Impact of the follicular fluid Coenzyme Q10 level in women undergoing intracytoplasmic sperm injection (ICSI) on the pregnancy rate

Mahmoud S Iwes[a], Mohamed Atef ELZarka[a*], Hanan M. Fayed[b], Ahmed Hashim Abdellah[a], Mohammad A.M. Ahmed[a]

[a]Obstetrics and Gynecology Department, Faculty of Medicine, South Valley University, Qena, Egypt.

[b]Clinical and Chemical Pathology Department, Faculty of Medicine, South Valley University , Qena, Egypt.

Abstract

Background: The most crucial problem with in vitro fertilization (IVF) cycles is still oocyte quality. The women age and the condition of their ovarian reserve are the primary determinants of oocyte quality.

Objectives: to assess the effects of intracytoplasmic sperm injection (ICSI) on the result of pregnancies and the coenzyme Q10 (CoQ10) value in follicular fluid (FF) in the women who had the procedure.

Patients and methods: this cohort investigation was conducted on 81 infertile patients (age between 20-42 years, both normal or poor responders' patients and patients with unexplained infertility) who underwent ICSI cycles.

Results: patients were divided into two groups: the pregnant group (n= 32) and the non-pregnant group (n= 49). There was a statistically insignificant difference in antral follicle count (AFC), number of retrieved oocytes, number of embryos, number of metaphase II (MII) oocytes, and maturation index between pregnant and non-pregnant females. CoQ10 level in FF was substantially greater in pregnant than non-pregnant females.

Conclusion: FF CoQ10 levels were positively correlated with eventual embryo quality and rates of conception. Our findings might be in favour of CoQ10 supplementation in women undergoing IVF for enhancement of the ovum and embryo quality.

Keywords: Coenzyme Q10; Follicular fluid; Embryo; Pregnancy rate; Assisted reproductive technique.

DOI: 10.21608/svuijm.2023.207121.1578

***Correspondence:** Amir.kamal@kasralainy.edu.eg

Received: 1 March, 2023.

Revised: 8 April, 2023.

Accepted: 2 May, 2023.

Published: 9 May, 2023

Cite this article as: Mahmoud S Iwes, Mohamed Atef ELZarka, Hanan Mahmoud Fayed, Ahmed Hashim Abdellah, Mohammad AM Ahmed. (2023). Impact of the follicular fluid Coenzyme Q10 level in women undergoing intracytoplasmic sperm injection (ICSI) on the pregnancy rate. *SVU-International Journal of Medical Sciences*. Vol.6, Issue 2, pp: 279-290.

Introduction

When ICSI was initially utilized on human gametes in 1988, it was done so in situations when normal IVF had failed to result in fertilization or when there weren't enough sperm cells available. In 1992, Belgium received their first reports of pregnancies. It is a procedure that occurs as part of an in vitro fertilization (IVF) cycle and involves injecting a single sperm directly into the cytoplasm of a mature egg **(Palermo et al., 1992)**.

The most crucial factor in IVF cycles is still oocyte quality, which is mostly influenced by the woman's age and ovarian reserve. The interplay of nuclear and cytoplasmic organelles, as well as dynamic alterations to the cytoskeleton that take place throughout oocyte development, all play important roles in the complicated process of oocyte maturation. The cytoplasmic organelle known as the mitochondria serves as the primary regulator of energy generation via the oxidative phosphorylation process, which is crucial for the maturation of oocytes. Any issue with oxidative phosphorylation might have an impact on the DNA content and oocyte quality **(Hüttemann et al., 2007)**.

The inner mitochondrial membrane contains the four complexes that make up the mitochondrial respiratory chain, which is important in oxidative phosphorylation **(Akarsu et al., 2017; May Panloup et al., 2007)**. These include cytochromes, flavoproteins, coenzyme Q10, and NAD-linked dehydrogenase. Ubiquinone, often known as coenzyme Q10, has structural similarities with vitamins K and E. The tricarboxylic acid's byproducts are oxidized by Complexes I and II, which then transport the electrons to CoQ10 **(Hargreaves et al., 2020)**. Electrons are transferred to complex III (cytochrome reductase) by CoQ10 **(May Panloup et al., 2007)**. The synthesis of ATP by ATP synthase as a consequence of the subsequent transfer of electrons to complex IV is essential for cell development and energy metabolism. Energy consumption is one of the key variables in oogenesis and oocyte maturation, hence CoQ10 has been shown to enhance the growth, cell proliferation, hatching, and ATP content of in vitro-created bovine embryos (**Gendelman et al., 2012**).

In women with low ovarian reserves undergoing IVF-ICSI cycles, a number of studies have suggested that pretreatment with CoQ10 may enhance ovarian response to the stimulation and embryological parameters. However, the results of these studies are conflicting, so more research is required to determine whether there is an impact on clinical endpoints. In this research, we looked at the connection between the clinical pregnancy rate (CPR) and the FF level of CoQ10 **(Gat et al., 2016; Xu et al., 2018)**.

Patients and methods

From August 2020 to December 2022, this cohort research was performed at the Assisted Reproduction Unit, Obstetrics and Gynecology Department, Qena University Hospital, South Valley University, Egypt.

Inclusion criteria: Poor responders aged 20–42 who are undergoing ICSI according to Bologna criteria and normal responders aged 20–42 based on ovarian reserve tests (Anti-millenarian hormone (AMH), 1.1–3.5 ng/ml or antral follicular count (AFC), 5–24); two or more of the next three characteristics must be existent: A prior POR (≤3 oocytes with a standard stimulation protocol), maternal age ≥40 years, any additional POR risk factor (Pelvic infection, endometrioma, and ovarian surgery), and atypical ovarian reserve test (AFC 5 follicles or AMH <1.1 ng/ml) **(Ferraretti et al., 2011)**.

Exclusion criteria: Patients with endocrine or metabolic disorders such as hyperprolactinemia, hypothyroidism, and hyperthyroidism, diabetes mellitus (DM), adrenal illness, patients with a severe male factor or Y chromosome anomaly, and patients with polycystic ovarian syndrome are examples of hyper responder patients. patients with uterine cavity pathology or abnormalities (myoma, hyperplasia, endometrial polyp, and congenital anomaly) discovered by transvaginal 3-dimensional ultrasonography as well as patients with systemic illness such as chronic renal failure, persistent liver disease, and systemic lupus disease.

Ethical considerations: The Qena Faculty of Medicine at South Valley University's regional Ethical Committee gave its approval to the research plan. Before the study began, all patients and their husbands provided written informed consent, and each patient had the right to discontinue the study at any time.

Ethical code number: SVU-MED-OBG024-SVU-2-2020-7-53.

Study tools

History taking: The length of the infertility, any prior ovarian surgery, such as a cystectomy, the male factor, and any past ICSI or IVF trials should all be considered. **Examination:** Examining the abdomen, vagina, and generally.

Investigations and Laboratory investigations: Routine laboratory investigations, serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), on day three (basal), AMH, Estradiol (E2), prolactin, and thyroid Stimulating Hormone (TSH).

Evaluation of the male factor: was done by the Andrology team in Qena university hospital. Full detailed history focused on any testicular trauma, smoking or drugs, the general and local testicular and inguinal examination done additionally routine laboratory investigation similar to female patients, and finally husband semen analysis done according to WHO 2010 criteria.

Uterine cavity examination: by transvaginal 3-dimensional ultrasound [Medison sonoacex8-3D endo-cavity transvaginal probe 6.5MHZ] was the tool of assessment of uterine cavity pathology or abnormalities (myoma, hyperplasia, endometrial polyps, and congenital abnormalities including a septate or bicornuate uterus).

Technical aspects of ICSI protocol: All patients willing to participate, and meeting the requirements for inclusion, after submitting the form for informed consent will receive combined oral contraceptive pills [Gynera, Bayer] starting cycle-day 2 (CD2) of the menstrual cycle and continue for 15 days. Patients were received agonist or antagonist protocol, patients who will receive long agonist protocol start with administration of 0.1mg/day subcutaneously GnRH agonist triptorelin acetate (Decapeptyl, Ferring) on cycle-day 21 followed by ovarian stimulation starting on CD2 and continue until the day of triggering. Ovarian stimulation with gonadotropins [150-300 IU] with recombinant FSH intramuscular [Gonapure, Minapharm] and highly pure IM menotrophin (Menopur, Ferring) will start on CD2 of the menstrual cycle. Follicular maturation was evaluated by vaginal ultrasonography (GE Logiq p5-trans vaginal endocavitary probe 4 to 11 MHZ) with triggering of ovulation when one or two follicles reached mean diameter of 18 mm or more in two ovaries by administration of 500 micrograms of recombinant HCG [Ovitrelle 250µg/.5ml, Merck, Serono, Inc] then retrieval of oocyte was done 36 hours post-triggering time. If those criteria were not achieved within 13-16 days of stimulation, the cycle was canceled for an inadequate response **(Heidar et al., 2015).**

While patients who received antagonist protocol, GnRH antagonist Cetrorelix acetate 0.25mg/day subcutaneously [Cetrotide, MERCK Serono Inc] was started when follicles reached ≥ 14 mm and continued until the triggering day **(Baruffi et al., 2007)**.

FF was collected, centrifuged, and tested for CoQ10 levels using a human CoQ10 ELISA kit (My Biosource company, San Diego, USA), which uses the competitive inhibition enzyme immunoassay approach. The kit's micro titer plate has been pre-coated with an antibody specific to CoQ10. Oocyte retrieval was completed 36 hours after triggering. It can detect between 3.12 ng/ml and 50 ng/ml.

Assessment of the endometrium done by vaginal ultrasound scan for endometrial thickness, volumes, echogenicity, and endometrial pattern (tri laminar or bi laminar pattern) ICSI were done. Fresh embryo transfer will be done if the appropriate endometrium thickness is (7-12mm). From the day after ovum retrieval until the day of HCG testing, all patients got daily IM progesterone 100 mg (Prontogest ampoules, IBSA) as luteal support. On day 14 after ET, the serum β HCG level will be evaluated and will be deemed positive if it is >5 MIU/ML **(Chen et al., 2014)**.

Follow up: by determining the serum β-HCG level 14 days after embryo transfer and the ultrasound appearance of fetal heart pulse.

Research outcome measures: Primary (main): Clinical pregnancy rates after ICSI and their associations with follicular fluid CoQ10. **Secondary:** According to the Istanbul agreement for embryo quality assessment, the rate of implantation and evaluation of embryo quality **(Balaban et al., 2011)**.

Statistical analysis

The gathered data were evaluated and coded. The Statistic Package for Social Science Version 22 (SPSS 22) program was used to do statistical analysis utilizing these numerical codes. Mean and standard deviation (mean SD) were utilized to display quantitative data, whereas numbers and percentages were used to communicate qualitative data. While comparing qualitative data, groups were compared using the Chi-square test (X2). Mann Whitney test for comparing quantitative data from two independent samples with variables that are not normally distributed, Student's "t" test for comparing quantitative data from two independent samples with a regular distribution and homogeneity of variance, and Pearson correlation for examining the connection between variables.

The best coenzyme Q cut-off points for pregnancy prediction were found using receiver operating characteristic curves (ROC).

Sensitivity = true positive/(false negative +true positive). Specificity = true negative/(false positive+ true negative). Statistics were judged significant at P0.05.

Results

In our study, 81 patients were included, and 32 cases were got pregnant where the pregnancy rate was 39.5% (**Table.1**).

Table 1. Analysis of Pregnancy outcome

Patients	**Number**	**%**
No pregnancy	49	60.5
Pregnant	32	39.5

There is no statistically substantial variation between study groups as regard age and sex (**Table. 2**). There is no statistically substantial variation between study groups as regards the infertility type or duration (**Table .3**).

Table 2. Age and BMI of the studied groups

Variables		**No pregnancy**	**Pregnant**	**t**	**P-value**	**Sig.**
		No. = 49	**No. = 32**			
Age (year)	Range	25 – 40	24 – 40	1.814•	0.075	**NS**
	Median [IQR]	34 [7]	30.5 [8.75]			
	Mean ± SD	33.408 ± 4.596	31.344 ± 5.258			
BMI	Range	20 – 32	20 – 33	-1.244•	0.218	**NS**
	Median [IQR]	28 [4.5]	29 [4.75]			
	Mean ± SD	27.857 ± 3.062	28.812 ± 3.569			

Table 3. Infertility characteristics of the studied groups

Variables		**No pregnancy**	**pregnant**	**t/x^2**	**P-value**	**Sig.**
		No. = 49	**No. = 32**			
Type of Infertility	1ry	29 (59.2%)	24 (75%)	2.141*	0.143	NS
	2ry	20 (40.8%)	8 (25%)			
Infertility Duration (years)	Range	1.5 – 6	1.5 – 5	1.595•	0.115	NS
	Median [IQR]	3 [1]	3 [2]			
	Mean ± SD	3.418 ± 1.057	3.047 ± 1.003			

There is no statistically substantial variation in AFC, number of retrieved oocytes, number of embryos, number of MII oocytes, and maturation index between study groups (**Table. 4**). Coenzyme Q level was statistically substantially greater in pregnant than non-pregnant females (**Table. 5**).

Table 4. Ovulation response of the studied groups

Variables		No pregnancy No. = 49	pregnant No. = 32	t	P-value	Sig.
AFC	Range	5 – 23	6 – 24	-1.962•	0.055	NS
	Median [IQR]	10 [6.5]	13.5 [10.75]			
	Mean ± SD	11.592 ± 4.439	13.969 ± 5.839			
Number of retrieved oocytes	Range	2 – 25	4 – 29	-1.943•	0.056	NS
	Median [IQR]	8 [8]	11 [6]			
	Mean ± SD	9.429 ± 5.766	12.094 ± 6.203			
Number of MII oocytes	Range	1 – 20	2 – 28	-1.881•	0.076	NS
	Median [IQR]	5 [4.5]	7.5 [5.75]			
	Mean ± SD	6.429 ± 4.601	8.562 ± 5.541			
Number of embryos	Range	1 – 17	1 – 26	-1.950•	0.057	NS
	Median [IQR]	3 [3]	4 [5]			
	Mean ± SD	3.898 ± 3.331	5.750 ± 4.649			
Maturation index	Range	0.25 – 1	0.25 – 1	-0.835•	0.407	NS
	Median [IQR]	0.67 [0.33]	0.71 [0.32]			
	Mean ± SD	0.662 ± 0.239	0.706 ± 0.223			

Table 5. Co-enzyme Q level in the studied groups

Variables		No pregnancy No. = 49	pregnant No. = 32	T	P-value	Sig.
Coenzyme Q level (ug/ml)	Range	0.1 – 4.3	0.2 – 4.8	-3.612•	**0.001**	HS
	Median [IQR]	0.4 [0.3]	0.65 [1]			
	Mean ± SD	0.449 ± 0.593	1.394 ± 1.400			

There were no statically substantial differences between the poor responder group and normal responder groups concerning the FF level of CoQ10 (**Table. 6**). CoQ10 level was significantly higher in good quality fertilized ova than fair and poor quality fertilized ova (**Table. 7**).

Table 6. Poor responder group and normal responder group according to the level of CoQ10 in follicular fluid

Coenzyme Q level (ug/ml)	Poor responder (AMH 0.5-1) (n=16)	Normal responder (AMH 1.1-3.5) (n=65)	U	p	Sig.
Min. – Max.	0.10 – 0.90	0.10 – 4.80	303.0	0.099	**NS**
Mean ± SD.	0.36 ± 0.24	0.94 ± 1.18			
Median (IQR)	0.35 (0.15–0.50)	0.50 (0.30–0.80)			

Table 7. Coenzyme Q level concerning the quality of fertilized ova

Variables		Good quality No.=62	Fair quality No. = 55	Poor quality No. = 43	f	P-value	Sig.
Coenzyme Q level (ug/ml)	Range	0.10 – 4.80	0.10 – 2.60	0.10 – 3.80	9.449•	**<0.0001**	**HS**
	Median [IQR]	0.5 [0.5]	0.4 [0.2]	0.4 [0.3]			
	Mean ± SD	0.972 ± 1.180	0.504 ± 0.404	0.502 ± 0.761			

ROC curve showed that cutoff value of CoQ10 level is 0.45 ug/ml with sensitivity and specificity were 87.5% and 69.4% respectively (**Table.8**). There is a substantial positive connection between coenzyme Q level and good quality fertilized oocytes, number of gestational sacs and implantation rate. However, coenzyme Q level has a statistically significant negative correlation with fair and poor-quality of fertilized oocytes (**Table. 9**).

Table 8. Sensitivity, Specificity, and cutoff value of co-enzyme Q that predict pregnancy

Variables	Cutoff value	Area Under Curve	Sensitivity %	Specificity %	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
Coenzyme Q level (ug/ml)	0.45	0.855	87.5%	69.4%	0.772	0.938

Table 9. Correlation of co-enzyme Q level and clinical data of the studied patients

	N	Coenzyme Q level (ug/ml)			
		No pregnancy (n=49)	Pregnancy (n=32)	Total (n=81)	p-value
		r_s	r_s	r_s	
Age (years)	**81**	-0.007	-0.027	-0.138	0.218
BMI (kg/m)	**81**	0.108	-0.103	0.153	0.174
Infertility duration (years)	**81**	-0.172	-0.171	-0.184	0.101
Total dose of gonadotropin IU	**81**	-0.246	-0.178	-0.144	0.199
Day 3 FSH miu/ml	**81**	0.149	0.063	-0.139	0.216
Basal E2 pg/ml	**81**	0.103	-0.021	-0.188	0.093
E2 level at trigger day	**81**	0.297	0.068	0.079	0.481
Anti-millenarian hormone (AMH)	**81**	0.131	0.260	0.182	0.104
Antral follicular count (AFC)	**81**	0.040	0.263	0.158	0.16

Number of retrieved oocytes	**81**	0.105	0.307	0.086	0.445
Number of MII oocytes	**81**	0.031	0.140	0.092	0.414
Number of embryos	**81**	0.173	-0.086	-0.013	0.906
Quality of fertilized ova					
• **Good quality**	**81**	0.543	0.157	0.389	**<0.0001**
• **Fair quality**	**81**	-0.140	-0.458	0.189	**0.042**
• **Poor quality**	**81**	-0.392	-0.252	-0.263	**0.018**
Endometrium thickness	**81**	-0.046	-0.077	-0.079	0.483
No. of transferred embryos	**81**	0.047	-0.275	0.092	0.414
No. of gestational sacs	**32**	-	-0.062	0.327	**0.003**
Implantation rate	**32**	-	0.133	0.363	**0.001**

Discussion

CoQ10 supplement has long been utilized to enhance infertility outcomes connected to an increased CPR, even if the data is still of poor quality. Additionally, there is insufficient data on its impact on ART clinical results, live birth rate (LBR), miscarriage rate (MR), and other factors (**Showell et al., 2020**).

This study's primary objective was to evaluate the effect of FF CoQ10 levels on pregnancy outcomes in women having ICSI.

81 infertile individuals who underwent ICSI cycles were the subject of this research. The pregnant group (n=32) and the non-pregnant group (n=49) were separated from the other patients. Regarding age and BMI, we discovered no statistically substantial variation between study groups, this was in line with **Akarsu et al.(2017).** In sixty infertile individuals who completed ICSI cycles, the relationship between FF CoQ10 levels, embryo morphokinetics, and pregnancy rate was examined. The study reported that statistically insignificant variation between study groups as regard age and BMI. Also, our findings were consistent with **Chen et al.(2022)** who revealed that BMI was not linked to the hCG positive rate, implantation rate, CPR, ectopic pregnancy rate, early miscarriage rate, continuing pregnancy rate, or live birth rate of IVF/ICSI pregnancies.

The present study showed a statistically insignificant variation between study groups as regards the infertility type or duration. This was in line with **Akarsu et al.(2017) and Alzubaidy et al. (2021)**.

In our research, we found no statistically substantial variation between study groups as regards the duration of stimulation and endometrial thickness. In agreement with our results **Lin et al.(2017)** revealed that there was no statistically substantial variation between study groups as regards the duration of stimulation and endometrial thickness. However, this was in contrast to **Al-Ghamdi et al.(2008)** who revealed the endometrial thicknesses assessed on the day of the hCG injection have a positive linear connection with PR that is

unaffected by other factors. Also, **Kovacs et al.(2003)** reported that Pregnancy rates are greater in correlation with increasing endometrial thickness. The disagreement with our results may be due to the differences in study settings.

In the present study, the ovulation response of the studied groups showed that statistically insignificant variation in AFC, number of embryos, number of retrieved oocytes, number of MII oocytes, and maturation index between study groups. This outcome was in agreement with **Akarsu et al.(2017).** who revealed that there was no statistically substantial variation between study groups as regards the number of MII oocytes, number of retrieved oocytes, and number of embryos. Also, the present study was in agreement with **Alzubaidy et al.(2021)** who reported a statistically insignificant variation between study groups as regards AFC. As well, **Al-Zaiyadi et al.(2019)** reported that No. of follicles and No. of retrieved oocytes have an insignificant effect on pregnancy results in women who underwent ICSI however No. of embryos transferred was substantially correlated with the outcome. Similarly, in agreement, **Lin et al.(2017)** reported a statistically insignificant variation between study groups as regards retrieved oocytes, number of MII oocytes, and number of embryos.

Our study reported that the CoQ10 level was substantially greater in pregnant than non-pregnant females. In agreement with the present study **Alzubaidy et al.(2021)** reported that Pregnant women had substantially greater levels of FF CoQ10 than non-pregnant women ($p < 0.05$). Furthermore, in agreement, **Mohammed et al. (2021)** assessed the relationship between CoQ10 value in the FF with oocyte maturity, embryo grading, fertilization rate, and pregnancy rate in 60 infertile women. CoQ10 total in pregnant was 0.79 ± 0.63 and in non-pregnant was 0.381 ± 0.2. The study concluded that the CoQ10 total was enhanced in pregnant women than in non-pregnant.

An accurate assessment of ova quality and selection of ova with top quality and developing potential for ICSI is thus of utmost relevance in ART as the enhancement of the ova quality may boost the rate of implantation and conception rate of ICSI-fertilized embryos (**Neri et al., 2008**). In agreement with our results **Lin et al.(2017)** revealed a substantial connection between pregnancy incidence and ova quality.

The current study found that the CoQ10 level was substantially greater in good-quality fertilized ova than in fair and poor-quality fertilized ova. This was in line with **Akarsu et al.(2017**)who revealed a link between the CoQ10 levels in follicular fluid and subsequently embryo quality. To test the diagnostic value of CoQ10 to predict pregnancy, the ROC curve was constructed, we found that at a cutoff of (0.45 ug/ml), the Sensitivity and Specificity were 87.5% and 69.4% respectively, with an AUC of 0.855. However, the study by **Akarsu et al.(2017)** revealed that the accuracy of CoQ10 in predicting pregnancy was 0.677 (95%

confidence interval: 0.53-0.81, p = 0.022). A CoQ10 cutoff value of 0.255 ug/ml showed a 53.8% specificity and a 68.8% sensitivity. Also, **Mohammed et al.(2021)** reported that The CoQ10 ROC curve for pregnancy prediction revealed that at a cutoff of 0.27, CoQ10 had an accuracy of 74%, a PPV of 88.0%, NPV of 45%, a specificity of 67.0%, and a sensitivity of 80.0%.

Conclusion

Follicular fluid CoQ10 levels were positively correlated with eventual embryo quality and rates of conception. Our findings might be in favor of CoQ10 supplementation in women undergoing IVF for enhancement of the ovum and embryo quality.

References

- **Akarsu S, Gode F, Isik AZ, Dikmen ZG, Tekindal MA. (2017).** The association between coenzyme Q10 concentrations in follicular fluid with embryo morphokinetics and pregnancy rate in assisted reproductive techniques. Journal of Assisted Reproduction and Genetics, 2017; 34:599-605.
- **Al-Ghamdi A, Coskun S, Al-Hassan S, Al-Rejjal R, Awartani K. (2008).** The correlation between endometrial thickness and outcome of in vitro fertilization and embryo transfer (IVF-ET) outcome. Reproductive Biology and Endocrinology, 2008; 6:1-5.
- **Al-Zaiyadi SM, Salih AM, Sabr IA, Al-Murshidi SY, Roomi AB, Dheyaa AM, Al-koofee MK. (2019).** Impact of fertilization rate on ICSI outcome and pregnancy rate for unexplained subfertile couples. Indian Journal of Public Health, 2019; 10(11):1897.
- **Alzubaidy HA, Alizzi FJ, Mossa HA. (2021).** The Correlation between Follicular Fluid Levels of Progesterone and Anti-Müllerian Hormone and Pregnancy Rate in ICSI-Cycle. 2021, 44(6):2551-2556.
- **Balaban B, Brison D, Calderon G, Catt J, Conaghan J, Cowan L, Ebner T, Gardner D, Hardarson T, Lundin K, Magli MC. (2011).** Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. Reproductive BioMedicine Online, 2011;22(6):632-46.
- **Baruffi RL, Mauri AL, Petersen CG, Felipe V, Martins AM, Cornicelli J, Cavagna M, Oliveira JB, Franco Jr JG. (2007).** Recombinant LH supplementation to recombinant FSH during induced ovarian stimulation in the GnRH-antagonist protocol: a meta-analysis. Reproductive biomedicine online, 2007 Jan 1;14(1):14-25.
- **Chen Y, Zhang Y, Hu M, Liu X, Qi H. (2014).** Timing of human chorionic gonadotropin (hCG) hormone administration in IVF/ICSI protocols using GnRH agonist or antagonists: a systematic review and meta-analysis. Gynecological Endocrinology, 2014 Jun 1;30(6):431-7.
- **Chen H, Li J, Cai S, Zeng S, Yin C, Kuang W, Cheng K, Jiang Y, Tao M, Chu C, Hocher JG. (2022).** Impact of body mass index (BMI) on the success rate of fresh

embryo transfer in women undergoing first in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment. International Journal of Obesity, 2022; 46(1):202-10.

- **Ferraretti A, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L. (2011).** ESHRE working group on Poor Ovarian Response Definition. ESHRE consensus on the definition of 'poor response to ovarian stimulation for in vitro fertilization: the Bologna criteria. Human reproduction, 2011; 26(7):1616-24.
- **Gat I, Blanco Mejia S, Balakier H, Librach CL, Claessens A, Ryan EA. (2016).** The use of coenzyme Q10 and DHEA during IUI and IVF cycles in patients with decreased ovarian reserve. Gynecological Endocrinology, 2016 Jul 2;32(7):534-7.
- **Gendelman M, Roth Z. (2012).** Incorporation of coenzyme Q10 into bovine oocytes improves mitochondrial features and alleviates the effects of summer thermal stress on developmental competence. Biology of reproduction, 2012; 87(5):118-.
- **Hargreaves I, Heaton RA, Mantle D. (2020).** Disorders of human coenzyme Q10 metabolism: an overview. International journal of molecular sciences, 2020; 21(18):6695.
- **Heidar Z, Bakhtiyari M, Mirzamoradi M, Zadehmodarres S, Sarfjoo FS, Mansournia MA. (2015).** Prediction of different ovarian responses using anti-Müllerian hormone following a long agonist treatment protocol for IVF. Journal of endocrinological investigation, 2015 Sep;38:1007-15.
- **Hüttemann M, Lee I, Samavati L, Yu H, Doan JW. (2007).** Regulation of mitochondrial oxidative phosphorylation through cell signaling. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 2007 Dec 1;1773(12):1701-20.
- **Kovacs P, Matyas SZ, Boda K, Kaali SG. (2003).** The effect of endometrial thickness on IVF/ICSI outcome. Human Reproduction, 2003; 18(11):2337-41.
- **Lin D, Ran J, Zhu S, Quan S, Ye B, Yu A, Kang Y, Lin Y. (2017).** Effect of GOLPH3 on cumulus granulosa cell apoptosis and ICSI pregnancy outcomes. Scientific Reports, 2017; 7(1):7863.
- **May Panloup P, Chretien MF, Malthiery Y, Reynier P. (2007).** Mitochondrial DNA in the oocyte and the developing embryo. Current topics in developmental biology, 2007; 77:51-83.
- **Mohammed AA, Al-Khafajy ZH, Abdullhameed AP. (2021).** Coenzyme Q10 in the Follicular Fluid and Its Relation to Oocyte Maturity, Fertilization Rate, Embryo Grading, and Pregnancy Rate. Indian Journal of Forensic Medicine & Toxicology, 2021; 15(1):753-60.
- **Neri QV, Takeuchi T, Palermo GD. (2008).** An update of assisted reproductive technologies results in the United States.

Annals of the New York Academy of Sciences, 2008; 1127(1):41-8.

- **Palermo G, Joris H, Devroey P, Van Steirteghem AC. (1992).** Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. The Lancet, 1992; 340(8810):17-8.
- **Showell MG, Mackenzie-Proctor R, Jordan V, Hart RJ. (2020).** Antioxidants for female subfertility. Cochrane Database of Systematic Reviews, 2020(8).
- **Xu Y, Nisenblat V, Lu C, Li R, Qiao J, Zhen X, Wang S. (2018).** Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reproductive Biology and Endocrinology, 2018 Dec;16(1):1-1.