOS and PCOM groups compared with women with normal ovaries. These data are consistent with the findings reported by Engmann et al., who compared IVF outcomes (up to three cycles) in 46 women with sonographic evidence of PCO but no clinical symptomatology associated with PCOS, with 145 women with normal ovaries [15].

Women with PCO required fewer ampules of gonadotropin for ovarian stimulation and produced more follicles and viable oocytes than women with normal ovaries[16].The reason why women with isolated PCOM with coexisting causes of infertility probably perform better than women with normal ovaries during IVF treatment may be because they produce more oocytes of comparable quality; thus even though they have similar fertilization rates, the wider choice of embryos for transfer increases the chance of conception [London women's clinic, pers comm]. Although the numbers of eggs and embryos and the fertilization rate were significantly higher among control and PCOS women with live birth positives, the number of good quality (G1) embryos was not significantly higher among PCOS patients. Finally,in agreement with other studies, our study demonstrated that PCOS had an independent effect on pregnancy rates [17].

This study was limited by the fact that women with normal ovaries were significantly older than women with PCOS or PCOM. We conclude that patients with full-blown PCOS and isolated PCOM respond similarly at all stages of ART. However, the availability of more fertilized oocytes and G1 embryos means that patients with PCOS or PCOM have higher clinical pregnancy rates per ET compared with control patients with normal ovaries.

6. Conflict of interest

There is no conflict of interest in relation to the current article

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