

# Physiological Research Pre-Press Article

## **Comparison of adiponectin levels during the menstrual cycle between normal weight and overweight/obese young females**

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Short title: adiponectin during menstrual cycle

## Summary

**Aim:** To compare serum adiponectin changes across the menstrual cycle between normal weight and overweight/obese young women and its correlation with serum estradiol.

**Methods:** Young women (n= 56) with regular menstrual cycle had been grouped according to their BMI into normal weight group (n=26) and overweight /obese group (n=30). Blood samples were drawn during early follicular (FP), pre-ovulatory (OP) and luteal phases (LP) of menstrual cycle for serum adiponectin and estradiol levels determination using enzyme-linked immunosorbent assay.

**Results:** Adiponectin serum level showed a significant decreasing pattern across the phases of menstrual cycle in normal weight group. This pattern was absent in the overweight/obese group. In addition, serum adiponectin was lower in overweight/obese group compared to normal weight subjects through all phases of menstrual cycle. No correlation was found between adiponectin and estradiol levels in both groups.

**Conclusion:** A significant variation of serum adiponectin level was detected across the menstrual cycle in females with normal weight. In comparison, overweight / obese group showed a relatively stable adiponectin level throughout the cycle. This lack of adiponectin variation might be added to the complex mechanisms lies behind obesity-related female infertility.

**Keywords:** Adipokines, adiponectin, menstrual cycle, estradiol, BMI

**Introduction:**

Obesity has been considered a new epidemic in the world. A dramatic increase in obesity prevalence was observed over the past 30 years. According to WHO, more than half a billion adults worldwide are complaining of obesity (Nguyen and El-Serag 2010). A high obesity prevalence of 28.7% was also recorded in Saudi Arabia with more prevalence among women than men (33.5% vs 24.1%) (Memish *et al.* 2014). It is well documented that obesity could reduce fertility in humans, obese females are at higher risk of subfertility and less likely to conceive than lean women (Best and Bhattacharya 2015). Recently, reproductive function has been found to be closely related to the energy homeostasis (Michalakis *et al.* 2013), there are increasing pieces of evidence for the role of adipokines in the link between reproductive function and nutritional status (Comminos *et al.* 2014).

Adiponectin, a 244 amino acids protein was discovered in 1995 (Scherer *et al.* 1995), it is the most abundant circulating adipocytokines produced exclusively in white adipose tissue (Maeda *et al.* 1996) with a higher levels in females than in males (Bottner *et al.* 2004). Three receptors for adiponectin AdipoR1, AdipoR2 and t-cadherin are found in the peripheral tissues.(Combs and Marliss 2014). Contrary to other adipose tissue hormones, adiponectin circulating levels are lower in obese individuals and increases with weight reduction (Balsan *et al.* 2015). The anti-diabetic effect of adiponectin in improving insulin sensitivity in liver and skeletal muscle as well as the regulation of energy homeostasis is well known. During the last 20 years, anti-inflammatory, anti-atherogenic and anti-apoptotic effects were further demonstrated (Michalakis *et al.* 2013). Recently, adiponectin has been linked with many obesity-related

disorders like metabolic syndrome, cardiovascular diseases, and hypertension (Blüher and Mantzoros 2015).

Both, expression of adiponectin receptors in the hypothalamic-pituitary-gonadal axis, as well as, the sexual dimorphism of adiponectin concentration, reflects a possible modulatory effect of this adipocytokine on the reproductive endocrine axis (Kawwass *et al.* 2015). Furthermore, an interrelationship between adiponectin and sex hormones have been elucidated by many studies, adiponectin levels were found to be higher during estrogen depletion at human menopause, than in pre-menopause period (Jurimae and Jurimae 2007a, Tamakoshi *et al.* 2007). Circulating adiponectin levels are also elevated when the GnRH secretion disturbed such in hypogonadotropic hypogonadism (Lanfranco *et al.* 2004). However, it seems that adiponectin predominately play an inhibitory action on the hypothalamus and pituitary, as it decreases GnRH secretion from hypothalamic neurons (Wen *et al.* 2008, Cheng *et al.* 2011) and suppresses the LH secretion in rodents pituitary explants (Lu *et al.* 2008). In contrast, the effect of adiponectin on the gonads is differed according to the sex, while it follows the overall inhibitory role in the male tests by decreasing testosterone secretion (Caminos *et al.* 2008), it plays a permissive effect on rodent ovaries by increase estrogen and progesterone secretion (Chabrolle *et al.* 2009).

Nonetheless, these accumulated shreds of evidence suggested a regulatory role of adiponectin in the endocrine system of reproduction, its exact role in female reproduction still debatable. Published results from previous studies are conflicting regarding adiponectin level during menstrual cycle and its relationship to the sex hormone, some studies failed to show any significant variation during the normal menstrual phases in humans or mice (Kleiblova *et al.* 2006, Asimakopoulos *et al.* 2009, Dafopoulos *et al.* 2009). On another hand, Sramkova *et al.*

(2015) reported a significant higher level of adiponectin during menstrual cycle (Sramkova *et al.* 2015).

These conflicting findings presenting earlier deliver a need for further investigation about the role of adiponectin in the field of female's reproductive endocrinology. Only a few studies have been investigated the variation of adiponectin during menstrual cycle in human. In addition, very limited studies were evaluating the difference in adiponectin levels between females with normal BMI and those with BMI above normal during different phases of the menstrual cycle. Hence, the primary objective of the current study is to compare the serum level of adiponectin during different phases of menstrual cycle between normal and overweight/ obese women and to correlate its level with the level of estrogen. In addition we investigated the pattern of adiponectin variation across the phases of menstrual cycle in the whole cohort as secondary outcome.

## Methods

This prospective cohort study was conducted at Imam Abdulrahman Bin Faisal University. Fifty-six, female students (18-25 years) with a regular menstrual period, were recruited by convenience sampling. Pregnant females, breastfeeding, with irregular menstrual cycle or were on oral contraceptives have been excluded. Ethical approval was obtained from the Institutional Review Board (2014 -01 - 173). Written consent was obtained from every subject.

Subjects were classified according to their body mass index into two groups: **normal weight group** included 26 females with body mass index between 18.5-24.99 and **overweight/obese group** (30 females) with body mass index  $\geq 25$ . BMI was calculated as

(kg/m<sup>2</sup>), weight and height were measured using Sicca digital scale and stadiometer respectively, waist and hip circumferences were measured with a non-stretchable plastic tape. The subjects were briefed about the project and they were instructed about how to make a basal body temperature chart.

The study was run over one menstrual cycle for each subject. Blood samples were collected during the menstrual cycle as follows: during the first 3-5 days of menstrual cycle (**Early Follicular Phase**), from days 11 to 16 before the onset of the next menstrual cycle (**Pre-ovulatory Phase**), and the third one at 3-5 days before onset of next menstrual cycle (**Luteal Phase**). The basal body temperature chart and serum estradiol level fluctuation were used for further verification of cycle phases (Latif and Rafique 2015).

To minimize the effects of diet and circadian rhythm on adiponectin and estrogen levels, blood samples were collected after an overnight fast between 8-10 AM. Five ml of blood were collected in and left to clot, samples were centrifuged, and the collected serum was stored at - 80 °C for future analysis. All samples from each subject's menstrual cycle were run together in one kit to control for inter-assay differences. Adiponectin was measured by manual sandwich enzyme-linked immunosorbent assay method using (Adiponectin (B-Bridge International, Inc) kits. The inter-assay and intraassay coefficient of variation (CV) was 7.3 % and 3.6 % respectively. Serum estradiol level was measured using estradiol Eliza kits (Sigma Aldrich), with a CV less than 10 %.

Data were expressed as arithmetic means  $\pm$  standard deviation, one-way repeated measure ANOVA with post hoc multiple comparisons were performed to compare each variable

within the same group at different menstrual phases. The differences between normal weight and overweight /obese groups were analyzed using unpaired t-test, a correlation between adiponectin and estradiol levels was tested using Pearson correlation coefficients. Statistical software (SPSS-version 20) was used and a P value of  $< 0.05$  was considered significant.

## Results

The participants' characteristics in the two study groups are listed in (**table 1**). The mean duration of the menstrual cycle was  $29 \pm 1$  (mean  $\pm$ SD) days (range = 27-31 days).

**Table 1: baseline anthropometric measurements of the participants**

<b>Variables (mean <math>\pm</math> SD)</b>	<b>Normal weight group (n= 26)</b>	<b>Overweight/obese group (n= 30)</b>	<b>P value</b>
<b>Weight (kg)</b>	52.60 $\pm$ 6.46	78.27 $\pm$ 12.16	<b>&lt; 0.001 *</b>
<b>Height (cm)</b>	154.60 $\pm$ 5.57	157.66 $\pm$ 5.84	<b>0.051</b>
<b>BMI (kg/m<sup>2</sup>)</b>	21.97 $\pm$ 1.89	31.39 $\pm$ 3.57	<b>&lt; 0.001 *</b>
<b>Waist circumference (cm)</b>	75.69 $\pm$ 5.88	87.25 $\pm$ 14.70	<b>&lt; 0.001 *</b>
<b>Hip circumference (cm)</b>	98.58 $\pm$ 7.05	111.43 $\pm$ 16.53	<b>&lt; 0.001 *</b>
<b>Waist / hip (W/H) ratio</b>	0.77 $\pm$ 0.06	0.78 $\pm$ 0.07	<b>0.711</b>

\*Significant level

Adiponectin serum level showed a decreasing pattern across the phases of menstrual cycle in normal weight group, the higher level during follicular phase ( $8.23 \pm 4.66 \mu\text{g/dl}$ ) was declined through ovulatory phase ( $7.10 \pm 3.25 \mu\text{/ml}$ ) to reach its lowest level ( $6.71 \pm 3.09 \mu\text{/ml}$ ,  $p = 0.049$ ) at luteal phase (**table 2**). This pattern of adiponectin variation was absent in overweight/obese group as well as when we combined both groups together. (**table 2 and 3**). In addition, between-groups comparison showed lower serum adiponectin in overweight/obese subjects compared to normal-weight subjects during follicular ( $5.30 \pm 2.96$  vs  $8.23 \pm 4.66 \mu\text{/ml}$ ,  $p = 0.02$  respectively) and preovulatory phases ( $5.24 \pm 3.11$  vs  $7.10 \pm 3.25 \mu\text{/ml}$ ,  $p = 0.03$  respectively) (**table 2**). **In contrast, estradiol was significantly increased from early follicular to pre-ovulatory phase with insignificant decrease from pre-ovulatory to the luteal phase in both study groups separately as well as in the whole cohort (table 2 & 3). No significant difference was found in serum estradiol level between normal weight and overweight /obese groups across all phases of menstrual cycle (table 2).**

**Table 2: Comparisons of serum adiponectin and estradiol levels within and between groups at different phases of the menstrual cycle**

hormones (mean $\pm$ SD)		Normal weight group	Overweight -obese group	P value (between groups)
<b>Adiponectin</b>  ( $\mu\text{g/ml}$ )	Follicular phase (F)	8.23 $\pm$ 4.66	5.30 $\pm$ 2.96	0.02*
	Preovulatory phase (PO)	7.10 $\pm$ 3.25	5.24 $\pm$ 3.11	0.03*
	Luteal phase (L)	6.71 $\pm$ 3.09	5.87 $\pm$ 5.13	0.07
	<b>P value</b> (within group)	0.049*	0.80	
<b>Estradiol</b>  (pg/ ml)	Follicular phase (F)	48.94 $\pm$ 23.18	41.04 $\pm$ 21.69	0.209
	Preovulatory phase (PO)	78.42 $\pm$ 45.02	74.79 $\pm$ 58.64	0.806
	Luteal phase (L)	67.83 $\pm$ 41.19	67.63 $\pm$ 32.51	0.985
	<b>P value</b> (within group)	0.045*	0.017 *	

\*Significant level

**Table 3: Serum adiponectin and estradiol levels in different phases of the menstrual cycle in all subjects of the study**

Hormones  (mean $\pm$ SD)	Phases of menstrual cycle			P value
	Follicular phase (FP)	Pre-Ovulation (OP)	Luteal phase (LP)	
Adiponectin( $\mu$ g/ml)	6.66 $\pm$ 4.08	6.10 $\pm$ 3.28	6.26 $\pm$ 4.29	0.51
Estradiol (pg./ml)	44.58 $\pm$ 22.62	77.36 $\pm$ 52.44	67.55 $\pm$ 36.75	0.001*

\* Significant level for FP vs both OP & LP using repeated measure ANOVA

No significant correlation was found between adiponectin and estradiol level in both groups (table 4).

**Table 4: Correlation between serum adiponectin and estradiol at different phases of the menstrual cycle:**

Parameters		Normal weight group			Overweight/obese group		
		FP	OP	LP	FP	OP	LP
Adiponectin vs  estradiol	Pearson correlation	0.008	0.07	-0.24	0.30	0.19	0.09
	P value  (two tailed)	0.96	0.71	0.22	0.14	0.35	0.66

FP= follicular phase, OP= pre-ovulatory phase, LP= luteal phase

## Discussion

The current study showed a significant decreasing pattern in adiponectin levels across the menstrual cycle of the normal weight group. This pattern was absent in overweight/ obese group and no correlation with estradiol levels was found in both groups.

Previous studies on the adiponectin variations during menstrual phases in human are limited and showed inconsistent results. Our findings are in accordance with a recent study investigating the level of adipokines and some steroid during the menstrual cycle of normal weight young women, adiponectin was found to be significantly higher during the middle of the cycle compared to late luteal phase (Sramkova *et al.* 2015).

However, several studies showed stable adiponectin level across menstrual cycle, two previous small studies of normal weight females showed no significant variation in adiponectin levels across the menstrual cycle despite the characteristic dramatic changes of estrogen level (Kleiblova *et al.* 2006, Asimakopoulos *et al.* 2009). Serum adiponectin levels were also found to be stable in young healthy women (Saxena *et al.* 2012) as well as in pre-menopausal women with regular cycles, whether the cycles were ovulatory or non-ovulatory (Hall *et al.* 2009, Rouen *et al.* 2010). It is important to note that, large variation in adiponectin levels were reported between individuals as well as many confounders such as BMI, age, physical activity, and food consumption, and the presence of various adiponectin isoforms in the blood could explain this variation. However, our study confirms the variation of adiponectin during menstrual cycle in normal weight young women. Although in the current study no correlation between estrogen and adiponectin had been detected, still the declined adiponectin level during the pre-ovulatory and

luteal phases where estrogen achieved its higher level might indicate a negative association that could explain the adiponectin variation during menstrual cycle in normal weight group.

The overweight/ obese group showed an insignificant pattern of adiponectin variation during menstrual phases, this is in agreement to Rouen *et al.* (2010) who studied the influence of body mass index and the menstrual cycle on adipokines secretion where overweight subjects showed a relatively stable adiponectin level across the cycle (Rouen *et al.* 2010). In addition, lower adiponectin levels were recorded in overweight-obese group (BMI  $\geq$  25) compared to normal weight group (BMI = 18.5-24.99), confirming the strong negative correlation between serum adiponectin and adiposity indices (BMI, waist and hip circumferences), as has been mentioned in many previous studies (Gavrila *et al.* 2003, Hoffstedt *et al.* 2004, Jurimae and Jurimae 2007b). This could explain the absence of adiponectin variation in overweight/obese group due to the negative effect of adipose tissue on circulating adiponectin.

Our findings of no correlation between adiponectin and estradiol during menstrual phases are in line with many previous studies (Kleiblova *et al.* 2006, Asimakopoulos *et al.* 2009, Dafopoulos *et al.* 2009, Hall *et al.* 2009, Chatzidimitriou *et al.* 2015). Moreover, serum adiponectin has been observed to be unchanged during menopause despite depleted estrogen. Further support has come from an in-vitro study, when estradiol administration to human fat cells did not affect adiponectin expression and secretion (Horenburg *et al.* 2008). However, the literature on the relationship between adiponectin and estradiol are very inconsistent. Serum adiponectin levels were found to be increased and decreased in postmenopausal compared to premenopausal women reflecting negative and positive correlation respectively. Unfortunately,

administration of exogenous estrogen to postmenopausal women failed to confirm either presence or absence of correlation between adiponectin and estrogen, instead, it increases further contradiction when showed no effect (Sieminska *et al.* 2005, Chalvatzas *et al.* 2009), an increase (Chu *et al.* 2006), and a decrease (Kunnari *et al.* 2008) in plasma adiponectin levels. Interestingly, serum adiponectin levels were unchanged in mice either post-ovariectomy or after estradiol treatment despite significant changes in adiponectin mRNA levels in perigonadal fat brought by these two interventions (Gui *et al.* 2004).

Although The reason for these discrepancies is not clear, it could be explained by the presences of many potential confounders in the existing studies that precluded a firm assessment of the relationship between adiponectin and estradiol, such as age (Koh *et al.* 2008), BMI (Hoffstedt *et al.* 2004), physical activity (Khoo *et al.* 2015), and food consumption (Izadi and Azadbakht 2015). However, we controlled the effect of BMI by the design of our study, an overnight fasting sampling had controlled the effect of food consumption, and all our subjects were in the same age group and with similar physical activity.

This contradiction in the results might highlight a complex multiloop mechanism controlling adiponectin-estradiol relation instead of being simple unidirectional. Hence, the absence of correlation between adiponectin and estradiol doesn't mean an absence of adiponectin's role in female reproduction.

In conclusion, a significant variation of serum adiponectin level was detected across the menstrual cycle in females with normal weight. In comparison, overweight / obese group showed a relatively stable adiponectin level throughout the cycle. This lack of adiponectin variation

might be added to the complex mechanisms lies behind obesity-related female infertility. Future researches on adiponectin effect on menstrual cycle physiology in females is needed, particularly comparisons between normal regular menstruating women and women with menstrual irregularities.

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