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Original Article

Assessment of oxytocin level, glucose metabolism components and cutoff values for oxytocin and anti-mullerian hormone in infertile PCOS women

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ABSTRACT

Objective: Comparing oxytocin level and some other parameters between infertile women with or without polycystic Ovary Syndrome (PCOS), to evaluate the correlation between oxytocin with anti-mullerian hormone (AMH), Body Mass Index (BMI) and insulin resistance (IR).
Materials and methods: This cross–sectional study was performed on 80 PCOS and 81 non-PCOS women as the control group. Oxytocin, various hormones, Oral glucose tolerance test (OGTT) and Homeostatic model assessment of insulin resistance (HOMA-IR) were compared between two groups. Correlations between parameters were assessed by the spearman's rank correlation coefficient. Cutoff values for oxytocin and AMH in PCOS were calculated by the ROC-Curve and DeLong method.
Results: The mean oxytocin level was statistically lower in the case group ($p \leq 0.001$). The mean BMI, AMH, HOMA-IR, fasting insulin and insulin 2-h after 75-g glucose were significantly higher in the PCOS group. Oxytocin was negatively correlated to AMH when evaluated for all participants or only among controls. Moreover oxytocin was negatively correlated to HOMA-IR among all participants. However the relationship between oxytocin and BMI was not statistically significant. The calculated cutoff value for oxytocin was 125 ng/L and for AMH was 3.6 ng/mL in the PCOS group.
Conclusion: The mean oxytocin level in the PCOS infertile women was lower than non-PCOS women. Oxytocin showed a significant reverse correlation with AMH and HOMA-IR.

Introduction

Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder among reproductive age women. The prevalence of PCOS depends on the diagnostic criteria, which are introduced. The prevalence of PCOS is reported to be 6.1–8.7% by the criteria of National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD) and to be 15.2–19.9% by the Rotterdam criteria and 12–15.3% by the Androgen excess and PCOS society criteria [1]. PCOS as a condition of chronic anovulation and hyperandrogenism is associated with obesity, Insulin resistance (IR) and lipid related abnormalities [2]. Obesity has been found in 38–66% of PCOS patients and obese PCOS women have decreased clinical pregnancy rates in both natural and assisted conception cycles [3]. Hyperinsulinemia exists in the patients with PCOS independently from their obesity. It is estimated that 40–75% of the obese PCOS women have IR [4]. Oral glucose tolerance test (OGTT)

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is recommended to be performed for the PCOS women with metabolic syndrome or premature adrenarche [5]. Since hyperinsulinemic euglycemic clamp as the gold standard method for the diagnosis of IR is not practicable in clinical situations, several other indirect methods are suggested including: Fasting insulin (FI), fasting glucose/fasting insulin and Homeostatic model assessment of insulin resistance (HOMA-IR) index [6].

Oxytocin is a neurohypophysial hormone with known essential roles during labor, lactation and sexual behaviors [7]. Oxytocin has important neuropsychiatric functions for modulating the social complex behaviors and neuroendocrine reflexes. Presence of oxytocin in other cell lines such as corpus luteum, placenta, leydig cells of testis supports its reproductive function [8]. Since oxytocin suppresses appetite and reduces the fear, anxiety and depression is recently used as a potential treatment for psychiatric disorders such as autism and borderline personality disorders [9]. Zhang and colleagues showed that feeding of the mice with high fat diet (HFD) led to up regulation of hypothalamic oxytocin receptors and administration of oxytocin had protective effect against HFD induced obesity [10]. Also the nasal spray of oxytocin not only decreased the body weight but also improved the lipid profile, glucose metabolism and insulin levels [11].

Results of an investigation published on 2002 showed that human granulosa-cell lines express functional oxytocin receptors and oxytocin promotes progesterone production [12]. There are studies on the positive effects of oxytocin on folliculogenesis and ovulation in rats [13]. Another study showed that addition of oxytocin to the medications that were used for the induction of ovulation in anovulatory women increased the clinical pregnancy rates [14].

We performed this study to compare the serum oxytocin levels between PCOS and non-PCOS infertile women and to evaluate the presence of any possible correlation between oxytocin with anti-mullerian hormone (AMH), Body mass index (BMI) or insulin resistance (IR). Also we calculated the cutoff values for oxytocin and anti-mullerian hormone (AMH) for PCOS.

Materials and methods

This case–control study was performed on 161 female partner of infertile couples with the age range of 20–35 years who were referred to the infertility clinic of Ghadir-Mother and Child Hospital affiliated to Shiraz University of Medical Sciences between January and August 2015. PCOS was diagnosed according to the revised Rotterdam 2003 criteria [5]. Accordingly two of the three following criteria should be present: 1- oligo- or anovulation, 2- clinical and/or biochemical signs of hyperandrogenism and 3- polycystic ovaries on ultrasound scan[5].

The participants with hyperprolactinemia, thyroid disorders, congenital adrenal hyperplasia, Cushing disease, neoplasms or those who used medications including Insulin–sensitizers, oral contraceptives, antiandrogens, corticosteroids and other hormones during the last 90 days were excluded from the study. This study was approved by the Institutional Review Board (Numbered: 93-01-01-8610) and the Ethics Committee of Shiraz University of Medical Sciences (code: ir.sums.rec.1394.s843). At the beginning the study was explained to all of the subjects and written informed consent was obtained from all individual participants included in the study. Finally 80 PCOS and 81 non-PCOS women as the control group were enrolled in this study.

Blood sample was taken after 10 h overnight fasting during the 2nd - 4th days of menstrual cycle. BMI was calculated for all of the participants with the formulation of; weight (kg)/square of height (m^2). Standard OGTT was performed by measurement of blood glucose levels at the baseline and 2-h after oral intake of 75-g glucose [15]. Simultaneously insulin levels were measured at the same time points. Plasma glucose was measured by photometry (Biomind,China) and insulin by enzyme linked immunosorbent assay (ELISA) method (Monobind,U.S.A.). HOMA-IR was calculated by the formulation of; Fasting insulin (μU/ml) × Fasting glucose (mg/dl)/405 and HOMA-IR ≥2.5 was considered as IR [6,16,17]. Dehydroepiandrosterone sulfate (DHEAS), total testosterone (T), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), prolactin and anti-mullerian hormone (AMH) were checked. ELISA method was used for the measurement of FSH, prolactin, TSH, total testosterone (Monobind,U.S.A.) and AMH (Beckman,U.S.A) and DHEAS (DRG,Germany). Enzyme linked fluorescent assay (ELFA) was used for the measurement of LH (Vidas Biomerio, France). The serum samples were centrifuged and frozen at −80 C° and the oxytocin levels were measured for all samples at the same time by ELISA (Crystal day biotech, U.S.A.) and were reported as ng/l.

Ultrasound examinations were performed between the 3rd - 5th days of menstrual cycle and polycystic ovaries were diagnosed if 12 or more follicles were present in at least one ovary and/or ovarian volume was >10 cm^3 [18].

Individuals with BMI>25, HOMA-IR≥2.5 and blood sugar≥140 (mg/dl) at 2-h after administration of 75-g glucose were detected and compared between the case and the control groups. The correlation of oxytocin with AMH, HOMA-IR and BMI was evaluated. The cutoff values for oxytocin and AMH in the PCOS group were calculated.

Statistical analysis

Data were analyzed by statistical package for social sciences for windows software (SPSS Version 22, Chicago, IL, USA). The normal distribution of the data was evaluated by Kolmogorov–Smirnov test and if the data had a normal distribution, then student T test was used. However if the data did not have a normal distribution nonparametric Mann–Whitney U-test was used to compare the mean hormone levels between the case and the control groups. The correlation between oxytocin with AMH, BMI or HOMA-IR was calculated by spearman's rank correlation coefficient. The cutoff values for oxytocin and AMH in the PCOS group were calculated by ROC-Curve and DeLong method. P-value <0.05 was considered significant.

Results

Our study was conducted on 161 infertile women. Eighty women had the criteria of PCOS as the case group and were compared to 81 non-PCOS women as the control group. The mean age and the mean years of primary and secondary infertilities were not different between the two groups. The mean oxytocin level was lower but the mean BMI, AMH, LH, testosterone, fasting insulin, insulin level 2-h after 75-g glucose and HOMA-IR were significantly higher among the PCOS group as shown in Table 1. Also the frequency of the women with BMI> 25 and HOMA-IR≥ 2.5 was significantly higher in the PCOS group.

The mean of BMI was 27.21 ± 3.99 (range 17.94–41.12) for PCOS subjects and 24.7 ± 3.86 (range 15.6–36.5) for non-PCOS group. To evaluate any possible impact of BMI on oxytocin, AMH and the components of glucose metabolism, all of the participants were classified to BMI >25 or BMI ≤25 and statistical analysis was performed. The relationship between BMI and oxytocin was not significant, however for FI, insulin after 2-h of 75-g glucose, HOMA-IR and AMH it was statistically significant. Indicating that BMI >25 could affect all of these mentioned parameters except oxytocin (Table 2). Subsequently, to study these parameters by more detail, we subdivided the case and control groups separately according to

Table 1
Comparison of demographic data, hormonal levels, components of glucose metabolism and insulin resistance between the women with and without PCOS.

Variables	PCOS	Non-PCOS	(P-Value)
Age (years)	28.27 ± 4.88	28.53 ± 4.25	0.721
Duration of Primary Infertility (years)	4.83 ± 3.46	4.7 ± 3.70	0.45
Duration of Secondary Infertility (years)	4.13 ± 2.34	3.41 ± 2.58	0.293
Oxytocin (ng/l)	124.94 ± 40.98	207.42 ± 108.7	≤0.001*
BMI	27.21 ± 3.99	24.7 ± 3.86	≤0.001*
AMH (ng/ml)	6.71 ± 5.08	3.56 ± 3.32	≤0.001*
LH (miu/l)	8.48 ± 7.77	4.75 ± 2.71	0.001*
Testosterone (ng/ml)	1.18 ± 2.31	0.58 ± 0.21	0.036*
FSH (miu/l)	5.85 ± 3.42	5.27 ± 2.89	0.16
TSH (miu/l)	2.74 ± 2.15	2.86 ± 3.05	0.875
Prolactin (ng/ml)	24.72 ± 51.58	22.6 ± 50.99	0.997
DHEAS (μg/ml)	1.31 ± 0.72	1.28 ± 0.69	0.743
Fasting Blood Sugar (mg/dL)	89.56 ± 10.74	89.93 ± 6.94	0.432
Blood sugar 2 h after 75gr glucose (mg/dl)	114.46 ± 30.8	108.85 ± 32.48	0.089
Fasting Insulin (μ iu/ml)	13.52 ± 11.12	8.34 ± 3.9	≤0.001*
Insulin 2-h after 75-g glucose (μ iu/ml)	71.02 ± 49.69	47.67 ± 40.03	≤0.001*
HOMA-IR	3.02 ± 2.94	1.8 ± 0.95	≤0.001*
BMI > 25	53 (70.7%)	28 (42.4%)	0.001*
HOMA-IR ≥ 2.5	33 (41.2%)	11 (13.6%)	<0.001*
Blood sugar 2 h after 75 g glucose ≥140	13 (16.2%)	7 (8.6%)	0.143

*p value < 0.05 is significant. Data are presented as mean ± SD or number (%).

BMI >25 or BMI ≤25. Among all studied parameters, only the HOMA-IR was statistically higher in the control individuals with BMI >25. Results are shown in Table 3.

To find the cutoff values for oxytocin and AMH in PCOS, we used ROC curve and DeLong method (1988). Accordingly the cutoff point for oxytocin in PCOS was 125 ng/l with 70% sensitivity and 85.2% specificity and area under the ROC curve (AUC) was 0.812 ± 0.033 (P < 0.001) (Fig. 1).

The cutoff value for AMH in our PCOS group was calculated to be 3.6 ng/ml with the sensitivity of 70% and the specificity of 74.7%. AUC: 0.713 ± 0.042 (P < 0.001) (Fig. 2).

To look for any possible correlation of oxytocin with HOMA-IR and AMH Spearman's rank correlation coefficient was used. We found a reverse correlation between oxytocin and AMH levels (p = 0.044, r = −0.160). This value despite being weak was statistically significant when was calculated for all subjects. The correlation of oxytocin with AMH was not significant when was calculated only in the case group (p = 0.68 r = 0.046), while it was weak, reverse and significant when studied in the control group (p = 0.012 r = −0.28). Also our results showed a weak statistically significant reverse correlation between oxytocin and HOMA-IR when calculated for all participants (P = 0.009, r = −0.204). Nevertheless, oxytocin was not statistically correlated to HOMA-IR when calculated only in the case or control group (P = 0.817, r = −0.026 for PCOS group and P = 0.469, r = −0.082 for the control group).

Also the correlation between HOMA-IR and BMI >25 was calculated. In spite of weak values, HOMA-IR was positively correlated to BMI >25 in both case (P = 0.007, r = 0.308) and control (P = 0.026, r = 0.274) groups.

Discussion

PCOS as the most common consequence of chronic anovulation may have various etiologies, complex pathogenesis and multiple clinical presentations. As this study showed oxytocin was significantly lower and BMI, AMH, LH, testosterone, FI, 2-h insulin after 75-g glucose and HOMA-ir were significantly higher in the PCOS group comparing with non-PCOS control group.

Oxytocin is a nanopeptide that is produced in the supraoptic and paraventricular nuclei of hypothalamous and is stored at the axones in the posterior pituitary gland and is secreted by the electrical activity of the hypothalamic cells [19]. The concentration of oxytocin in the brain is 1000 times more than the peripheral tissues [20]. There are few animal or human studies that reported a positive effect for oxytocin in the folliculogenesis or increasing the clinical pregnancy rate after administration of oxytocin [13,14].

Our results showed significant lower mean oxytocin level in the PCOS women. According to the World Health Organization classification for chronic anovulation, PCOS patients are normogonadotropic and defined as type 2 [21]. They suffer from hormonal imbalances in their hypothalamic-pituitary-ovarian (HPO) axis. This defect is probably connected to the lower oxytocin levels in PCOS. So it is possible that lower oxytocin production from the posterior hypophysis is also involved in the pathophysiology of chronic anovulation.

According to the literature 38–66% of PCOS women are obese [3]. The central type of obesity is associated with insulin resistance, metabolic syndrome, diabetes and infertility. In our study 70.7% of PCOS women were overweight with the BMI >25 compared to 42.4% in the control group. However 21.33% of the PCOS women in our study were obese (BMI ≥ 30) compared to 6.06% of the women

Table 2
Comparison of oxytocin, AMH, and glucose metabolism components between all of the subjects with BMI >25 or BMI ≤25.

	BMI>25	BMI≤25	P value
Oxytocin (ng/l)	151.42 ± 76.38	183.58 ± 112.11	0.06
AMH (ng/ml)	6.30 ± 4.89	4.59 ± 4.26	0.03*
Fasting Insulin (miu/ml)	13.00 ± 11.21	9.37 ± 3.91	0.008*
Insulin 2-h after 75-g glucose (miu/ml)	70.41 ± 52.73	49.54 ± 38.50	0.01*
HOMA-IR	2.94 ± 2.95	1.98 ± 0.90	0.007*

* p value < 0.05 is significant. Data are presented as mean ± SD.

Table 3
Comparison of oxytocin, AMH and glucose metabolism components in the case and control groups with BMI >25 or BMI ≤25.

Variables	PCOS		P-value	Non-PCOS		P-value
	(BMI>25)	(BMI≤25)		(BMI>25)	(BMI≤25)	
Oxytocin (ng/l)	124.55 ± 46.73	125.21 ± 40.43	0.407	219.50 ± 123.24	201.04 ± 101.19	0.824
AMH (ng/ml)	7.48 ± 5.142	5.874 ± 4.69	0.074	4.337 ± 3.909	3.642 ± 3.245	0.2389
Fasting Insulin (μ iu/ml)	14.81 ± 13.18	11.41 ± 4.40	0.128	9.57 ± 4.47	8.20 ± 3.09	0.967
Insulin 2-h after 75-g glucose (μ iu/ml)	76.99 ± 53.73	58.09 ± 38.87	1.459	58.57 ± 45.72	43.61 ± 38.19	1.752
HOMA-IR	3.416 ± 3.4911	2.38 ± 0.95	0.245	2.118 ± 1.018	1.691 ± 0.813	0.0455*

*p value < 0.05 is significant. Data are presented as mean ± SD.

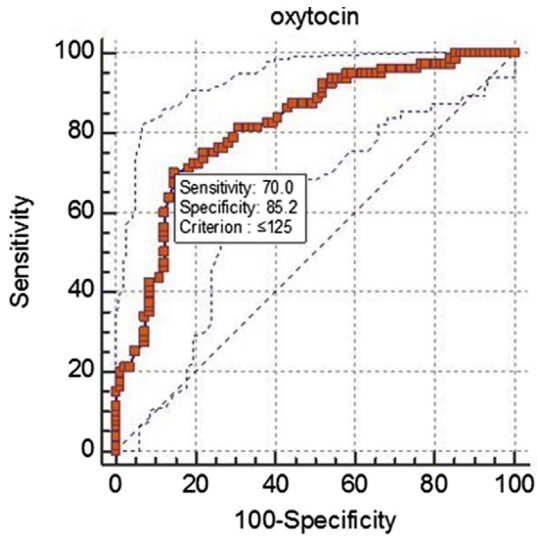

Fig. 1. Cutoff point for oxytocin.

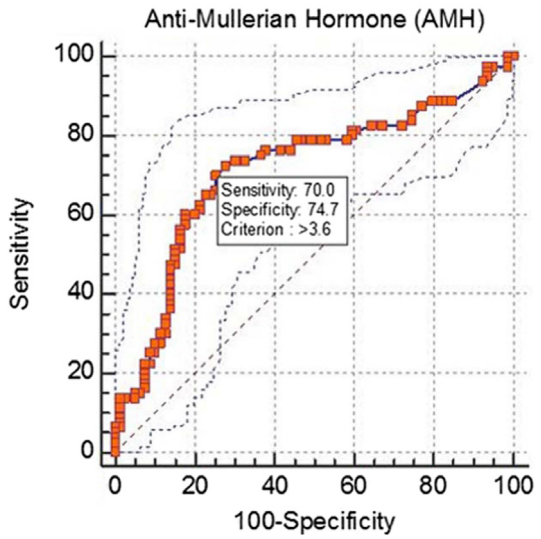

Fig. 2. Cutoff point for AMH.

in the control group. This observation is in agreement with literature.

Previous studies showed that oxytocin is higher among the normal weight subjects without IR [11]. In our study oxytocin levels were higher in normal weight women (BMI ≤ 25) too. While this difference was not statistically significant, probably by a larger sample size, the difference might reach statistically significant values. Expectedly FI, insulin after 2-h of 75-g glucose, HOMA-IR and AMH were statistically higher in overweight individuals (Table 2).

Our results showed that HOMA-IR is related to BMI >25 in the control group but not in the PCOS group as shown in Table 3. Logically the people who are overweight are at a higher risk to develop IR as was shown in our control group. But it should be considered that our case group consisted of the infertile PCOS women, who had a mean of about 5 years infertility that were under prolonged managements. As the first line of PCOS management weight reduction and healthy life style has been instructed to them. We believe that these weight reduction programs may have altered their natural condition.

The prevalence of IR among the women with PCOS is reported to be about 40–75% and it is more common in the overweight PCOS women [4,22]. In our study HOMA-IR ≥ 2.5 was seen in 33 individuals (41.2%) of the PCOS women compared to 11 individuals (13.6%) in the non-PCOS group. According to our results OGTT by considering the mean FBS and the 2nd hour blood glucose showed no statistical difference between the case and control groups. Our results showed that HOMA-IR could more frequently distinguish the metabolic disturbance and subsequently argue that the measurement of blood sugar during OGTT probably is not a good indicator for diagnosis of IR among PCOS patients (Table 1).

Anti-mullerian hormone (AMH) as a member of the transforming growth factor β family with important role in male fetus is secreted from the Sertoli cells and inhibits mullerian duct development [23]. AMH in the female ovaries is secreted from the granulosa cells of preantral and antral follicles and has high levels in PCOS women [24]. AMH has been introduced as a diagnostic tool for PCOS with different cutoff values from 3.14 to 4.45 or even higher [24,25].

In this study we calculated the cutoff point of 3.6 ng/ml as the best discriminatory point for AMH among our PCOS cases. Also we calculated the cutoff value for oxytocin to be 125 ng/l. To the best of our knowledge this is the first study that revealed the oxytocin cutoff point for PCOS discrimination and accordingly it seems that oxytocin levels may be used as discriminatory diagnostic tools for PCOS.

We found a significant reverse correlation between oxytocin and AMH levels when was calculated for all participants or only the non-PCOS individuals. However we did not see any significant correlation between oxytocin and AMH among PCOS patients. The later may be due to the previous managements applied to these patients. We found a significant anti-correlation between oxytocin and HOMA-IR. This is known that the cases with severe PCOS have higher levels of AMH and higher grades of insulin resistance. Accordingly more severe PCOS is accompanied by lower oxytocin level.

Finally we suggest other studies for more precise evaluation of oxytocin role as a diagnostic factor in PCOS and also as a prognostic factor for ovarian response and success rates in infertility treatments. To improve PCOS management we suggest studies in future

with the aim of finding the effect of different doses of oxytocin in PCOS women to accelerate ovulation induction, weight reduction and to balance their hormonal profile.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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