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Clomiphene citrate response in PCOS patients with abnormal lipid profile and impaired glucose tolerance test

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ABSTRACT

Objective: To assess the clomiphene citrate(CC) response to 200mg in women not responding to 150mg for ovulation induction in PCOS women with abnormal lipid profile and impaired glucose tolerance test, and to assess the postprandial triglyceride response to high fat meal in PCOS women

Design: controlled clinical study.

Setting: infertile PCOS women attending infertility centre in Al-Batool maternity Teaching Hospital.

Materials and methods: 50 infertile women with PCOS, who failed to respond to 150 mg clomiphene citrate (CC) fore 4cycles (25 non-obese and 25 over weight) were given 200mg of CC, and 25 healthy women as controls, were selected. Assessment for; Clinical, anthropometric measurement, fasting serum glucose, fasting lipid profile, oral glucose tolerance test, postprandial triglyceride, cholesterol, high and low density lipoprotein, hormonal assay, and ovarian ultrasound.

Results: Both obese and non-obese PCOS women with CC resistant (CCr) to 150mg when 200mg is used had a significant higher waist-to-hip ratio than controls at $P \leq 0.05$. PCOS women had higher levels of fasting, and 2-hour postprandial blood sugar (2h PPBS) and high-density lipoproteins (HDL) levels in a significant difference at $P \leq 0.05$. High-density lipoprotein was significantly lower in PCOS women than controls at $P \leq 0.05$. Clomiphene citrate response (CCR) was significantly less in PCOS groups with impaired glucose tolerance (IGT) 33.4% than those with normal blood sugar (BS) (81.8%), and higher in women with type 2 diabetes mellitus (DM) as (100%) were (CCr). CCr was more in PCOS women with abnormal lipid profile compared to normal (71.4% in abnormal triglyceride (Tg), 78.2% in abnormal cholesterol (Ch) and 67.7% with abnormal HDL.

Conclusion: PCOS women with IGT test; non-insulin dependent DM and abnormal lipid profile had more CCr in ovulation induction, than those with normal blood sugar and lipid profile. PCOS women had postprandial hypertriglyceridemia that is related to high waist-to-hip ratio, and insulin resistance regardless of obesity.

Key words: PCOS, clomiphene citrate, abnormal lipid profile, impaired glucose tolerance.

Polycystic ovary syndrome (PCOS) is most frequent encountered endocrinopathy in women at reproductive age (1). The following characteristics are very often associated with PCOS; hirsutism, polycystic ovaries, obesity and infertility (2).

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PCOS is associated with a significant morbidity of both reproductive and non reproductive events, and increases morbidity, and mortality by the time of menopauses. PCOS women have profound insulin resistance, prevalence of IGT in 31-35%, type 2 diabetes mellitus (DM) in 75-100%, Lipid abnormalities, cardiovascular disease, and endometrial carcinoma (2, 3). PCOS women do not

ovulate in predictable manner, and produce excessive quantities of testosterone (4). It has been found that 38-50% of PCOS women are overweight, with body mass index (BMI)>25 kg/m^2 which increase directly with the serum luteinizing hormone (LH) concentration greater than 10IU/L(5,6,7). It was found that PCOS is a metabolic as well as reproductive disorder (8). The association between disorders of carbohydrate metabolism and hyperandrogenism was first described in 1921 by Achard and Thiers, and was reported to occur frequently in women with hyperandrogenism and DM by Kierland et al in 1947. Brown and Winkelmann noted in 1968 that it was insulin-resistance DM, which got genetic basis (9, 10), and in 1980 Burghen and colleagues reported that there are significance positive linear correlations between insulin and androgen levels (11). Hyper insulinemia; which directly reduce serum levels of sex hormone binding globulin (SHBG), has been shown in several epidemiological studies that there is increase risk factors for cardiovascular disease such as; central obesity, hypertension hyperglyceridemia, low level of (HDL) cholesterol, abnormal glucose metabolism, and hyperinsulinemia (12). Most PCOS women ovulate intermittently and are deficient in progesterone secretion may take longer to conceive, with an increase miscarriage rate, the mechanism of which is poorly understood (13).

Several biochemical abnormalities were noticed all of which contribute to increased ovarian production of androgens; as testosterone, 17 hydroxy progesterone (17O.H.P), Dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone sulphate (DHEAS), growth hormone (GH), insulin growth factor 1 (IGF1)(14). Insulin is progonadotropins; in synergy with LH they act on ovarian theca stroma cells to stimulate the expression of cytochromes P450c17 and excessive androgen production (15). Insulin resistance in PCOS is not due to obesity primarily or hyperandrogenism (16). The cellular mechanism of insulin resistance in PCOS suggested being due to reduced binding of insulin to its receptor, and/or reduced insulin mediated glucose transport, suggesting a post receptor defect (17). In PCOS reduced amount of follicular fluid (IGF BP-1) potentiates IGF mediated ovarian androgen secretion (18). The presence of obesity and insulin resistance may predispose women to coronary heart disorder) (19).

The majority of women with PCOS have anovulatory infertility; this may be treated effectively but is not a simple manner (20). However up to 10% of women may have CCr and fail to response to doses as high as 150 mg daily for 5 days, due to lack of adequate ovarian response 16. Recently promising results have been demonstrated with the use of metformin and insulin sensitizing agents such as troglitazone and D chiro-inositol (16, 20).

Aims of the work: To assess CCR to 200mg CC in PCOS women failed to respond to 150mgCC for ovulation induction, with impaired glucose tolerance test and abnormal lipid profile, and to assess the role of postprandial lipemia and important of waist-to-hip ratio in PCOS women.

MATERIALS AND METHODS

From first of January 2003 to the first of January 2004, fifty infertile PCOS women, aged 18-37 years, were selected randomly according to the day of presentation in the infertility clinic in Al-Batool teaching Hospital. All women were in good health for at least one month before study, not tacking any medication known to affect sex hormone or carbohydrate and lipid metabolism. The criteria of PCOS were based on the finding of polycystic ovaries appearance on ultrasound, in oligomenorrhea, hirsutism, and serum testosterone > 0.7 ng/ml. The study groups; Twenty-five PCOS women had normal weight and BMI between18-25 kg/m2, and Twenty-five were over weight BMI between 25 -30 kg/m^2.

The control group consists of 25 healthy women, had regular menstrual cycle, not hirsute, and had normal weight and BMI between18-25 kg/m^2. To control for conditions altering insulin action and lipid profile, controlled women did not engage in regular aerobic exercise, nor did have history of hypertension, DM, cardiovascular disease, and first-degree relative with these disease.

Anthropometric Measurements; Weight and height were recorded when the women were wearing

Table 1. Descriptive characteristics of PCOS groups and control.

Variable	PCOS Over weight	PCOS Normal	Control
Age (year)	24.1 ± 0.51	23.59 ± 0.54	23.62 ±0.78
BMI (Kg/m^2)	27.28 ± 0.36^c	23.37 ± 0.57^b	20.54 ± 0.21^a
Testosterone	2.67 ± 0.15 ^{c}	1.82 ± 0.13^b	0.53 ± 0.02^a
LH/FSH	2.15 ± 0.02 ^{c}	1.77 ± 0.03^b	0.83 ± 0.02^a
W/H	0.90 ± 0.03 ^{b}	0.83 ± 0.01^b	0.66 ± 0.01^a
FBS	7.11 ± 0.14 ^{c}	4.83 ± 0.17^b	3.72 ± 0.06^a
2h.BG	9.16 ± 0.29 ^{c}	6.99 ± 0.21^b	5.59 ± 0.10^a
Tg	2.43 ± 0.09 ^{c}	1.78 ± 0.09^b	1.35 ± 0.05^a
Ch	5.19 ± 0.25 ^{c}	4.03 ± 0.18^b	3.33 ±0.06^a
HDL	0.75 ± 0.02 ^{b}	1.08 ± 0.12^b	1.94 ± 0.15^a
LDL	3.75 ± 0.21 ^{b}	3.15 ± 0.22^b	1.56 ± 0.33^a
Atherogenic index	7.14 ± 0.46 ^{b}	5.74 ± 0.59^b	3.82± 0.62^a
VLDL	0.45 ± 0.02 ^{c}	0.35 ± 0.02^b	0.27 ± 0.01^a

Values are mean±SE. Different letters horizontally means significant difference between the groups and at $P \leq 0.05$.

light clothing and without shoes. Accurate balance scales were used and weight was recorded to the nearest 0.1 kg. Height was recorded to the nearest centimeters using measuring rod in the same room, also waist and hip were recorded. Subject was breathed quietly and normally; dresser marker measuring tapes was used tacking care that it was applied horizontally. Waist girth was measured at the mid point between iliac crest and the lower margin of 10th ribs. An approximate indicator of this level was ascertained by asking the subject to bend sideways. Hip girth was recorded as the maximum circumference around the buttock posteriorly and indicated anteriorly by symphysis pubis.

Modified Oral Glucose Tolerance Test (OGTT) was done; by a standard 75g oral glucose given to the subject after 10-12 hr overnight fasting at day 2 or 3 of menstrual cycle. Venous blood sample was taken before and 2 hr after glucose load for fasting (FBS) and postprandial blood sugar (PPBS) measurements.

High Fat Meal Test; The high fat meal was carried out 3 days after the OGTT, after 10-12 hr overnight fast, in the morning (about 8:30 am) the subject were given a high fat meal consisting of 66% as fat, 18% as carbohydrate, and 16% as protein. It consisted of wheat bread with margarine and pasteurized cream, whole milk and cooked egg. Blood samples for triglycerides, cholesterol and HDL were drawn before the meal and at (4, 5 and 6 hrs) after meal without allowing further eating.

Biochemical Assessment; venous blood 5ml taken each time, the sera separated for determination of fasting lipid profiles (total cholesterol, total triglyceride (Tg), LDL cholesterol, very low density lipoprotein-cholesterol VLDL, HDL cholesterol) and atherogenic index was determined. Serum was stored at 20^{o}C for hormone analysis (LH, FSH, and Testosterone). They were determined by combines an enzyme immunoassay sandwich method with a final florescent detection (ELFA). Results are automatically calculated by VIDAS in relation to the calibration curve stored in memory and then printed out.

Lipid Profile; Serum Tg and Cholesterol (Ch) were determined by commercial enzymatic methods, kit used was Biomerieux Ltd., France. HDL was measured after precipitation of chylomicrons and lipoproteins of very low-density lipoprotein (VLDL), and LDL with phosphotungstic acid and magnesium ions (Biomerieux, France). Values determined as follow; VLDL =Tg/5, LDL = Total cholesterol - (HDL + VLDL), and Atherogenic index = Cholesterol / HDL.

Table2. 6hr postprandial triglyceride for PCOS groups and control.

Groups	Tg (6hr. mmol/L)
Overweight PCOS	16.75 ± 1.46ab
Normal weight PCOS	13.61 ± 3.02ab
Control	9.95 ± 1.71

Different superscripts (a and b) represent statistically significant differences between the groups at $p<0.0001$. a. Overweight or normal weight vs. controls, b. Overweight vs. normal weight.

Table 3. Response to ovulation induction by 200mg CC in PCOS groups.

Parameters	No response	Positive response	P-value	Significance
BMI	26.79 ± 0.51	24.31 ± 0.59	< 0.01	S
Testosterone	2.40 ± 0.20	2.13 ± 0.14	> 0.05	NS
LH/FSH	2.03 ± 0.05	1.91 ± 0.04	> 0.05	NS
W/H	0.86 ± 0.03	0.86 ± 0.02	> 0.05	NS
FBS	6.53 ± 0.25	5.58 ± 0.28	< 0.05	S
GTT	8.73 ± 0.32	7.63 ± 0.32	< 0.05	S
Tg	2.41 ± 0.08	1.89 ± 0.11	0.001	S
CH	5.19 ± 0.24	4.20 ± 0.21	< 0.01	S
HDL	0.69 ± 0.01	1.07 ± 0.10	< 0.01	S
LDL	3.79 ± 0.22	3.22 ± 0.21	> 0.05	NS
ATH	7.56 ± 0.33	4.82 ± 0.57	0.001	S
VLDL	0.45 ± 0.02	0.36 ± 0.02	< 0.01	S

Note: Values are mean ± stander error mean (SEM) significant difference between groups at $P \leq 0.05$

Lipid Profile Normal Range for our lab was; Serum cholesterol (3.9-6.5) mmol/L, Tg (0.9-2.4) mmol/L, HDL (0.9-1.4) mmol/L, LDL (1.8-4.3) mmol/L, VLDL (<0.93) mmol/L, and Atherogenic index (<5).

Glucose tolerance (GT) was assessed by WHO criteria. The subjects were classified into the following three groups: Non diabetic group with FBS <6.1 mmol/L or 2 hour blood sugar (2hr BS) <7.8 mmol/L, Diabetic group with FBS≥7.8 mmol/L or 2hr BS≥11.1 mmol/L following OGTT, and impaired Glucose Tolerance (IGT) group included subjects who had 2hr BS values ranges from 7.8-11.06 mmol/L following OGTT.

Induction of Ovulation; CC was used in induction of ovulation, it was orally administered by the women in a maximum dose of 200 mg in 2 divided dose for 5 days from day 2 of the menstrual cycle for 4 months (patients previously failed to ovulate in smaller dose). During each cycle, determination of mature follicle was attempted by serial ultrasounds every other day. Evidence of follicular growth of at least a single dominant follicle obtained by ultrasound at mid cycle 5-10 day after the last dose of CC (mature follicle considered when 17-22 mm was the diameter).

RESULTS

The clinical and biochemical characteristics of normal weight, overweight PCOS groups and control group were summarized in table1. Results of the three groups were also compared using Duncan multiple range test at $p \leq 0.05$.The results showed that there was no significant difference in mean age; between PCOS group and control group, while PCOS group had significantly higher waist-to-hip ratio than control group (over weight vs. control) and (non obese vs. control). FBS and 2hr PPBS level were significantly higher in PCOS normal weight women than control and much higher in PCOS overweight women.

Table 4. Response to 200mg CC in both normal and overweight PCOS groups

CC response	Total	Normal weight No. (%)	Overweight No. (%)
Positive(CCR)	26	19 (73)	7 (27)
Resistant(CCr)	24	6 (27)	18 (73)
Total	50	25 (100)	25 (100)

Table 5. CCR to 200mg CC in women with IGT test and NIDM

CC Response	Normal PG 2h No.□(%)□	I GTT 2h No.□(%)	Diabetic No.□(%)	P-value
Positive(CCR)	18□(81.8)	8□(33.4)	0□(0)	P < 0.05
Resistant(CCr)	4 (18.2)	14□(66.6)	6□(100)	
Total	22□(100	22□(100)	6□(100)	

The lipid profile, fasting Tg and Fasting total cholesterol levels were significantly higher in PCOS groups and the highest value was observed in overweight subjects (overweight vs. non-obese) and (overweight vs. control). Fasting HDL levels were significantly lower in PCOS groups but no significant differences within PCOS groups were observed. VLDL and LDL levels were significantly higher in PCOS groups and significant differences were observed between control and PCOS groups. Atherogenic index was significantly higher in PCOS groups between the control and PCOS groups.

The result of Pearson correlation analysis in overall PCOS groups shows: A significant correlation;($p<0.0001$) between BMI and Tg, ($p<0.01$) between W/H and Tg , ($p<0.01$) between testosterone and Tg , ($p<0.0001$) between FBS and Tg ,and ($p<0001$) between 2h PG and Tg . Postprandial Triglyceride Response in the 2 PCOS groups and control were summarized in Table 2. Results showed significant difference between overweight PCOS groups and normal weight PCOS group with control ($p<0.0001$). On the other hand, a significant difference between the two PCOS groups was found at ($p<0.0001$).

The responses to induction of ovulation by 200mg CC (CCR) in PCOS women are summarized in Table 3. There was a significant difference to CCR in relation to BMI at $p<0.01$, A significant differences to CCR was noticed in relation to; FBS, and 2hrBS at $P<0.05$. Also CCR showed significant differences in relation to the lipid profile (Tg, cholesterol, HDL, and VLDL) at $P<0.001$, and the atherogenic index at $P<0.001$. On the other hand there was no significant difference between CCR with LDL.

CCR in relation to weight is shown in table 4. From the 25 normal weight PCOS patient 19 (73%) had a CCR, while 6 (27%) were CCr. On the other hand from the 25 overweight PCOS patient, 7 (27%) had CCR and 18 (73%) were CCr.

CCR in; IGTT and NIDDM is shown in Table (5).

Table 6. CCR to 200mg CC in women with abnormal total cholesterol Tg, HDL, VLDL, LDL, and Atherogenic index.

CC Response	Normal No.□(%)	Abnormal No.□(%)	P-value
Ch /CCR	21□(77.8)	5□(21.8)	(< 0.01) S.□
Ch/CCr	6□(22.2)	18□(78.2)	
Total	27□(100)	23□(100)	
Tg /CCR	22□(62.2)	4□(28.6)	(< 0.05) S
Tg/CCr	14□(38.8)	10□(71.4)	
Total	36□(100)	14□(100)	
HDL /CCR	16□(84.3)	10□(32.3)	(< 0.0001) S□
HDL/CCr	3□(15.7)	21□(67.7)□	
Total	19□(100)	31□(100)	
VLDL/CCR	21□(56.8)	5□(38.5)	(> 0.05) NS
VLDL/CCr	16□(43.2)	8□(61.5)	
Total	37□(100)	13□(100)	
Atherogenic index/CCR	5□(72.5)	11□(37.9)	(< 0.0001) S
Atherogenic index/CCr	6□(28.5)	18□(62.1)	
Total	21□(100)	29□(100)	

PCOS patients were divided into 3 groups according to the WHO criteria, 1st group whose BS 2h were normal, 2nd group were IGTT, and the 3rd group were NIDDM. There was good CCR in the 1st group 81.8%, in the 2nd group it was only 33.4%, and there was no response in the diabetic group.

CCR in women with Abnormal Lipid Profile is presented in Tables 6: In PCOS groups with abnormal and normal cholesterol level, 21.8% and 77.8% had CCR respectively, with a significant difference at $P < 0.01$. The normal and abnormal Tg of PCOS groups showed 62.2%and 28.6% respectively in CCR with significant difference at ($p<0.05$). Also there was significant difference observed between CCR in normal and abnormal HDL (84.3% and 32.3%) were responders subsequently at ($p<0.0001$), there was difference observed between normal and abnormal VLDL of PCOS groups in CCR, as 62.5%, and 10.0% subsequently showed positive CCR ($p<0.01$), but there was no significant difference between normal and abnormal LDL of PCOS groups in CCR ($p>0.05$), as the normal LDL PCOS women showed higher percent (56.8%) than abnormal LDL PCOS women (38.5%). Significant difference was observed between normal and abnormal atherogenic index in CCR ($p<0.0001$) as 72.5%, and 37.9% showed CCR subsequently.

DISCUSSION

Research in the last decade has revealed metabolic stigmata in premenopausal women with PCOS, such as hypertriglyceridemia, hyperinsulinemia and insulin resistance (21).In this study evaluation of the post prandial lipemia in PCOS women, and the respective role of waist to hip ratio (as an indicator of abdominal fat distribution) on the post prandial lipemia response to high fat containing meal. Women who are clinically and biochemically defined as PCOS(both normal weight and over weight groups) found to have higher levels of triglyceride and cholesterol, LDL, VLDL and atherogenic index were found to be significantly, and lower level of HDL.

Risk factors that predispose to heart disease in PCOS patients include dyslipidemia, impaired glucose tolerance, android obesity, hyperandrogenism and hypertension (20). So women with PCOS appear at increased cardiovascular risk due to in part dyslipidemia characterized by increase plasma Tg and reduced (HDL) and they speculate that altered activity of hepatic lipase or lipid transfer production could explain this aspect of the dyslipidemia (21). This study showed a positive correlation between fasting lipid profile and FBS at $P < 0.0001$.

Hyperinsulinemia (insulin resistance) appears to be the most important contribution to the lipid abnormalities particularly the elevation on triglycerides, approximately one half of patients with PCOS demonstrate insulin resistance (23), patients with insulin resistance and normal pancreatic B cell function will develop hyperinsulinemia detected either basally, or following a glucose challenge (23).

Hyperandrogenism in women results in higher mean serum Tg and VLDL cholesterol levels, but lower HDL cholesterol levels (23). The postprandial lipemia response to a high fat containing meal in this study was positive in all PCOS women, starting at higher threshold for Tg as mentioned in Table 1, and they had higher postprandial Tg response than controls. A striking observation from this study was noticed that non-obese PCOS group had a higher postprandial triglyceride response than did non-obese control suggesting that even in absence of obesity, early lipid abnormalities could be present(24).

The fact that postprandial lipaemia persist for 3-6 h after meal and is exacerbated by the next meal emphasize the concept that humans are in a postprandial state for most of each 24 h (25). In both groups of the PCOS a significant correlation was found at $P < 0.0001$ between postprandial Tg response and waist to hip circumference ratio. Postprandial Tg has been found to be positively correlated with intra abdominal fat in obese women, until now there have been one report dealing with postprandial lipemia in PCOS patient, which showed abnormal postprandial pattern in non obese subjects with android body fat distribution, suggesting that over weight per-se was not the only determinant of the lipid abnormalities in PCOS women (22). This study confirmed that postprandial increase in Tg is directly related to its fasting serum concentration

and serum 2h-BS .Hyperinsulinemia leads to increase fasting and postprandial triglycerides levels(17), and some authors concluded that postprandial hypertriglyceridemia is associated with increased carotid IMD in patients with type 2 diabetes and that postprandial hypertriglyceridemia>2.27 mmol/L may be atherogenic, positive correlation between the postprandial Tg response to an oral lipid and carotid artery wall thickness has been reported(24). These studies suggest that prolonged presence of triglyceride-rich lipoproteins in plasma may indeed play a role in atherogenesis (25).

PCOS is associated with infertility due to an ovulation caused by this disorder. Many treatments can increase both ovulation and fertility rates in these women (7). PCOS women classified into group II according to WHO classification system, CC initiation of ovulation is the treatment of choice in this group of anovulatory women (26). In this study 52% of PCOS patient had response to CC and 16% of them get pregnancy, in recent study by Marilyne et al; CC administration result in; ovulation in 50- 60% of PCOS patients, pregnancy in 30%, and multiple gestation in 3% (27). While in another study by Elizabeth Anna approximately 80% of women with PCOS will ovulate with CC treatment, and roughly 60% will conceive (7). It is author tendency not to exceed 150 mg daily as the likelihood of achieving conception above this dose is poor, and are usually best treated with gonadotropin (12),but this is expensive and the condition in the country let to use maximum dose of CC in this study ,and this might be the cause of low percentage of ovulation in response to CC.

Also this study showed that women with IGT test and NIDDM were CCR more than PCOS patients with normal FBS and 2h-BS (18.2%, 66.6%subsequantly), the 6 diabetic patients (8%) were resistance subsequently, and 73% of these patients with CCR were over weight. It is more likely that hyperinsulinemia and insulin resistance contribute to the mechanism of ovulation (20), so all over weight, anovulatory women with polycystic ovaries are hyperinsulinemic, more CCR, and the best therapy for these women who are obese is weight loss and insulin-sensitizing agents alone or as adjuvant to CC (7).

Dyslipidemia in PCOS women has been reported by several studies, elevated free fatty acid, Tg and LDL levels and reduced HDL levels relative to age, sex and weight match control subject were found, insulin rather than androgen levels are correlated with lipid abnormalities (25).

In this study there was a positive correlation between abnormal lipid profile and abnormal FBS and/or 2hrPPBS levels, and evaluation of response to CC on the PCOS patients with abnormal lipid profile was assessed; there was a significant difference in CCR between women with; normal and abnormal cholesterol levels at $p<0.01$, normal and abnormal Tg levels at $p<0.05$, normal and abnormal HDL levels at $p<0.0001$, normal and abnormal VLDL levels at $p<0.01$, normal and abnormal atherogenic index levels at $p<0.0001$,and no significant difference in normal and abnormal LDL levels at $p>0.05$.This type of work had not been done before, so the results could not be compared with others.

CONCLUSION

Hyperinsulinemia and insulin resistance contributes to ovulatory disturbance and hyperandrogenism that is characteristics of PCOS, may also lead to decrease CCR to ovulation induction in PCOS women. PCOS women with IGTT, NIDDM and abnormal lipid profile had more CCR in ovulation induction than those with normal BS and lipid profile, PCOS women had fasting and postprandial hypertriglyceridemia, which is directly related to high waist-to-hip ratio and insulin resistance regardless of obesity. This justify intervention trials to asses the benefits of lowering hyperinsulinemia by losing weight and using of insulin sensitizing agents in order to achieve a good response to ovulation induction methods.

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