



Life Style Exercise Modification Effect in Infertility Women with PCOS Diseases

KEYWORDS

Exercise-PCOS, infertility women, reproductive hormones

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ABSTRACT Reproductive failures in women with Polycystic ovary syndrome (PCOS) are common due to endocrinal disorders. The clinical expression of PCOS varies. They are oligo-ovulation, anovulation, and hyperandrogenism with polycystic ovaries. The conventional medicines (eg: Metformin) are usually not recommendable for routine use for improvement in reproductive health due to side effect. Low cost and first line treatment of lifestyle management, physical exercise with or without diet or hypo-diet are recommended in current treatment. To explore low cost treatment, lifestyle modification, for improvement of reproductive hormones, here we reviewed by a study of meta-analysis, before and after hormones level changes by lifestyle modification with exercise, in infertile PCOS women from reported scientific articles.

Introduction

Polycystic Ovarian Syndrome (PCOS) is common condition in women that destructs hormones and causes physical and psychological damage. PCOS is a complex hormonal disturbance that affects entire body and has numerous implications in general health. Women with this syndrome have an increased risk of coronary disease, diabetes and endometrial cancer in any time of the life period. However, the hormonal imbalance appears in the reproductive age group and it leads to infertility. Exploring affordable PCOS treatments in infertile population for hormone balance also improves the conceive rate. There are several medical treatment options for the numerous diverse abnormalities common in PCOS, with some of those (eg: Metformin) capable of ameliorating more than one abnormality. Drugs like oral contraceptive pill and clomiphene citrate (CC) are well known drugs to treat PCOS, targeting the metabolic activity. Aromatase inhibitors, statins, and anti-inflammatory drugs show some promise as potential treatment options, but much more clinical research is needed in order to demonstrate efficacy and benefit over cost.

Hormonal balance response to physical activity, environmental, nutritional, social and psychological factors. One of the cause of hormonal imbalance in obesity can effect ovulation; pregnancy rate which leads to infertility and PCOS. Here we have chosen the key reproductive hormones and their functions in the reproductive system of humans.

Stein and Leventhal described syndrome has pathognomonic ovarian findings and the clinical triad of hirsutism, amenorrhea, and obesity. The reported prevalence of PCOS ranges between 2.2% to 26% in various countries. It has been suggested that this condition occurs in as many as 4-10 % women of reproductive age, with onset manifesting as early as puberty [1].

Primarily, PCOS is characterized by hyperandrogenism, insulin resistance, and chronic anovulation. Today, patient usually presents clinically with concerns regarding menstrual irregularities, infertility, and hirsutism. The syndrome is also associated with dyslipidemia and acanthosis nigricans, and may increase the risk for cardiovascular disease and hyperestrogen-related cancers such as endometrial and breast cancers.

Conversely, PCOS and its clinical features are more common in women who are overweight and obese compared to those of normal weight [2, 3].

Even though, there is differential expression of PCOS by considerable ethnic variation, including the prevalence and severity of obesity, metabolic disturbances, and their correlates. There are differences in psychosocial aspects affecting QOL and health-seeking behaviors. As many as one in six couples encounter problems with fertility, defined as failure to achieve a clinical pregnancy after regular intercourse for 12 months [4, 5].

Generally in society, an obese woman compared to normal weight women is lower in natural cycles and infertility treatment cycles. Guzik et al., 1994 reported that young, middle aged and elderly women benefit from the hard or stress exercise training programme and study showed that with the aerobic exercise of 3 to 6 months with diet control had a beneficial effect of weight loss and it has the improvement in reproductive system [6]. Further, Clark et al. (1995) reported that reduction of a low weight loss in anovulatory infertile women like obesity, achieved in a group setting over a six month period and improvement in ovulation, pregnancy rate and pregnancy outcome and endocrine parameters. These studies also showed that a BMI ≥ 27 is associated with an increased risk of ovulatory infertility [7].

Although, Clinical studies have showed major role of insulin resistance in development of hyperinsulinemia further effects in the pathophysiologic mechanism of PCOS to its concurrent metabolic derangements [8]. It shows that insulin resistance control is very important in PCOS patient's management.

In general, there is difficult in obesity people maintenances in selection of specific food as specified calories in routine food habit and another point is other physical methods like walking and stress exercise showed some good results in improvement. Hence, programmed diet also plays very important role for the lifestyle management for infertility PCOS patients, the high protein diet (35% protein, 45% carbohydrate and 20% fat along with tab multivitamin/mineral supplement and minimum a 800 KCal deficit per day) [9].

However, 5%–10% of body weight loss can improve nearly all abnormal reproductive, metabolic, hormonal, lipid profile, and psychological parameters in women with PCOS [10,11,12,13,14,15,16,17,18,19,20]. However, it is understood that the diet alone cannot change or improve in short duration for above factors effectively. So, researchers might have believed on the physical activity for PCOS women, specifically reproductive hormones balance.

Huber-Buchholz et al., 1999 [21] reported that after insulin level improvement by exercise in obese women with PCOS, the normal menstrual function have restored and fertility increased. The other thing is by using a lifestyle program that sets realistic weight loss and exercise goals, subjects were able to sustain an improvement in carbohydrate metabolism over a 6-month period and hence improve their likelihood of pregnancy. Although weight loss as a percentage of body weight was small, a 70% improvement in insulin sensitivity index was obtained, and this change was associated with the return of reproductive function.

Palomba et al., 2008 [9] hypothesized that after clinical study, insulin sensitivity improvement itself is the central factor involved in the restoration of ovarian function in PCOS. Exercise training improves autonomic function and inflammatory pattern also in PCOS women [22].

Women with PCOS may be sub-fertile. This may be explained by the effects of obesity and/or metabolic, inflammatory, and endocrine abnormalities on ovulatory function, oocyte quality, and endometrial receptivity. Ovarian hyperandrogenism and hyperinsulinemia may promote premature granulosa cell luteinization, and paracrine dysregulation of growth factors may disrupt the intrafollicular

environment and impair cytoplasmic and/or nuclear maturation of oocytes. These features are not universal, and oocyte quality, fertilization, and implantation rates in an individual woman with PCOS can be normal [23].

Currently, PCOS, recognized as the leading cause of anovulatory infertility, it is the most common endocrinopathy in reproductive-aged women [24,25,26,27].

In meta-analysis of Boomsma et al., 2006 [28] report, pregnancy outcomes were reported in women with PCOS were compared with controls, 15 studies were included, involving 720 women presenting with PCOS and 4,505 controls. Women with PCOS demonstrated a statistically significantly higher risk of developing gestational diabetes mellitus (GDM) (odds ratio (OR) 2.94; 95% confidence interval [CI], 1.70–5.08), pregnancy-induced hypertension (OR 3.67; 95% CI, 1.98–6.81), preeclampsia (OR 3.47; 95% CI, 1.95–6.17), and preterm birth (OR 1.75; 95% CI, 1.16–2.62). Their babies had a statistically significantly higher risk of admission to a neonatal intensive care unit (OR 2.31; 95% CI, 1.25–4.26) and a higher perinatal mortality (OR 3.07; 95% CI, 1.03–9.21), unrelated to multiple births [28]. Although, in pregnancy women with PCOS, there is a higher incidence of gestational diabetes (GDM) (40% to 50%) and associated fetal macrosomia, gestational hypertensive disorders (5%), and birth of small-for-gestational-age (SGA) babies (10% to 15%). The use of metformin for women with anovulatory PCOS has no benefit with respect to enhancing either fertility or live-birth rates, hence Fauser et al., 2012 has not recommended its routine use [22].

There are relatively few randomized controlled studies of life style modification including exercise on PCOS are reported, Moran et al., 2011 [13] analyzed these are summarized in a Cochrane review with percentage of change data (median change: -7.00%; 95% CI, -10.1, -3.90; $P < .00001$). Metabolically, lifestyle treatment improved the fasting insulin concentrations (median: -2.02 mIU/mL; 95% CI, -3.28, -0.77; $P = .002$) and the oral glucose tolerance test (OGTT) insulin (median -1,714.59 mIU/mL/minute; 95% CI, -2,122.50, -1,306.68; $P < .00001$). Reproductively, lifestyle modification improved total T levels (median: -0.27 nmol/L; 95% CI, -0.46, -0.09; $P = .003$) and the Ferriman- Gallwey score (median: -1.20; 95% CI, -2.36, -0.04; $P = .04$).

Advances in assisted reproductive techniques led to an increase in efficacy of infertility treatment. Environmental factors, availability of treatment and level of awareness about women's health proved to have the strongest effect on the distribution of infertility causes between urban and rural areas.

Assisted reproduction, in the form of IVF with or without intracytoplasmic sperm injection, is usually indicated as third-line medical treatment or in the presence of other infertility factors [29]. However, Farquhar et al., 2013 [30] reviewed on Cochrane reviews on ART that thirty reviews identified interventions that were effective ($n = 17$) or promising ($n = 13$), 13 reviews identified interventions that were either ineffective ($n = 3$) or possibly ineffective ($n = 10$), and 11 reviews were unable to draw conclusions due to lack of evidence. Costello and Ledger 2012 [31] reported that there is an ongoing debate concerning the relative merits of IVF and ovulation induction in PCOS, comparing the higher multiple pregnancy rate of ovulation induction with the greater cost and psychological stress of IVF [30].

Few other studies have reported that combination therapy of diet and exercise. The results showed reduced ovarian volume and microfollicle number and can restore ovulatory cycles, spontaneous pregnancy [32, 11]. Most of them, however, were not randomized trials and exercise was not supervised but rather consisted of lifestyle counseling. Although weight loss alone appears to improve menstrual frequency, the contribution of exercise alone could not be determined in these studies. Another author reported that regular physical activity is an important component of weight loss programme, because it is associated with better long-term weight loss maintenance [19]. However, its independent role to bring the weight reduction and improved reproductive outcome is less obvious. Increased physical activity is recommended for obese women with PCOS, but always while considering the possible orthopaedic and cardiovascular limitations [11]. Palomba et al., 2010 [33] reported a randomized controlled clinical trial that the six week of structured exercise training and hypo caloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome. Results showed that SET plus hypo caloric diet for 6 weeks, with one cycle of CC after the first 2 weeks significantly reproductive outcome was higher than other groups. Concluded that the C.C resistant PCOS patients should be considered continuing SET programs [33]. However, Karimzedah et al., 2010 [34] evaluated comparative study on the reproductive improvement between diet or with exercise and Metformin, CC and CC+ Metformin drugs in 340 PCOS women and maximum women pregnancy rate resulted by lifestyle modification. It shows that lifestyle modification should be implemented in the medication of the infertility PCOS women in first line treatment. But scientific data on only exercise in infertility PCOS women with clinical trials is less. So, more multiple clinical centers trails to be explore for lifestyle management reproductive improvement.

Data analysis

This systematic review focused on studies involving hormonal changes of exercise life style modification effect in infertility women with PCOS. Due to large studies on PCOS capturing the full range of diagnostic criteria and pathology etc., we searched exercise in infertility PCOS and also life style modification in hormonal changes are scientific data base like NCBI, Google scholar database, MEDLINE and PsycInfo EMB Reviews. We screened full text article data and included 5 groups' studies in this review analysis. Randomized control (RCT) and non-randomized were also considered in the study. Abstracts data, other physical factors like electro-acupuncture interventions were also excluded or restricted. Studies that compared exercise therapy, SET training or aerobic or resistance exercise or a combination with walk were conserved in hormonal changes analysis. Hypo-diet with exercise were considered as exercise group for simplify the data analysis in the present review. Hormonal status at Baseline and study end were considered, average was taken for different time intervals where ever required in study analysis.

Results

For reproductive improvement, exercise Lifestyle modification in infertility women with PCOS were taken to evaluate hormonal effect has summarized below in table form (table-2,3,4).

Infertility is one of the economic burdens for the world health expenditure. Approximately 15% infertility of world population is due to PCOS infertility women. There is no

perfect treatment for infertility in PCOS, except few drugs Metformin, C.C drugs usually used for the treatment of hormonal balance and IVF is the final level of treatment for infertility. However the endocrinological hormonal balance if not recovered, conceive and baby rate are not fruitful.

Meta analysis interpreted from scientific research reports data of lifestyle modification by exercise in infertility PCOS women as followed below-

1. Data was available from 3 Australian continent population study other two were from European continent population which are Italy and Sweden, below 2% Fertility.
2. Total net subjects undergone treatment with the lifestyle modification by exercise in infertility PCOS women 108 persons and with mean values 21.68.
3. Physical characters BMI (Kg/m²) = 33.76 mean value and Range is 27.7 to 36.2 with mean Age= 29.87.
4. Before Lifestyle modification (exercise) in infertility women PCOS, mean hormone levels are 30.91 (SHBG nmol/l), 7.85 (LH IU/ml), 4.36 (FSH (mIU/ml), 2.007 (Testosterone nmol/l), 2.7 TSH μ U/ml), 15.25 insulin (mU/l), 2.983 HOMA, 0.4 Progesterone nmol/l, 6.192 Androstenedione (nmo/l), 128.85 Fasting insulin (pmol/l), 5.05 Fasting Glucose (nmol/l), 2.92 DHEA-S (μ g/ml), 222.7 E2 (pmol/ml), 9.9 FAI % (with P=0.5+/-0.2).
5. After exercise the mean hormone levels are 35.84 (SHBG nmol/l), 7.51 LH (IU/ml), 4.51 FSH(mIU/ml), 1.800 Testosterone (nmol/l), 2.90 TSH (μ U/ml), 10.95 insulin (mU/l), 1.8 HOMA, 0.138 Progesterone (nmol/l), 6.175 Androstenedione (nmo/l), 113.7632 Fasting insulin (pmol/l), 5.077 Fasting Glucose (nmol/l), 2.755DHEA-S (μ g/ml), 189.12 E2 (pmol/ml), 8.196 FAI % (with P=0.5+/-0.2).
6. Maximum Reproductive hormones are improved (SHBG, LH, Testosterone, Progesterone, FSH).
7. Other hormones, insulin and Fasting insulin were also showed -4.3 (mU/l) and -15.086 (pmol/l) respectively decreased changed with mean difference with P value (0.3+/- 0.5).

Discussion

An elevated level of LH is the hallmark of the PCOS disease in women. LH level was decreased after Physical exercise with or without Diet. FSH is also minimal level decreased. LH and FSH hormones released by pituitary gland to stimulate follicle in ovary to mature. Hyper stimulation of FSH & LH may attach Germ line progenitors in the menstrual cycle, instead of single normal ovary to Polycystronic which leads Oligo or Non Ovulation occur. Because, those may had stimulated and distributed in equal to all germ line progenitors. However Estrogen and Progesterone are inhibit the FSH and LH hormones by feedback mechanisms. Hence in PCOS patients Ovary drilling may helpful for pregnancy. However in our study analysis Ovulation was responded after physical exercise [14]. SHBG hormone is lower in the infertility PCOS women, also increased in after lifestyle modification. A low SHBG level will result in increased bioavailable testosterone [35] and may cause the Hyper androgenism [36, 37].

Other Hormones, Insulin, is the main factor for abnormal condition of obesity to PCOS infertility also improved after Exercise. HOMA and FAI are decreased in infertility PCOS population.

The total study population was very less to make clear decision so it is need to conduct multicentre clinical trials for

lifestyle modification for improvement in infertility PCOS patients.

Conclusion

The women need to take precautions in their lifestyle adaption. Diet alone cannot be effective without exercise PCOS women with Infertility and or Obesity need to go SET like exercise along hypo-diet in their life for reproductive improvement and good health.

Table 1: Important hormones in reproductive function

Hormone names	Origin site	Induced organs	Effects in female reproductive system
Gonadotropin releasing hormone (GnRH)	Hypothalamus	Anterior pituitary gland	Stimulates the release of FSH and LH from the anterior pituitary
Follicle stimulating hormone	Anterior pituitary	Ovaries and tests	Stimulates the development of the sex organs and gamete production
Luteinizing hormones (LH)	Anterior pituitary	Ovaries and tests	Triggers ovulation, and (with FSH) stimulates estrogen release
Estrogen	Ovary (follicle)	Entire body	Stimulates the development of the female reproductive tract and secondary sex characteristics
Progesterone	Ovary (corpus luteum)	Uterus	Causes uterine thickening
Testosterone	Tests (interstitial cells)	Entire body	Minor
Inhibin	Tests (sertoli cells)	Anterior pituitary and hypothalamus	Inhibit FSH production

Table 2: Before exercise or at base line hormones levels in the infertile PCOS women of different study groups

Before exercise /Baseline level Hormones	Palomba et al 2008 (I)	Thomson et al 2008 (II)	Jedal et al 2010 (III)	Hutchson et al 2011(IV)	Huber Buchloz et al 1999(V)	Mean	SD	N
SHBG (nmol/L)	27.4	35	40.5	29	22.65	30.91	6.94	5
LH (IU/ml)	9.7		7.19		6.75	7.88	1.59	3
FSH (mIU/ml)	4.7		4.02			4.36	0.48	2
Testosterone (nmol/l)	2.8	2.57	0.015	2.9	1.75	2.007	1.20	5
TSH (μ U/ml)	2.7					2.7	0	1
Insulin (mU/l)		15.25				15.25	0	1
HOMA	2	1.95		5		2.983	1.74	3
Progesterone (nmol/l)	0.4					0.4	0	1
Androstenedione (nmol/l)	5.4		6.984			6.192	1.12	2
Fasting insulin (pmol/l)	139.8			141.6	105.15	128.85	20.54	3
Fasting glucose (mmol/l)	5.1			5		5.05	0.07	2
DHEA-S (μ g/ml)	3.91		1.93			2.92	1.40	2
E2 (pmol/ml)	169.6		275.8			222.7	75.09	2
FAI %	10.2	8.8		10.7		9.9	0.98	3

Table 3: After exercise therapy hormones levels in the infertile PCOS women

After exercise value	I	II	III	IV	V	Mean	SD	N
SHBG (nmol/L)	38.083	43.25	46.58	29.8	21.5	35.84	10.21	5
LH (IU/ml)	9.719		7.56		5.26	7.51	2.23	3
FSH (mIU/ml)	4.756		4.28			4.51	0.33	2
Testosterone (nmol/l)	2.175	2.1	-0.105	2.8	2.03	1.80	1.10	5
TSH (μ U/ml)	2.907					2.90	0	1
Insulin (mU/l)		10.95				10.95	0	1
HOMA	1.622	1.4		4.2		1.80	1.75	4

After exercise value	I	II	III	IV	V	Mean	SD	N
Progesterone (nmol/l)	0.415					0.13	0.23	3
Androstenedione (nmol/l)	5.4		6.95			6.17	3.62	2
Fasting insulin (pmol/l)	121.849			118.8	100.64	113.76	11.46	3
Fasting glucose (mmol/l)	5.255			4.9		5.07	0.25	2
DHEA-S (µg/ml)	3.810		1.7			2.75	1.49	2
E2 (pmol/ml)	167.785		210.46			189.12	30.17	2
FAI %	8.139	6.05		10.4		8.19	2.17	3

Table 4: Difference/change mean values of hormones levels of the after exercise infertile PCOS women.

Change after exercise hormones levels	I	II	III	IV	V	Mean	SD	N
SHBG (nmol/L)	10.683	8.25	6.08	0.8	-1.15	4.932	4.98	5
LH (IU/ml)	0.019		0.37		-1.49	-0.366	0.98	3
FSH (mIU/ml)	0.056		0.26			0.158	0.14	2
Testosterone (nmol/l)	-0.624	-0.47	-0.12	-0.1	0.28	-0.206	0.35	5
TSH (µU/ml)	0.207					0.207	0.000	1
Insulin (mU/l)		-4.3				-4.3	0.000	1
HOMA	-0.378	-0.55		-0.8		-1.177	0.21	3
Progesterone (nmol/l)	0.0156	0				0.015	0.01	2
Androstenedione (nmol/l)	0		-0.034			-0.017	0.02	2
Fasting insulin (pmol/l)	-17.95			-22.8	-4.51	-15.086	9.47	3
Fasting glucose (mmol/l)	0.155			-0.1		0.027	0.18	2
DHEA-S (µg/ml)	-0.099		-0.23			-0.164	0.09	2
E2 (pmol/ml)	-1.814		-65.34			-33.577	44.91	2
FAI %	-2.060	-2.75		-0.3		-1.703	1.26	3

Fig. 1 Physical characters values of the PCOS participants in Exercise therapy for improve fertility showed in bar graph.

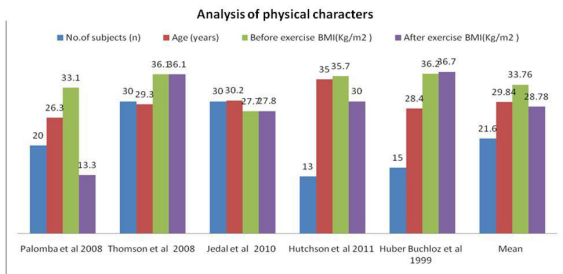
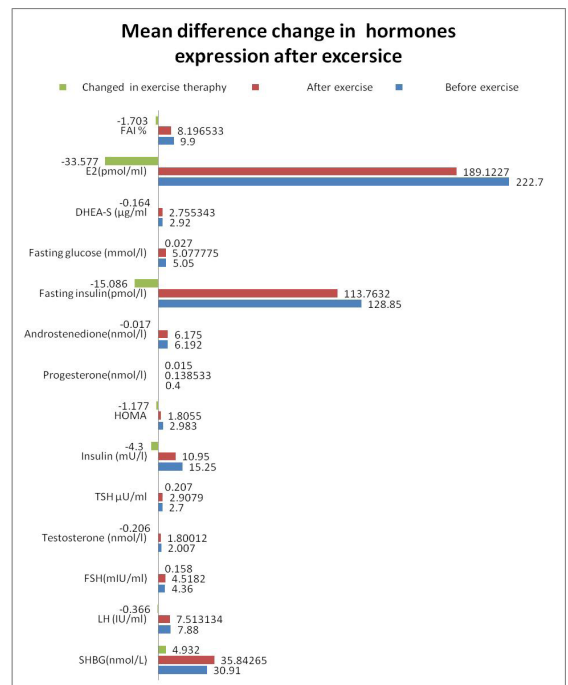


Fig. 2 Mean difference change in hormones expression after exercise and before and after hormone levels presented in bar graph.



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