International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Nagaria T et al. Int J Reprod Contracept Obstet Gynecol. 2019 Feb;8(2):702-709
www.ijrcog.org

pISSN 2320-1770 | eISSN 2320-1789

DOI: http://dx.doi.org/10.18203/2320-1770.ijrcog20190309

Original Research Article

Effect of Myoinositol and Metformin in combination on clinical and hormonal profile in patients of polycystic ovarian syndrome

Tripti Nagaria, Arpita Mohapatra*, Jyoti Jaiswal

Department of Obstetrics and Gynecology, Pt. JNM Medical College, Raipur, Chhattisgarh, India

Received: 10 December 2018
Accepted: 15 January 2019

***Correspondence:**
Dr. Arpita Mohapatra,
E-mail: redruby89@rediffmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) also known as hyperandrogenic anovulation syndrome or Stein – Leventhal syndrome is an endocrine disorder, characterized by anovulation, oligomenorrhea, amenorrhea, features of androgenic hormone excess (hirsutism, acne, alopecia, seborrhea) and insulin resistance. The global prevalence ranges from 2.2% to 26%.
Methods: A prospective observational study was conducted from December 2015 to December 2016 in Department of Obstetrics and Gynecology at Pt. Jawahar Lal Nehru Memorial medical college and associated Dr. Bhim Rao Ambedkar memorial hospital, Raipur (C.G.) after obtaining permission of ethical committee of the institute to evaluate the effect of myoinositol and metformin on clinical profile in patients of polycystic ovarian syndrome. 70 women were included in the study who received a combination of myoinositol 600mg and metformin 500mg (twice a day) for 3 months for the management of PCOS. Prior to the start of the therapy, a detailed history and baseline investigations were recorded. Cases were reassessed at the end of three months of therapy for evaluation of change in clinical and hormonal profile.
Results: 90.09% (63/70) cases showed improvement in the menstrual complaints. Spontaneous onset of menses occurred in all the cases presented with amenorrhea, in nearly 90% within 2 months of start of treatment. Regularization of cycles was observed in nearly 50% of patients with infrequent menses. Amongst all the cases with cutaneous manifestations, maximum improvement was seen in cases of acne (4/6) i.e. 66.66%. 25% (5/20) patients with infertility conceived during the study period.
Conclusions: Myoinositol with metformin in combination has resulted in significant improvement in the clinical profile with reduction in individual drug dosage in cases with PCOS.

Keywords: Metformin, Myoinositol, PCOS

INTRODUCTION

Polycystic ovarian syndrome (PCOS) also known as hyperandrogenic anovulation syndrome or Stein-Leventhal syndrome is an endocrine disorder, characterized by anovulation, oligomenorrhea, amenorrhea, features of androgenic hormone excess (hirsutism, acne, alopecia, seborrhea) and insulin resistance. Global prevalence ranges from 2.2% to 26%.[1] PCOS is one of the leading causes of female subfertility. The consequences of PCOS include menstrual irregularities and skin problems while on long term it can result in infertility, obesity, diabetes and cardiovascular diseases.

In 2003, the Rotterdam European Society for Human Reproduction/ American Society of Reproductive Medicine (ESHRE/ASRM) proposed that the diagnosis of

PCOS include any two of the following three criteria viz. oligo- and/or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound; other etiologies must be excluded.

Hyperinsulinemia is the mainstay of the pathophysiology of PCOS. A decrease in the insulin resistance is reflected in terms of clinical and biochemical improvement in PCOS. Hyperinsulinemia contributes to hyperandrogenism by the following mechanism: [2,3]

- By binding to IGF-1 receptor, it augments the thecal androgen response to LH.
- Inhibition of hepatic synthesis of SHBG (Sex hormone binding globulin), resulting in greater concentration of free androgen.[4]
- Inhibition of hepatic synthesis of Insulin –like growth factor binding protein -I, which allows an increase in circulating levels of IGF-I and greater local activity of IGF-I in the ovary.

Increased levels of testosterone, itself reduces the hepatic synthesis of SHBG, resulting in a vicious cycle of hyperandrogenism and the clinical features corresponding to same.

Metformin, a time-tested drug for PCOS and has been used since long, in a dose of 500 mg three times a day with a success rate of 20 to 96%.[5-11] It acts by suppressing hepatic gluconeogenesis. It also increases insulin sensitivity, enhances peripheral glucose uptake, and decreases insulin induced suppression of peripheral fatty acid oxidation. However, in such a dose it is often associated with side effects such as nausea, vomiting, abdominal cramps and diarrhoea.

Myoinositol is an upcoming drug in the management of PCOS. A deficiency of inositols has been postulated as a key factor in the pathogenesis of PCOS. An increased excretion of inositol in urine has also been observed in patients of PCOS thus leading to its deficiency.[12] Based on these findings, inositols were used for the management of PCOS.

Inositols (6 carbon polyols) are second messengers which are responsible for glucose transport intracellularly. It also increases the translocation of GLUT 4 to the cell membrane. At ovarian level, it has been observed that myoinositol based second messenger is involved in both glucose uptake and FSH signalling. Various studies have found a success ranging from 22 to 88% in the management of PCOS.[13-19] Though the side effects are minimal, the cost of treatment with 2-4g/day for 3-6 months duration, is one of the major constraints.

As both myoinositol and metformin have different mechanisms of action in improving insulin resistance and controlling hyperinsulinemia, it has been postulated that both the drugs in combination may have additive effect in management of hyperinsulinemia in PCOS with the reduction in the doses of individual drug to achieve similar efficacy.

The study was conducted with the aim to find out the effect of myoinositol and metformin in combination on clinical profile in patients of PCOS.

The objectives of this study were to study the effect of Myoinositol and Metformin on menstrual irregularity, Infertility, skin problems, obesity in cases of polycystic ovarian syndrome, to study the effect of myoinositol and metformin on LH, FSH, testosterone, progesterone and Estradiol in cases of polycystic ovarian syndrome, to evaluate serum fasting insulin in cases of polycystic ovarian syndrome, to evaluate the HOMA index (Insulin resistance) in cases of polycystic ovarian syndrome, to evaluate the Glucose to Insulin ratio (Insulin Sensitivity) in cases of polycystic ovarian syndrome.

METHODS

This prospective observational study was conducted during December 2015 to December 2016 in Department of Obstetrics and Gynecology at Pt. Jawahar Lal Nehru Memorial Medical College and Associated Dr. Bhim Rao Ambedkar Memorial Hospital, Raipur (C.G.) after obtaining permission of ethical committee of the institute to evaluate the effect of Myoinositol and Metformin on menstrual irregularity, ovulation induction, infertility, weight gain and skin problems along with side effects if any. 70 women receiving a combination of Myoinositol 600mg and Metformin 500mg (twice a day) continuously for 3 months for the management of PCOS, were recruited in the study.

Prior to the start of the therapy, a detailed history was recorded, and blood investigations were noted down to obtain baseline investigations. Related parameters namely BMI, LH/FSH ratio, Insulin sensitivity (Fasting glucose/fasting insulin), and HOMA index (Fasting glucose x fasting insulin/22.5) were also calculated. Cases were reassessed at the end of three months of therapy for regularity of menstrual cycle, weight, height, BMI and improvement in skin problems. BMI is calculated as (weight (kg)/height (m^2). Guidelines for obesity and overweight based on body mass indices (BMI) for Asian Indians were revised in 2014 based on consensus developed through discussions by the prevention and management of obesity and metabolic syndrome group. It was previously suggested by the regional office for the WPRO (western pacific region of WHO) in 2000. The revised guidelines categorize overweight as a BMI of 23.0-24.9 and obesity as a BMI≥25 using values lower than the ethnic specific BMI previously advocated for Asian Indians.

Inclusion criteria

- All young girls and women attending OPD/IPD of Department of Obstetrics and Gynecology having

Polycystic ovarian syndrome as defined by Rotterdam Criteria, 2003 who consented for the study were included.

Exclusion criteria

- Congenital adrenal hyperplasia
- Idiopathic hyperandrogenism or hirsutism
- Pelvic inflammatory disease or any adnexal pathology
- Diagnosed or suspected malignant neoplastic disease
- Hyperprolactinemia
- Adrenal tumor
- Liver disorder
- Renal disorder
- Bleeding disorder
- Thyroid disorder.

Stastical analysis

At the end of three months, data was compiled in MS-Excel and analyzed for accuracy. Students paired T-test was the statistical test for analysis of the pre-test and post- test results with a combination of myoinositol and metformin. A p-value<0.05 was considered as significant.

RESULTS

In the present study, a total of 70 cases that fulfilled the inclusion criteria were included. The mean age of the patients was 21.15±4.15 years i.e. mostly comprising of a younger population. Most of the patients were observed to be overweight i.e. BMI>23.

Table 1: Demographic profile of study subjects.

Parameter		N= 70	%
Age	Range	11-40 years	
	Mean	21.15 ±4.15 years	
BMI	<18.5	3	4.29
	18.5-22.9	20	28.6
	23-24.9	24	34.32
	>25	23	32.89
Occupation	Student	40	57.24
	Housewife	20	28.57
	Private job	6	8.57
	Govt. service	2	2.85
	Laborer	2	2.85
Family history	Diabetes	31	44.33
	Hypertension	9	12.87
	Menstrual abnormality	8	11.42
	Obesity	11	15.71
	Difficulty in conception	4	5.71

In the present study, more than half i.e. 57.24% cases were students who came with complain of menstrual abnormality and cutaneous disorders. As PCOS is also responsible for anovulatory infertility, about 28.57% (20/70) of cases were housewives and majority were registered for infertility related problems.

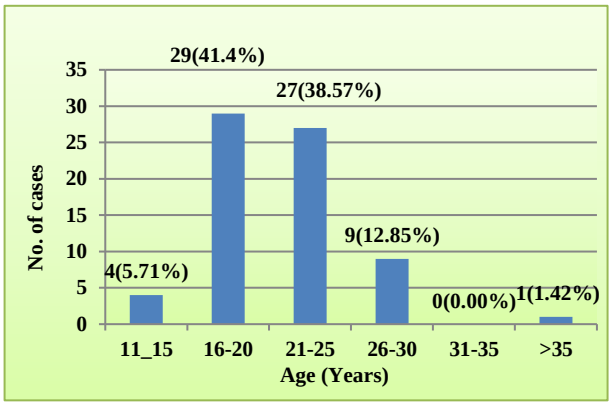

Figure 1: Distribution of cases according to age.

Maximum numbers of cases were students, who usually are more aware regarding various clinical manifestations of disease and open for consultation and discussion regarding changes in their body. PCOS is a multifactorial disease and is found to have association with those who have family history of type 2 diabetes mellitus, hypertension, obesity, glucose intolerance, dyslipidaemia, cardiovascular diseases.

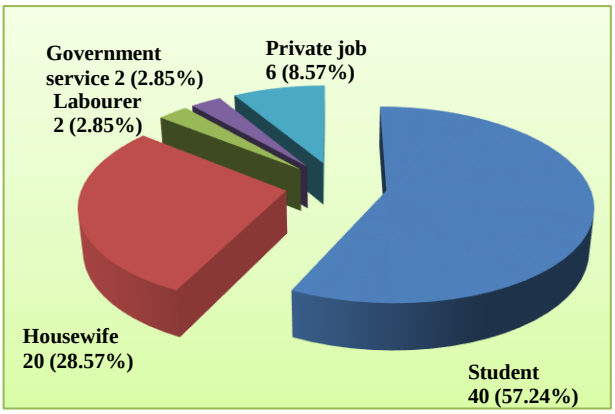

Figure 2: Distribution of cases according to occupation.

In the present study, 44.33% cases had family history of diabetes mellitus type 2, 12.87% cases had family history of hypertension, 11.42% had family history of menstrual abnormalities, 15.71% had family history of obesity and 5.71% cases had family history of difficulty in conception. The demographic profile of study subjects is as shown in Table 1 and Figure 1, 2 and 3.

Clinical presentation varied a wide range; most common was menstrual abnormality (91.42%) and dermatological changes. As per FIGO guidelines, amenorrhea is defined as no menses for 90 days and oligomenorrhea is defined as 1-2 menses in 90 days.

Most common menstrual abnormality was Oligomenorrhea (35.75%), followed by amenorrhea (34.32%) and then Oligo hypomenorrhea (11.42%). Clinical/biochemical hyperandrogenism is an important criterion for PCOS.

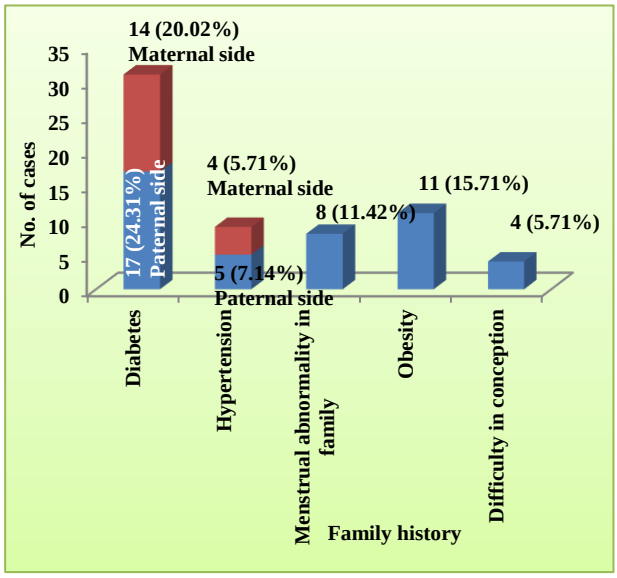

Figure 3: Distribution of cases according to family history.

Increased levels of LH and coexisting Insulin resistance are important contributors of hyperandrogenism. Hyperandrogenism results in a variety of cutaneous manifestations as hirsutism, oily skin, acne etc. Amongst all cases, 48.62% had hirsutism, 8.53% cases had oily skin, 8.53% had acne and 2.85% had acanthosis nigricans. As authors know, PCOS is a condition of oligo/anovulation, this results in ovulatory dysfertility and infertility which needs proper evaluation and management.

Table 2: Clinical presentations of study subjects.

Clinical presentation	Number of cases n=70	%
Menstrual abnormality	64	91.42
Amenorrhea	24	34.32
Oligomenorrhea	25	35.75
Oligo hypomenorrhea	8	11.42
Menorrhagia	4	5.71
Polymenorrhea	2	2.85
Hypomenorrhea	1	1.42
Infertility	20	28.6
Primary	19	27.17
Secondary	1	1.42
Skin problems		
Oily skin	6	8.53
Acne	6	8.53
Hirsutism	34	48.62
Acanthosis Nigricans	2	2.85
Weight gain	18	25.74

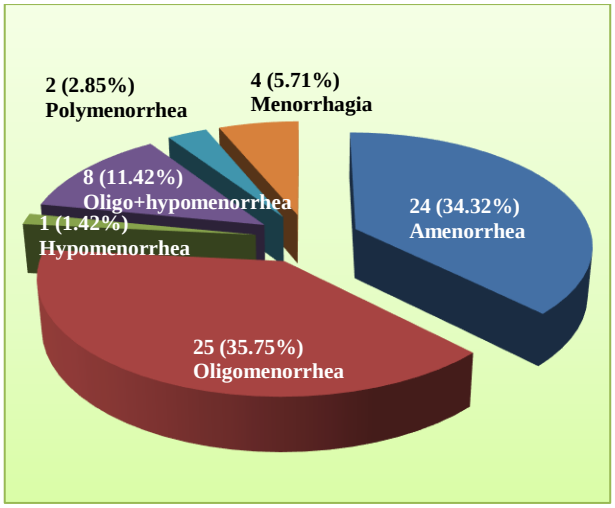

Figure 4: Distribution of cases according to the type of menstrual abnormality.

In present study 28.6% of total patients had complaint of infertility. Clinical presentation of the cases is as shown in Table 2 and Figure 4 and 5.

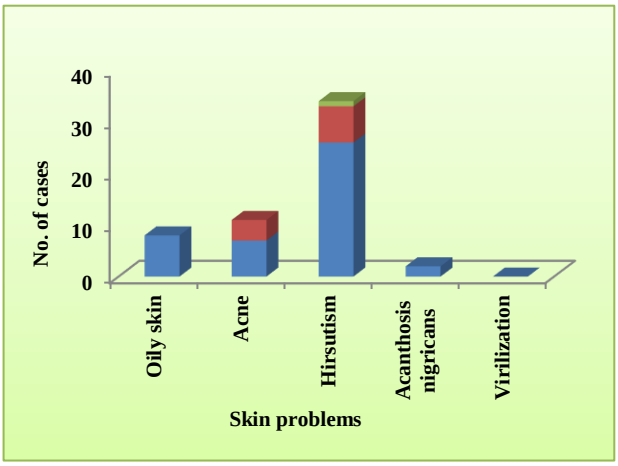

Figure 5: Distribution of cases according to skin problems.

Amongst the cases included in the study, most of the cases showed improvement in menstrual complaints (Table 3 and Figure 6).

Amongst these cases, 50% cases showed improvement in the oily skin. 8.53% cases had complaint of acne of which 66.66% cases showed improvement.48.62% cases had complaint of hirsutism out of which 29.41% cases showed improvement. In the present study, 20 cases had infertility, out of which, 19 cases had primary infertility and 1 case had secondary infertility.

Out of all the cases of infertility, 5/20(25%) patients conceived all the 5 cases belonged to the primary infertility group. Clinical assessment was done monthly and at the end of three months i.e. completion of therapy (Figure 7 and 8).

Table 3: Effect of myoinositol and metformin on improvement of clinical profile in patients of PCOS.

Clinical parameter	No. of cases	Post treatment improvement	
		No.	%
Menstrual abnormalities			
Amenorrhea	24	24	100
Oligomenorrhea	25	20	80
Oligo+Hypomenorrhea	8	6	75
Menorrhagia	4	4	100
Polymenorrhea	2	2	100
Hypomenorrhea	1	1	100
Infertility			
Total no. of cases	20	5	25
Primary	19	5	26.3
Secondary	1	0	0
Skin problems			
Oily skin	6	3	50
Acne	6	4	66.66
Hirsutism	34	10	29.41
Acanthosis Nigricans	2	1	50
Weight gain	18	8	44.44

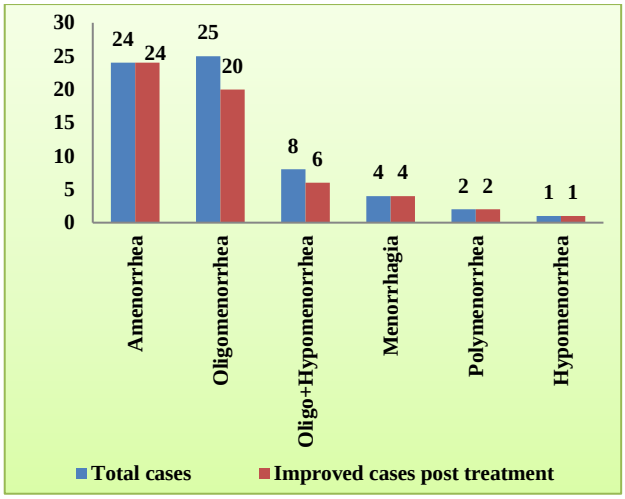

Figure 6: Effect of Myoinositol and Metformin on menstrual abnormalities.

Amongst the cases who showed improvement in menstrual abnormalities, interval since start of therapy was recorded (Table 4).

Table 4: Distribution of cases according to time taken for improvement in the menstrual abnormality after treatment.

Menstrual abnormality	Inter menstrual interval before start of treatment			Onset of spontaneous menses after treatment			Subsequent spontaneous menses
	Interval	No.	%	Duration since start of therapy	No.	%	
Amenorrhea N=24	No menses within 90 days	24	100	1 month	1	4.16	Yes
				1-1.5 month	10	41.67	Yes
				1.5-2 month	12	50.00	Yes
				2- 2.5 month	1	4.16	Yes
				3 months	-		-
		24	100	Total	24	100	
Oligomenorrhea N=25	1.5 months	4	16	1 month	3	75	Yes
	2 months	15	60	1 month	9	60	Yes
	2.5 months	6	24	1 month	3	50	Yes
				1-1.5 months	2	33.33	Yes
				1.5-2 months	1	16.67	-
		25	100	Total	25	100	

Table 5: Effect of myo-inositol and metformin on hormonal profile of the cases.

Hormone	Pre-treatment (Mean±SD)	After treatment (Mean±SD)	P value
LH (mIU/ml)	17.15±9.98	12.21±5.77	0.0005
FSH (mIU/ml)	5.93±2.57	6.39±1.911	0.2315
LH/FSH	4.28±7.90	1.98±0.95	0.0169
Estradiol (pg/ml)	76.55±33.52	74.33±38.88	0.7180
Progesterone (ng/ml)	1.14±2.37	1.31±1.72	0.6279
Testosterone (pg/ml)	0.52±0.22	0.40±0.14	0.0002
Prolactin (ng/ml)	15.82 ±11.58	14.01±9.53	0.3144
Fasting insulin (µu/ml)	12.72±5.74	9.20±3.42	<0.0001
Homa index	2.62 ±1.24	1.85±0.80	<0.0001
Insulin sensitivity	8.20±4.93	11.67±9.52	0.0076

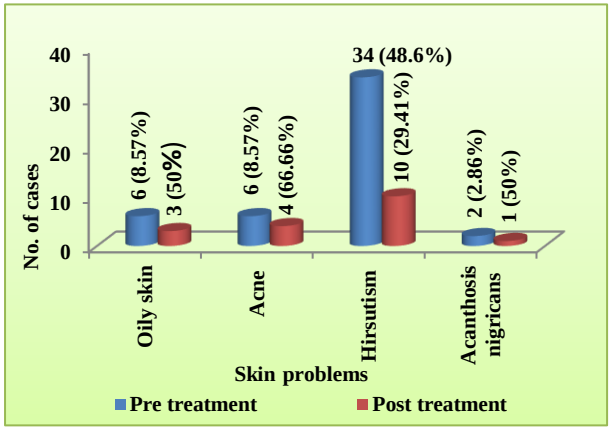

Figure 7: Effect of myo-inositol and metformin on skin problems.

Three months after treatment, the improvement in hormonal milieu was as shown in Table 5.

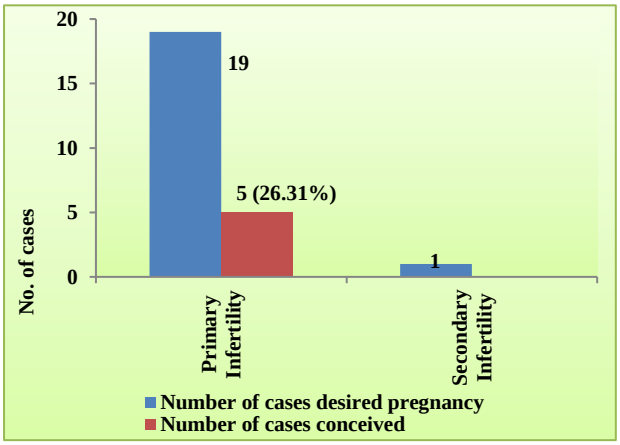

Figure 8: Effect of myo-inositol and metformin on infertility.

Significant improvement was seen in post treatment Serum LH (p=0.0005), LH/FSH ratio (p=0.0169), serum Testosterone (p=0.0002), fasting insulin (p<0.0001), HOMA index (p<0.0001) and insulin sensitivity (p=0.0076).

DISCUSSION

PCOS is a multifactorial disease and is found to have association with those who have family history of type 2 diabetes mellitus, hypertension, obesity, glucose intolerance, dyslipidemia, and cardiovascular diseases. In the present study, 44.33% cases had a family history of diabetes mellitus type 2, 12.87% had a family history of hypertension (Table 1). Similar association was observed in the studies conducted by other authors.[10,21,22]

In PCOS, under the unopposed action of estrogen, the endometrium undergoes hyperplasia and according to the level of estrogen in the body, may present with normal and regular menstrual cycle/regular cycle with menorrhagia/oligomenorrhea or amenorrhea followed by menorrhagia. Hyperandrogenism may lead to thinning of endometrium which may be associated with scanty bleeding during menses or spotting only. In present study, menstrual abnormality was the most common presentation, nearly 70% of study subjects presented with the complaints of amenorrhea and oligomenorrhea (Table 2). 90.09% (63/70) cases showed improvement in the menstrual complaints.

Amongst amenorrhoeic patients, spontaneous onset of menses was observed in most of the cases. Vast majority of patients started menstruating within 2 months of treatment. Nearly 50% of patients showed regularization of cycles in oligomenorrheic patients (Table 3). Similar improvement in menstrual complaints was observed by other authors, as shown in Table 6.

Table 6: Improvement in menstrual complaints post treatment in various studies in cases of PCOS.

Author	Treatment given	Improvement in menstrual cycle	P value
Papaleo E et al[14]	MYO 2g BD	88%	
Genazzani ADet al[15]	MYO 2g/day	100%	
Venturella R et al[17]	MYO 2g/day	100%	
Raffone et al[7]	MYO (4g) vs MET (1.5g)		<0.003
Nazari T et al[5]	MET 500mg TDS	67%	< 0.0004
Le Donne et al[8]	MET 1000mg/day		NS
	MYO+MET (4g+500mg/day)		<0.05
Chirania K et al[11]	MYO 1g/day	66.66%	<0.001
	MET 1000mg/day	15.78%	> 0.05
	MYO+MET (1 gm+1000mg/day)	57.14%	<0.001
Ranwa M et al[19]	MYO 1g BD	74.65%	
Present study	MYO+MET (600mg+ 500mg BD)	90.09%	

As we know, PCOS is a condition of oligo/anovulation, this results in ovulatory dysfertility and infertility which needs proper evaluation and management. In present study 28.6% of total patients had complaint of infertility. Increased levels of LH and coexisting Insulin resistance are important contributors of hyperandrogenism. Increased levels of testosterone itself decreases hepatic synthesis of SHBG, which results in increased levels of free testosterone which further decreases SHBG synthesis and a vicious cycle ensues. Hyperandrogenism results in a variety of cutaneous manifestations as hirsutism, oily skin, acne etc. Amongst all the cases with cutaneous manifestations, hirsutism is the most common clinical presentation in the patients recruited for present study (Table 2). Due to short duration of therapy, not much significant change was observed in skin problems and weight. Maximum improvement was seen in cases of acne (4/6) i.e. 66.66%. Three out of 6 cases with oily skin showed improvement post treatment (50%). 10 of 34 cases of hirsutism showed improvement, and 1 out of 2(50%) cases of acanthosis nigricans improved after therapy (Table 3).

Zacche M et al, observed a comparable improvement of 53% in cases of acne on treatment with Myoinositol for 6 months.[16] Ranwa M et al, observed an improvement of only 33.3% in cases of acne, and an improvement of 34.4% in oily skin in cases of PCOS on administration of 2gm Myo per day.[19] This suggests that the additional effect of Metformin with myoinositol in the present study results in significant reduction of insulin levels, thereby reducing hyperandrogenism and its clinical consequences, as compared to myoinositol alone. Le Donne et al, Zacche et al, and Genazzani et al, observed significant improvement in Ferriman Galloway score.[9,16,15] This could be because the duration of treatment given in these patients was for a longer duration of time. Also, these studies selected mostly obese cases of PCOS, who had more chances of insulin resistance, and more free androgens, thus in them, significant improvement was seen.

Chronic anovulation is the main cause of infertility in cases of PCOS. Chronically elevated estrogen levels may not permit the increase in FSH secretion required to stimulate or sustain progressive follicular development. Poor follicular development may not generate or sustain the estradiol level required to induce the ovulatory LH surge. In the present study, 20 cases presented with infertility, out of which, 19 cases had primary infertility and 1 case had secondary infertility. Out of all the cases of infertility, 5/20(25%) patients conceived. All the 5 cases belonged to the primary infertility group. Thus, we observe that myoinositol and metformin combination significantly improves the fertility of patients of PCOS. In the studies conducted by Ashrafi M et al, 20% of the cases conceived.[6] Improvement in fertility was found to be even more by Papaleo E et al i.e. 40% of the patients conceived.[14] Significant improvement was also observed by Angik R et al and Chirania K et al, ($p<0.001$).[9,11]

Significant improvement was seen in post treatment serum LH ($p=0.0005$), LH/FSH ratio ($p=0.0169$), serum Testosterone ($p=0.0002$), fasting insulin ($p<0.0001$), HOMA index ($p<0.0001$) and insulin sensitivity ($p=0.0076$). Hyperinsulinemia as a consequence of Insulin resistance alters FSH to LH shift, preventing the selection of a dominant follicle and impending ovulation, thus leading to infertility. A significant improvement in post treatment serum Insulin was also observed by other authors.[6,9,11,16,18] A similar study conducted by Ranwa M et al using myoinositol alone for 12 weeks had a significantly lower improvement than present study.[19] Many studies suggest that insulin resistance is the causative factor for PCOS. HOMA index is a measure of the insulin resistance. It improved significantly in the present study ($p<0.0001$) and a similar result was also observed in other studies.[9,10,15,16,18]

Insulin sensitivity represents the response of the body to raised blood sugar. Higher the insulin sensitivity, better is the response against raised blood sugar. A highly significant improvement was observed in the present study ($p=0.0076$) indicating that Myoinositol and Metformin have the ability to significantly reduce fasting blood glucose and fasting insulin thereby positively affecting HOMA index and insulin sensitivity. Thus, the combination of these drugs can improve the clinical outcome in the cases of PCOS and also reduces the risk of developing diabetes as a long-term complication. In cases of PCOS, alteration in the GnRH pulse frequency leads to raised serum LH but normal or low serum FSH. Normally, LH: FSH=1:1, but in PCOS it becomes >2:1. In the present study, serum LH/FSH ratio before treatment was 4.28 ± 7.90 and the post treatment mean was 1.98 ± 0.9 which was highly significant ($p=0.0169$). A significant improvement was observed in post treatment serum LH ($p=0.0005$) and LH/FSH ratio ($p=0.0169$) in present study similar to that observed by other authors.[5,9-11,15,16] Serum testosterone levels improved significantly ($p=0.0002$) in present study, which was also observed by various other authors.[5,6,9,14-16]

CONCLUSION

PCOS is a common endocrine disorder affecting about 5-10% of women of reproductive age group. Hyperinsulinemia is the mainstay of the pathophysiology of PCOS. A decrease in insulin resistance is reflected in terms of clinical and biochemical improvement in PCOS. The synergistic action of myoinositol with metformin has resulted in significant reduction in drug dosage, but not at the cost of efficacy. Thus, present study concludes that myoinositol in combination with metformin can be an effective treatment for management of cases of PCOS.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Joshi B, Mukherjee S, Patil A, Purandare A, Chauhan S, Vaidya R. A cross-sectional study of polycystic ovarian syndrome among adolescent and young girls in Mumbai, India. Indian J Endocrinol Metabol. 2014;18(3):317.
2. Chang RJ, Nakamura RM, Judd Hl, Kaplan SA. Insulin resistance in nonobese patients with polycystic ovarian disease. J Clinical Endocrinol Metabol. 1983;57(2):356-9.
3. Buyalos RP, Geffner ME, Bersch N, Judd HL, Watanabe RM, Bergman RN, et al. Insulin and insulin-like growth factor-I responsiveness in polycystic ovarian syndrome. Fertil steril. 1992;57(4):796-803.
4. Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, et al. A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clinical Endocrinol Metabol. 1991;72(1):83-9.
5. Nazari T, Bayat R, Hamedi M. Metformin therapy in girls with polycystic ovary syndrome: a self-controlled clinical trial. Archives Iranian Med. 2007;10(2):176-81
6. Ashrafi M, Zafarani F, Baghestani AR. Effects of metformin on ovulation and pregnancy rate in women with clomiphene resistant polycystic ovary syndrome. Int J Fertil Steril. 2007;1(1):39
7. Raffone E, Rizzo P, Benedetto V. Insulin sensitiser agents alone and in co-treatment with r-FSH for ovulation induction in PCOS women. Gynecol Endocrinol. 2010;26(4):275-80.
8. Le Donne M, Alibrandi A, Giarrusso R, Lo MI, Muraca U. Diet, metformin and inositol in overweight and obese women with polycystic ovary syndrome: effects on body composition. Minerva Ginecol. 2012;64(1):23-9.
9. Angik R, Jajoo SS, Hariharan C, Chimote A. A comparative study of metabolic and hormonal effects of myoinositol vs. metformin in women with polycystic ovary syndrome: A randomised controlled trial. Int J Reprod Contracept Obstet Gynecol. 2017;4(1):189-4.
10. Awalekar J, Awalekar C, Jadhav M, Chivate CG, Patwardhan MH. Effect of metformin and myoinositol and lifestyle modification in patients of PCOD. Int J Biomed Res 2015;6(09);698-704
11. Chirania K, Misra S, Behera S. A randomised clinical trial comparing myoinositol and metformin in PCOS. Int J Reprod Contracept Obstet Gynecol. 2017;6(5):1814-20.
12. Baillargeon JP, Diamanti-Kandarakis E, Ostlund RE, Apridonidze T, Iuorno MJ, Nestler JE. Altered D-chiro-inositol urinary clearance in women with polycystic ovary syndrome. Diabet Care. 2006;29(2):300-5.
13. Gerli S, Mignosa M, Di Renzo GC. Effects of inositol on ovarian function and metabolic factors in women with PCOS: a randomized double blind placebo-controlled trial. European Review Medical Pharmacol Sci. 2003 Nov;7:151-60.
14. Papaleo E, Unfer V, Baillargeon JP, De Santis L, Fusi F, Brigante C, et al. Myo-inositol in patients with polycystic ovary syndrome: a novel method for ovulation induction. Gynecol Endocrinol. 2007;23(12):700-3.
15. Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecol Endocrinol. 2008;24:139-44.
16. Zacchè MM, Caputo L, Filippis S, Zacchè G, Dindelli M, Ferrari A .Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. Gynecol Endocrinol. 2009;25(8):508-13.
17. Venturella R. Assessment of the modification of the clinical, endocrinal and metabolical profile of patients with PCOS syndrome treated with myo-inositol]. Minerva Gynecol, 2010; 64:239-43
18. Genazzani AD, Despini G, Santagni S, Prati A, Rattighieri E, Chierchia E, et al. Effects of a combination of alpha lipoic acid and myo-inositol on insulin dynamics in overweight/obese patients with PCOS. Endocrinol Metab Synd. 2014;3(140):2161-017.
19. Ranwa M, Nagaria T, Jaiswal J, Arya A. Study of effect of myoinositol on menstrual irregularities and skin problems in polycystic ovarian syndrome cases. Int J Reprod Contracept Obstet Gynecol. 2017;6(6):2310-7.
20. Misra A, Chowbey P, Makkar BM, Vikram NK, Wasir JS, Chadha D, et al. Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. JAPI. 2009;57(2):163-70.
21. Moini A, Eslami B. Familial associations between polycystic ovarian syndrome and common diseases. J Assisted Reprod Genet. 2009;26(2-3):123-7.
22. Saxena P, Prakash A, Nigam A, Mishra A. Polycystic ovary syndrome: Is obesity a sine qua non? A clinical, hormonal, and metabolic assessment in relation to body mass index. Indian J Endocrinol Metabol. 2012;16(6):996.

Cite this article as: Nagaria T, Mohapatra A, Jaiswal J. Effect of Myoinositol and Metformin in combination on clinical and hormonal profile in patients of polycystic ovarian syndrome. Int J Reprod Contracept Obstet Gynecol 2019;8:702-9.