A RANDOMIZED CONTROL TRIAL COMPARING METFORMIN VERSUS METFORMIN PLUS CALCIUM LACTATE AMONG POLYCYSTIC OVARIAN DISEASE WOMEN ON MENSTRUAL REGULARITY

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ABSTRACT

The prevalence of polycystic ovarian syndrome (PCOS) in reproductive age women is around 8% to 13%. Many treatment options are available for PCOS associated symptoms including obesity, abnormal glucose metabolism, infertility, menstrual irregularity and hyperandrogenism. Double blinded, randomized clinical trial (RCT) was conducted on 302 PCOS women who referred to subfertility and gynaecology clinic, Teaching hospital, Kandy. Interviewer administered questionnaire was used for data collection. Mean age of the PCOS population was 30.82(SD=4.76) years and mean BMI was 27.64(SD=3.06kg/m^2).Majority were overweight (67.9%) and the obesity prevalence was 13.2%. 8.94% had regular menstrual cycles and the majority were with irregular cycles (91.1%). 73.9% were oligomenorrheic, while 17.2% were amenorrhoeic among PCOS. The prevalence of acne was 70.2%. Hirsutism and acanthosis nigricans occurred in 66.89% and 55.29% of patients, respectively. In this study, 17.88% (n=54) were calcium deficient and 15. 23% were having impaired fasting glycaemia. 5.62% (n=17) of them were Diabetics. After treatment menstrual regularities were not significantly different between two groups. (p=0.477) But, the percentage difference within each group was statistically significant t(p=0.000). Both groups had a significant effect in their treatment while a notable better improvement on menstrual regularity observed within Metformin plus calcium group. Although the after treatment-BMI, among the groups was not significant (p=0.380), BMI reduced almost significantly within each group with their treatments. (p=0.000) Better reduction was seen with metformin plus calcium group.This trial showed an improvement with calcium on metformin in menstrual regularity and BMI in PCOS patients. Adding of cheap, safe and freely available calcium on metformin in Sri Lankan population would bring better clinical outcomes.

Key words: polycystic ovary syndrome, Calcium, Metformin, Menstrual regularity

INTRODUCTION

The prevalence of Polycystic ovarian syndrome (PCOS) in reproductive age women is around 8% to 13%. [1,2,22] Rotterdam European Society for Human Reproduction suggested in 2003, that to diagnose PCOS needs to have two out of three criteria: oligo /anovulation, excess androgen (clinical/biochemical) and polycystic ovaries on gynecologic ultrasound. According to new guidelines in November 2015 by the American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), and Androgen Excess and PCOS Society (AES) diagnostic criteria for PCOS includes two of the following three criteria: chronic anovulation, hyperandrogenism (clinical/biologic), and polycystic ovaries. [3] The presence of ≥10 cysts measuring 2–8 mm around a dense core of stroma or scattered within an increased amount of stroma is taken as polycystic ovaries by pelvic ultrasound. [4] PCOS is a disease with unknown etiology, but suggested to have genetic and environmental influences. Among first-degree relatives of PCOS women (mother or sister) hyperandrogenism and insulin resistance are commonly seen. [5] Environmental factors like diet, lifestyle is also important. *CYP11A* gene, insulin gene, and a region near the insulin-receptor gene are suggested as possible genes for the pathogenesis of PCOS. [6] In adipocytes, glucose transport and antilipolysis are impaired due to abnormal insulin action although insulin binding is normal. Excess insulin causes hyperandrogenemia. Ovarian theca cells increase their androgen production in response to elevated insulin level. Insulin increases granulosa cells' response to
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Luteinizing hormone (LH)leads to abnormal follicular differentiation, premature follicular arrest, and anovulation. Excess androgen causes decreased Sex hormone binding globulin(SHBG)level. Greater free androgen level is responsible for a greater clinical outcome (acne. hirsutism). Evidence of clinical hyperandrogenism can be seen among most of PCOS patients. Gonadotropin dynamics are altered and a higher LH pulse and amplitude is commonly seen in PCOS women. [7] Although more androgen is produced by ovarian theca cells due to elevated LH level, reason for anovulation may be low follicle-stimulating hormone (FSH). The LH / FSH ratio is increased among most of PCOS women; But, However, in obese women with PCOS the mean LH pulse amplitude is reduced. [8] 50%–70% of women with PCOS women will get number of co-morbidities due to insulin resistance. Menstrual disturbances in PCOS include mainly oligomenorrhea and amenorrhea. 30% of PCOS women are having no menstrual irregularities. 85%–90% of oligomenorrhic and 30%–40% of women with amenorrhea will have PCOS. In current practice, PCOS treatment involves weight management, correction of menstrual irregularity, preventing insulin resistance, and if necessary, fertility treatment. Reduction of weight has been associated with improvement of insulin resistance and menstrual regularity. Adipose tissue is a precursor of additional estrogen, so a decrease in weight and adipose loss results in alteration of hormones that affect the menstrual cycle and improves menstrual regularity.

METHODS

The randomized clinical trial was conducted on PCOS women who referred to subfertility clinic, gynecology clinic, ward 6, Teaching hospital, Kandy from September 2016 to September 2018.

The inclusion criteria were:

Patients with PCOS were diagnosed according to Rotterdam criteria:

- Oligo-ovulation or anovulation, clinical and/or biochemical hyperandrogenism .
- Polycystic ovaries in ultrasound examination.

The exclusion criteria were:

- Patients with other menstrual disorders (e.g.-hypothyroidism, cervical polyp)
- Patients who are contraindicated for metformin, calcium.
- Diagnosed patients with medical or surgical diseases associated with hypocalcaemia.

The clinical evaluation involved a questionnaire-based interview. Patients were interviewed regarding their socio-demographic characteristics, menstrual history and clinical features of hyperandrogenism. History and clinical examinations were carried out by an intern house officer or relief house officer available at the particular clinic and documented in their clinical records as well as a data collection sheet. Demographic characteristics were name, age, date of birth and ethnicity. Extensive menstrual history was taken and classify patients into menstrual regularity, oligomenorrheric, amenorrhearic and other menstrual disorders. The average menstrual cycle is 28 days long. The regularity of menses assessed according to cycle interval. Cycles from 21 to 35 days were taken as menstrual regularity.Oligomenorrhea defined as a menstrual cycle lasting >35 days. Amenorrhea was defined as no menstruation for 6 months. A small calendar was given to all participants to mark their menstrual days to avoid recall bias of women`s menstrual history. It made much easier to take data on menstrual regularity with that especially after the treatment.

Physical examination included height, weight, and features of hyperandrogenism such as the presence of hirsutism, acne, AN. Weighing was carried out on patients with no foot ware using a calibrated weighing machine. Two readings were taken and get the average. A trained clinic nursing officer or attendant did these measurements. In measuring heights, mothers are made to stand on an even surface on the floor against a wall on which a measuring tape is mounted. Again two measurements were taken and get the average to calculate BMI according to formula (weight in kg)/height in m2. Calculated BMI values were classified according to The World Health Organization(WHO) BMI categorization.

The mFG score was used to grade hirsutism after assessing terminal hair.23 It was assessed using a scale from 0 to 4over nine body areas such as chin, upper and lower abdomen, upper lip ect. Terminal hair was identified by its nature: coarse, pigmented and longer than 5mm.The presence of acne was noted in the history and clinical examination.AN was diagnosed by the appearance of a velvety, dark, skin thickening over skin folds such as the posterior and lateral folds of the neck, axillae, knuckles, etc. It was assessed on neck, axillae, face and knuckles and documented in the data collection sheet. Computer generated block randomization in excel is used to divide the population into two groups. Metformin plus calcium group named as group I and other named as group II. The available senior house officer at the clinic prescribed calcium 1tablet(300mg) tds with metformin 500mg bd for the group I and metformin 500mg bd for the group II. Effects of treatment on menstrual regularity

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and BMI after six months were evaluated in both groups. Menstrual regularity was assessed by history and the calendar given to them to mark their menstrual days. It was done by the Senior house officer or relief house officer at the clinic. At the same time the individual was assessed again for height, weight and BMI was calculated. The mean BMI of two groups after six months of treatment was calculated. Throughout the study period Main Investigator (MI) and Patient were kept blind. Data were assessed for the distribution and it was within the normal distribution. The independent T test is used to see the difference in continuous (interval data) like fasting blood sugar, BMI between the two groups. Categorical data were assessed for the difference by the chi - square test. The percentage difference and percentage improvement were calculated in both groups. The differences between the groups I and group II before and after the treatment were measured by using Chi-Square test. Percentage of menstrual regularity within each group was assessed before and after the treatment with the chi - square test. The differences between BMI in the two groups with the treatment were measured by using t tests. BMI was assessed within each group before and after the treatment with the paired t test. The statistically significant level was taken as $p<0.05$

RESULTS

Data from 302 PCOS patients was collected. Two groups were divided by block randomization.145 patients were included in group I while 157 patients into group II. The actual dropout rate, including pregnancies was 10.26%. The total pregnancy rate in the study population is 6.9% (n=21). More pregnancies were noted among patients with regular menstrual cycles previously. For the comparison of treatment effect, there were 127 patients in group 1 and 144 in group II.

Irregular menstrual cycles were observed in 275 (91.1%). Out of them 223(73.9%) were oligomenorrheic while 52(17.2%) were amenorrheic. Almost all the cases in group I,133(91.7%) and group II 142(90.4%) had experienced irregular menstrual cycles prior to study. Among calcium plus metformin group PCOS patients, 110 (75.9%) of them experienced oligomenorrhea (Figure 2).

Mean calcium concentrations in group 1 and group II were 2.34±0.13 and 2.33± 0.14 mg/dl respectively. In this study, 54 (17.88%) women were Calcium deficient; that is 25 (17.24%) and 29 (18.47%) women in groups I and II respectively. None of the patients were previously diagnosed with Diabetes mellitus, prior to the recruitment. Mean fasting glucose in the study population was 92.08±13.04mg/dl. A group I had a mean of 91.90±13.02mg/dl, while group II had a mean of 92.25±13.11mg/dl. In metformin plus calcium group had 116 (80%) of normal glycaemic PCOS population and metformin only group had 123(78.3%). This study has found IFG in 46 (15.23%) patients and in diabetic range in another 17 (5.62%). 21 (14.5%) patients Group I and 25 (16%) patients in group II had impaired fasting glucose levels. Out of 145,8 (5.5%) were diagnosed to have type II diabetes mellitus in metformin plus calcium group while 9 (5.7%) out of 157 were found to have diabetes in the metformin only group. Mean calcium level in the population was2.34±0.13mmol/L and it was within the normal range.
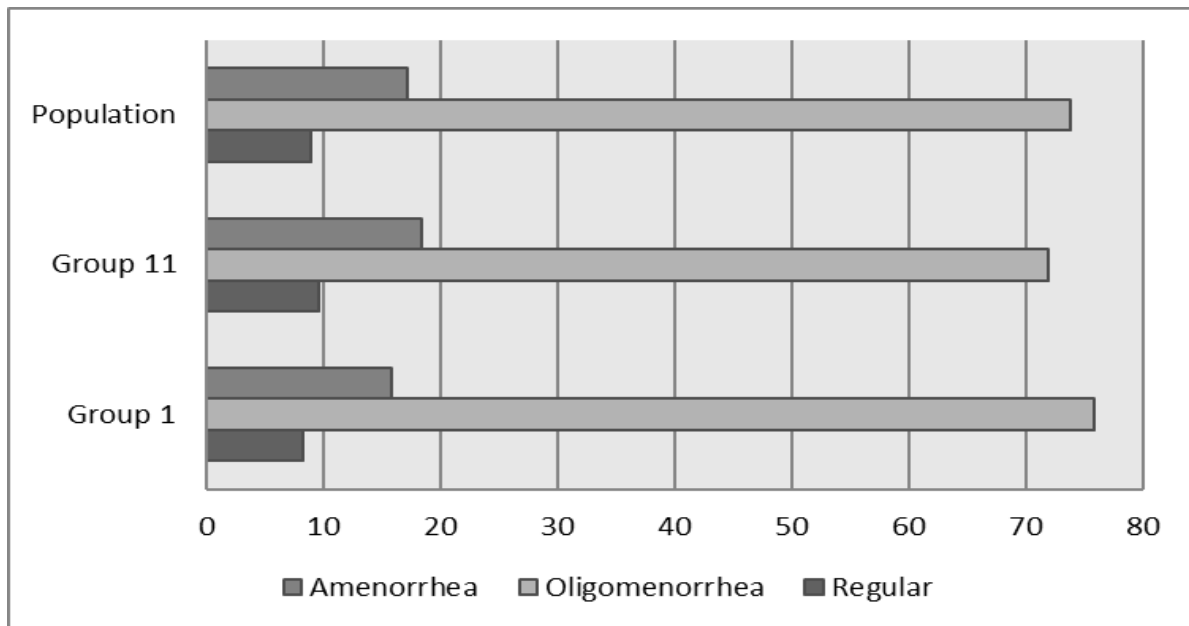
Figure 2 -Prevalence of menstrual pattern in PCOS

In this study, 54 (17.88%) women were Calcium deficient. Mean calcium level in group I and II were 2.34±0.13mmol/l and 2.33±0.14mmol/l, respectively. In group I 25 (17.24%) patients were calcium deficient and in group II, it was 18.47% (Table 1).

	Group I Metformin+Calcium	Group II Metformin	Population
Calcium level (mmol/l)			
Mean	2.34	2.33	2.34
SD	0.13	0.14	0.13
Calcium deficiency			
Present	25(17.24%)	29(18.47%)	54(17.88%)
Absent	120(82.76%)	128(81.53%)	
Fasting glucose (mg/dl)			
Mean	91.90	92.25	92.08
SD	13.02	13.11	13.04
Normal	116(80%)	123(78.3%)	239(79.15%)
Impaired fasting	21(14.5%)	25(16%)	46(15.23%)
DM	8(5.5%)	9(5.7%)	17(5.62%)

Table 1: Calcium level and fasting blood sugar in PCOS

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Although, 81.45%(224/275) of PCOS patients within BMI $\geq$ 25kg/m^2 group had menstrual irregularity, there was no significant association between menstrual irregularity and BMI $\geq$25kg/m^2(p=0.641) and calcium deficiency (p=0.822). Among dysglycemic patients, 95.23%(n=60) were having irregular menstrual cycles. There was no significant association of obesity and calcium deficiency ((p=0.645). No significant association between obesity and dysglycemia was detected in this study (p=0.357). There was no significant association between calcium deficiency and dysglycemia (p=0.889) (Table 2).

	Group I Metformin+Calcium	Group II Metformin	P Value
Age(years)	31.09 $\pm$ 5.09	30.58 $\pm$ 4.43	0.356
Height(cm)	151.78 $\pm$ 3.58	151.45$\pm$ 3.90	0.439
Weight (kg)	64.00$\pm$8.66	63.22$\pm$7.21	0.397
BMI (kg/m^2)	27.75 $\pm$ 3.40	27.54 $\pm$ 2.72	0.544
FBS(mg/dl)	91.90$\pm$13.02	100.64$\pm$13.64	0.812
Serum calcium(mmol/l)	2.34$\pm$0.13	2.33$\pm$0.14	0.743
Regular cycles	8.3%	9.6%	0.488
Acne	71.7%	68.8%	0.797
Hirsutism	65.5%	68.2%	0.231
Acanthosis nigricans	54.5%	56%	0.135

Table 2: Comparison of Clinical and biochemical variables among two PCOS groups.

Irregular menstrual cycles were observed in 100(36.9%) out of 271 PCOS patients in the study. In group I 36 (28.3%) patients and group II 64(44.4%) had experienced irregular menstrual cycles after the intervention. In the study population, 171 (63.1%) patients had a menstrual regularity after the treatment. Menstrual regularity was observed after six months of intervention in 91 (71.7%) in group I and 80(55.6%) in Group II. The numbers of subjects who dropped out of the study were 18 of 145 (12.41%) in the metformin plus calcium group and 13 of 157 (8.28%) in the metformin group. During the study, 11 pregnancies were detected in group 1(7.59%) and 10(6.37%) in group II. The total pregnancy rate in the study population is 21 (6.9%). More pregnancies were detected among who had regular cycles previously (Table 3).

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	Group I Metformin+Calcium	Group II Metformin	Population
Before intervention			
Irregular	133(91.7%)	142(90.4%)	275(91.1%)
Oligomenorrhea	110(75.9%)	113(72%)	223(73.9%)
Amenorrhea	23(15.8%)	29(18.4%)	52(17.2%)
Regular	12(8.3%)	15(9.6%)	27(8.9%)
After treatment			
Irregular	36(28.3%)	64(44.4%)	100(36.9%)
Regular	91 (71.7%)	80(55.6%)	171(63.1%)
Pregnant	11(7.59%)	10(6.39%)	21(6.9%)
Dropouts	7	3	10
Total dropout preg. women.	18(12.41%)	13(8.28%)	31(10.26%)

Table 3: Menstrual pattern with the treatment

Menstrual regularity was reported six months after the intervention in 71.7% of the patients in group I and 55.6% of the patients in group II. With the treatment of metformin plus calcium menstrual regularity was improved from 8.3% to 71.7%. Metformin only group showed a menstrual cycle regularization from 9.6% to 55.6%. The percentage difference and percentage improvement in group I were 63.4%& 763.85% and in group II were 46%& 479.17%. Therefore, menstrual regularity has improved in both groups, but there was a more obvious improvement in Metformin plus calcium group. There was significant difference of menstrual regularity among the two groups after the treatment (p = 0.477). After the treatment, percentage of menstrual regularity change within the group was assessed by the chi - square test. Metformin plus calcium as well as metformin treatment in PCOS improved the menstrual regularity significantly in both groups(p<0.05). Therefore both treatments were effective on menstrual regularity (Table 4 & 5).

Improvement of menstrual regularity			
	Group I Metformin+Calcium	Group II Metformin	P value
Regulated menstrual cycle			
Before treatment	8.3%	9.6%	0.488
After treatment	71.7%	55.6%	0.477

Table 4: Effect of the treatment on menstrual regularity among the groups

Improvement of menstrual regularity - Regulated menstrual cycle				
	Before	**After**	**Percentage Difference**	**P value**
Group I Metformin+Calcium	8.3%	71.7%	63.4%(763.85%)	0.000
Group II Metformin	9.6%	55.6%	46%(479.17%)	0.000

Table 5 : Effect of the treatment on menstrual regularity

Out of 271 PCOS patients after the intervention, a total of 82(30.3%), i.e. 40(31.5%) in group I and 42(29.2%) in group II, were non-obese within normal BMI, as many as 174(64.2%), i.e. 79(62.2%) in group I and 95(66%) in group II, were overweight, and the rest of them 15(5.5%), i.e. 8(6.3%) in group I and 7(4.8%) in group II, were obese. Majority of PCOS patients were in the study were overweight.(64.2%) as before. (Table 5.10) (Figure 3).
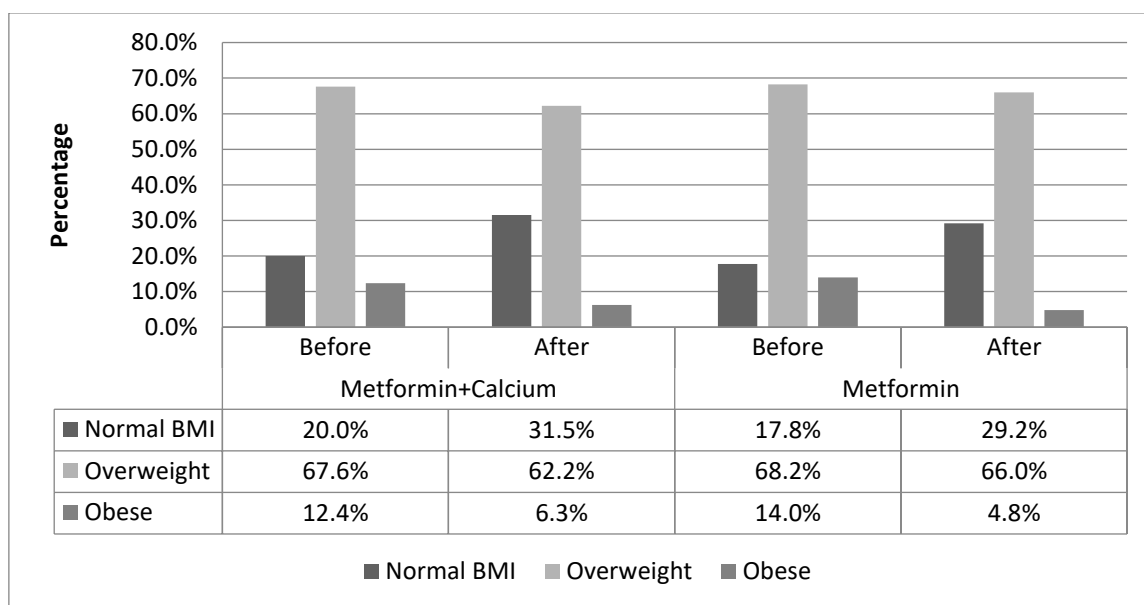

	Before	After	Before	After
	Metformin+Calcium		Metformin	
■ Normal BMI	20.0%	31.5%	17.8%	29.2%
□ Overweight	67.6%	62.2%	68.2%	66.0%
■ Obese	12.4%	6.3%	14.0%	4.8%

Figure 3: Comparison of BMI changes after intervention

With the intervention of metformin plus calcium, BMI was improved by 1.55kg/m^2 in Group I. It was a 5.59% reduction in BMI with the intervention. Metformin only group showed a reduction of BMI by 1.05kg/m^2 and it was a 3.81% reduction. Therefore, BMI has improved in both groups, but there was a more obvious improvement in Metformin plus calcium group over metformin group (5.59% Vs 3.81%). BMI was assessed within the group before and after the treatment with the paired t test. It showed both groups had a significant change in BMI with their intervention. Therefore, both treatments were effective on BMI. (p<0.05) (Table 6 & 7).

	Group I Metformin+Calcium	Group II Metformin	P value
Before	27.75 $\pm$ 3.40	27.54 $\pm$ 2.72	0.544
After	26.20$\pm$2.95	26.49$\pm$2.23	0.380

Table 6: Effect of the treatment on BMI among the two groups

	Before	After	Improvement	P value
Group I Metformin+Calcium	27.75 $\pm$ 3.40	26.20$\pm$2.95	1.55	0.000
Group II Metformin	27.54$\pm$ 2.72	26.49$\pm$2.23	1.05	0.000

Table 7: Effect of the treatment on BMI within the group

DISCUSSION

In Sri Lankan setting, there is a resource limitation, particularly for biochemical tests like free testostorne, SHBG, free androgen index(FAI) etc. Recent PCOS guideline states a comprehensive history and clinical examination need to be done for clinical hyperandrogenism.[23]Clinical assessment of hypeandrogenism to diagnose PCOS was used due to three reasons: (1)Clinical assessment by FG score detects more patients compared to serum testosterone[24], (2) testosterone level does not correlate with degree of clinical symptoms (3).

In Sri Lankan cross sectional study, the prevalence of hirsuitism was74.6%[22] and this study, had a prevalence of 66.89%. In 2014, a Sri Lankan case-control study of 100 women, assessed the markers of hyperandrogenism and it had a prevalence of 76%. [24] All studies were assessed it with a similar criteria, as mFG cutoff scores are the same across ethnicities. [23] There might be an underestimation of hirsutism in this study population (66.89%) as relief house officers, house officers have different ability to differentiate terminal hair (pathological hirsutism) vs vellus hair.

Acne was present in 39.2% of patients in Sri Lankan cross sectional study[22] while this study showed a higher prevalence of 70.2%. In the mentioned previous study recorded the acne by area(s) of distribution and degree of affection (mild, moderate, severe). It included lesions like comedones, papules, pustules, ect. Present study, it was assessed by history and examination. Such difference in acne between the studies might suggest, there could be recall bias and the patient`s knowledge on its appearance in this study and importance of having a universally accepted visual evaluation method for acne.[23] It might lead to a higher prevalence of acne. Among clinical features of hyperandrogenism, hirsutism was the mainstay of expression in Sri Lankan study.[22]

Irregular menstrual cycles were observed in 91.1% in the study and it was comparable to the Sri Lankan cross sectional study (92.32%). Patients with irregular menses

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73.9% were oligomenorrheic while 17.2% were amenorrheic. Only 8.94% had menstrual regularity. The prevalence of menstrual regularity in two Iranian studies were very low (3%)[12,13].That finding might be due to smaller sample sizes(60 and 100 patients respectively)

The case-control study done in Iran[13]and descriptive cross sectional study in Sri Lanka[22]found a mean BMI of $28.21kg/m^2$ and$26 kg/m^2$ respectively. In the present study it was 27.64 ± 7.94. It was lower than the non-South Asian studies.[12,13] South Asians with PCOS are with comparatively low BMI but has a higher prevalence of metabolic syndrome.[34]Sri Lankan study shows 30% of patients above the BMI of 27.5 kg/m2 and 16% were$> 30 kg/m^2$.This study showed 6.3% in the obese group, but the majority were in the overweight group. In this study, prevalence $>27.5kg/m^2$ was not assessed to compare with the Sri Lankan study. These current results of this study, further strengthen of having a smaller body habitus in South Asians.

Mean calcium level in the population was 2.34 ± 0.13mmol/l and it was within the normal range. In this study, 54 (17.88%) women were Calcium deficient. In an Indian study has done to determine serum calcium and vitamin D levels in women with PCOS and they have observed a higher prevalence of calcium deficiency among them over general population, in 2017.[19]There mean calcium level was 8.2 ± 1.5mg/dl (2.05mmol/dl) Which was much lower than our observation.

The evidence showed that abnormal calcium homeostasis are responsible for PCOS. An observational study revealed that abnormal calcium homeostasis may be responsible for the follicular development arrest in PCOS women and may contribute to its` pathogenesis.[16]Animal investigations have established that calcium is needed in oocyte activation and maturation, the resumption and follicular development

progression.[10] It was proposed that calcium may have a universal role in egg activation and regulation of meiotic and mitotic cell division cycles in mammalian oocytes.[11]The importance of calcium in oocyte activation and maturation was demonstrated in animal researches as well and they hypothesized calcium homeostasis disturbances may mediate its pathogenesis [17]

Being a South Asians have a higher risk of Diabetes and it became a serious problem nowadays with higher prevalence of diabetes in our population.In a cross-sectional study in 2005,concluded that one in five adults in Sri Lanka has either diabetes or pre-diabetes and one-third of those with diabetes are undiagnosed.[28] Although the study populations were different, in this study, nearly One in five(20.85%) has either diabetes or pre diabetes and all were undiagnosed.It implies the importance of screening of diabetes among high risk group like Sri Lankan PCOS population at their first visit. There was a higher diabetes prevalence with high body mass index. In my study, 85.7% of patients with dysglycemia were in BMI ≥ 25 kg/m^2 group. But,no significant association between them was detected in this study(p=0.357)It may due to that study had a larger sample size (5000) , advanced mean age(46.0$\pm$14.6years) and done in 2005. Therefore more vigilant care should be recommended with Sri Lankan PCOS population.

In a double-blinded, placebo controlled trial study in 2013, evaluated the effect of metformin versus metformin plus calcium and vitamin D on menstrual regularity. In both groups menstrual regularity was improved. The effectiveness of metformin with Vitamin D and calcium on menstrual regularity was more significant than metformin alone according to before-after results. (65% vs. 45% for menstrual regularity) My study was also a double blinded randomized controlled trial as that study and it concluded a similar result of a

more obvious improvement in Metformin plus calcium group (63.4% Vs 46%). It is possible that calcium supplementation may have a positive outcome in menstrual regularity and BMI

In recent PCOS guideline concluded with evidence, Metformin in addition to lifestyle changes, can be recommended in PCOS patients with BMI $\geq$25kg/m^2 for treatment of weight and metabolic complications.It emphasized that metformin offers a greater benefit in PCOS patients with diabetes risk factors,impaired glucose tolerance or high risk ethnic group. Although Metformin is usually recommended to prescription for PCOS patients with DM or IGT,with considering following facts it can be used as first line pharmacological treatment for PCOS.Those are :(1.)Among Sri Lankan PCOS population 20% have dysglycaemia.[22](2.) Sri Lanka has higher IR (65-70%)[11]and lower insulin sensitivity[25] among PCOS women.(3.) Higher prevalence of AN(2/3rd of PCOS population)[22](4.)BMI $\geq$25kg/m^2(5)South Asian ethnicity has higher complication rate (6) acts on insulin level which mediates the pathophysiology of PCOS.(6.)Higher family history of DM.(63.8%)[29]. (1),(3)(4) and (5) facts were confirmed with my study.

Metformin is a low cost, freely available and extensively used drug over decades for DM type 2,PCOS,Gestational diabetes mellitus(GDM) and weight management. Metformin is widely used across health professional specialty and there is variability in recommendations.

As the study population was confined to women in reproductive age group, metformin has additional benefits. It has been used for ovulation induction in women with PCOS who are obese(BMI $\geq$ 30kg/m2)

with anovulatory infertility. Clomiphene citrate can be added to improve ovulation, pregnancy and live birth rates.But letrozole is the first line agent for ovulation induction.[23]Adjunct metformin therapy is used to improve the clinical pregnancy rate and reduce the risk of ovarian hyperstimulation syndrome in In Vitro Fertilization. Metformin is safe during pregnancy and is used in GDM widely, so can continue during pregnancy. Especially age>35 yr old subfertile or longer duration of subfertility women were started with ovulation induction with clomiphene on top of metformin might affect the results in this study. But they were not excluded as calcium and metformin do not have potential effects on pregnancy.

CONCLUSIONS

This study showed an improvement with calcium on metformin in menstrual regularity and BMI in PCOS patients. Adding of cheap, freely available calcium on metformin for PCOS treatment in Sri Lankan population would bring a better clinical outcome in menstrual regularity and weight and it is cost effective. Further long-term, RCT, prospective studies with larger sample size and long duration is recommended to determine its efficacy to PCOS patients. It is important to assess acanthosis nigricans like clinical hyperandrogenism symptoms among patients in primary care setting to direct patients to respective care. It is the time to have resources freely to do IR,OGTT,vitamin D levels in managing PCOS patients as well as in future researches. It can prevent the serious metabolic complications related to PCOS and future health burden in Sri Lanka.

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