

Alternative Therapies in Polycystic Ovarian Syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is characterized by oligo-anovulation, clinical or biochemical hyperandrogenism and/or polycystic ovaries.^{1,2,3} Insulin resistance (IR) accompanied by compensatory hyperinsulinaemia constitutes another major biochemical feature of PCOS.^{4,5,6,7} The condition affects 5-10% of women during reproductive age.⁸ There appears to be four times greater incidence of metabolic syndrome association in south-Asian population than in Caucasian counterparts.⁹ Because of the link between IR and PCOS, metformin either alone or in combination with clomiphene citrate is now the most widely used insulin-sensitizer for ovulation induction in women with PCOS.^{10,11} The rationale of this treatment was based on only a few small studies with conflicting results.¹² Current treatment options e.g. oral contraceptives (OCs), lifestyle modification, and insulin sensitizers are not considered satisfactory by most gynaecologists.

Basis for the treatment with OCs is to reduce androgen levels and thus cause improvement in menstrual cycles in adolescents with PCOS. Few studies have been reported in obese adolescents. Whether OCs worsen glucose tolerance or metabolic dysfunction in PCOS is controversial.¹³ Nonetheless, OCs has remained a first-line therapy for the adolescent with PCOS, because of absence

of any superior alternative. Lifestyle modification has been shown to be effective in the restoration of ovulation but has not been studied well in obese adolescents with PCOS. There is growing evidence that obese adolescents with PCOS are at increased risk for metabolic consequences and that treatment of obesity at this critical developmental juncture may provide long-term health benefits. Metformin, which has peripheral insulin-sensitizing effects, has been shown to exert several beneficial effects in trials of adult women with PCOS. However it is not without side-effects. Apart from gastrointestinal problems like bloating etc, it is known to cause vit B₁₂ deficiency and lactic acidosis.¹⁴ At Dr. Palep's Medical Research Foundation, we have looked into our ancient wisdom of Ayurveda in search of an effective alternative modality and found that Ayurveda has described number of herbs that act at the level of hypothalamo-pituitary-axis. These herbs are described as Aartava-dosha-hara. There are other herbs that act on organic diseases of genital tract. These are termed as Yoni doshahara. There are other herbs described, which aid the bleeding and clotting mechanisms, these are termed as Raktpitta hara. There are herbs indicated to correct the lipid and carbohydrate metabolism. Herbal formulations, viz., Cap. Gynocare, Tab.Diapal and Cap. Pentaphyte P-5 have been created by Dr. Palep's Medical Research Foundation and these are based on the ancient experiential wisdom of Ayurveda.

Constituents of Gynocare:
Standardized extract of *Saraca indica*

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(Ashoka), *Symplocos racemosus* (Lodhra), *Cyperus rotundus* (Musta), *Berberis chirta* (Rasanjan), *Adhatoda vasica* (Vasa), *Cynodon dactylon* (Durva), *Glycerrhiza glabra* (Yashtimadhu), *Hemidesmus indicus* (Anantamool sariva), *Tribulis terrestris* (Gokshuru), *Boerhavia diffusa* (Punarnava), *Mesua ferea* (Nagkeshar), *Santalum album* (Chandan), *Andropogon muricatum* (Usheer), *Bombax malabaricum* (Shalmali), *Rubia cordifolia* (Manjishta).

Gynocare acts on the hypothalamo-pituitary-ovary-uterine axis and thereby regularizes the menstrual cycles. It causes the proliferation of endometrium. An interesting observation in experimental animals is the reduction in ovarian and adrenal size and volume without affecting the normal cellular architecture. Similar action is seen in women with PCOS on ultrasound, where in significant reduction in the increased ovarian volumes.

Constituents of Diapal : Standardized extract of *Aegle marmelos* (Bilwa patra), *Embllica officianalis* (Amlaki), *Curcuma longa* (Haridra), *Gymnema sylvestre* (Gurmar), *Syzygium cumini* (Jambool beej), *Momordia charantia* (Karavella), *Tinospora cordifolia* (Guduchi), *Commiphora mukul* (Guggulu), *Aspatham* (Shilajatu), *Trigonella foenum graecum* (Methi), *azardirachta indica* (nimba), *Tribulis terrestris* (Gokshuru), *Pterocarpus marsupium* (Vijaysar), *Terminalia chebula* (Haritaki), *Terminalia belerica* (Vibhitaki), *Terminalia arjuna* (Arjuna).

Experimental studies have demonstrated that Diapal protects beta cells of Islets of Langerhans and sensitizes tissues to the action of insulin. It reduces blood sugar levels in the diabetic animals.

Constituents of Pentaphyte P-5:

Standardized extract of Panchavalkal comprising of *Ficus bengalensis* (Vata), *Ficus religiosa* (Ashwatha), *Ficus glomerata* (Udambara), *Ficus lacor* (Plaksha), *Albizia lebec* (Shirisha).

Pentaphyte P-5 contains phytosteroids, which modulate immune and inflammatory reactions in body beneficially. It has a broad spectrum antimicrobial action.

Cap. Torchnil is another herbal research product of Dr. Palep's Medical Research Foundation being widely used by obstetricians in management of repeated implantation failures in assisted reproductive technology, recurrent pregnancy loss (RPL) and TORCH infections. Its constituents modulate cytokines and have a positive effect on ovulation as well as placentation.

Objective

To evaluate the efficacy of herbal formulation Capsule Gynocare either singly or in combination with tablet Diapal or Capsule Pentaphyte P-5, in the management of PCOS in adolescents and married, infertile women.

Material and methods

We conducted a retrospective study of case records of women attending gynaecological outpatient at Dr. Palep's Priyank Maternity Nursing Home between the periods from January 2006 to December 2009. Out of the total women attending the OPD, women presenting with menstrual irregularities with evidence of PCOS associated with or without infertility were selected for the study.

Inclusion criteria were :

- History of oligomenorrhoea with or without other menstrual irregularities.

- Polycystic ovaries on ultrasonography (USG)
- Evidence of anovulation, e.g. on histopathology or USG
- With or without hirsutism/obesity/ acne.
- Complete medical record of history, clinical findings, lab investigations, and follow-up of at least 3 or more months.

The cases were further classified according to marital and fertility status. Data was analyzed for duration of treatment with herbal drugs, change in menstrual pattern, changes in ovarian volume, effect on obesity, hirsutism, acne, conceptions and pregnancy outcome.

Observations and Results

Total number of women attending Obstetric and Gynaec OPD from Jan 2006-Dec 2009 were = 1064. Out of which women presenting with menstrual irregularities were 200. Of these, 68 women had followed up for more than 3 months with complete data entry. Out of these 36 were diagnosed cases of PCOS on basis of history of oligomenorrhoea, USG evidence, evidence of an ovulation with or without hirsutism, obesity or acne were identified for the study.

27 (36) cases were married with infertility and 9 were unmarried adolescents.

Out of the 27 infertile women, 8 had oligomenorrhoea, 7 had regular cycles but with evidence of anovulation, 3 had oligomenorrhoea with scanty flow and 9 had oligomenorrhoea with heavy flow.

Out of the 9 adolescents, 3 had oligomenorrhoea with heavy flow, 3 menorrhagia, 3 oligomenorrhoea (Table 1).

Table 1

Menstrual irregularity	No
I) Married with infertility	
Oligomenorrhoea	: 8
Oligomenorrhoea with scanty flow	: 3
Oligomenorrhoea with heavy flow	: 9
Regular cycles with anovulation	: 7
II) Adolescent	
Oligomenorrhoea	: 3
Oligomenorrhoea with heavy flow	: 3
Menorrhagia	: 3

After complete history and examination, lab investigations to exclude other metabolic disorders 12 cases were started on Cap. Gynocare, 12 on Gynocare and Diapal, 3 on Gynocare and Pentaphyte P-5 based on the Ayurvedic concepts. Three cases were found to be suffering with hypothyroidism and one was a case of mild hyper prolactinaemia. Hence, along with these herbal formulations 3 cases had received Thyroxine, 1 received Cabergoline. Eight cases received supplementation with Cap. Torchnil. (Table 2)

Table 2

PCOS in married women with infertility and treatment given

G : Gynocare

No	G	G+D	G+P	* Thy	* C	* T
27	12	12	3	3	1	8

G+D : Gynocare with Diapal

G+P : Gynocare with Pentaphyte P5

Thy : Thyroxine

C : Cabergoline

T : Torchnil

* in addition to Gynocare and Diapal

In the married group 20 (27) women had menstrual irregularity with long

periods of amenorrhoea. Some would only respond to progestogen challenge. With initiation of treatment in 15 (75%) cases menstrual cycles (MC) got regularized with average flow within 1-2 cycles of starting treatment. In 5 (25%) women the cycles remained irregular (Table 3).

Table 3

Cyclicity in married women on follow-up > 3 months

Of the 24 (27) married women with

	Regularised	Irregular cycles	Not applicable
No cases	15	5	7

PCO on USG, 6 (25%) showed a significant reduction in ovarian volume of almost 3.5 cubic cc. In four patients no significant change was observed. In other 8 cases no follow up (FU) USGs were available. In other 6 women only follicular study was done with no reference to ovarian size (Table 4).

Table 4

USG changes on follow-up (volume) > 3 months in married women with PCOS

In 17 cases ovulation was

	N vol	Same	reduced	Increased	Not known	Under treatment
No cases	3	4	6	-	3	5

documented. In total of 6 cases, spontaneous ovulation occurred with only Ayurvedic medication. In 11 cases ovulation was induced with letrozole and triggered with inj. hCG (Table 5).

Table 5

Ovulation on follow-up while on Gynocare ± Diapal ± Pentaphyte

There were 11 (40.7%) conceptions.

	Spontaneous ovulation	After induction with Letrozole+Ov trigger with inj hCG
No cases	6	11

Six patients (54.5%) needed more than one year of treatment. Three (27.3%) conceived in little over six months. Two (18.2%) required 3-6 months of treatment for achieving conception (Table 6).

Table 6

Treatment-conception interval :

	< 3 mnths	3-5 mnths	6-11mnths	>/12 mnths
No. of cases	1	1	3	6

There were eight (72.7%) spontaneous conceptions (on herbal formulation only). One patient (9.1%) conceived following ovulation induction with Letrozole, two patients (18.2%) required ovulation induction with IUI.

Pregnancy outcome

Six patients (54.5%) progressed to full term delivery. Currently one patient (9.1%) is in mid trimester. There were four (36.4%) ended in first trimester spontaneous abortions (Table 7).

Table 7

Conceptions

No. of cases	* Spont concept	>ov induc only	<ov induc with IUI	Outcome		
				FTDel	In mid trimester	Spont abortions
27	8	1	2	6	1	4

* While on Gynocare ± diapal

Of the nine adolescent unmarried girls with PCOS, one received only Gynocare, four received Gynocare and Diapal, other four received Gynocare and Pentaphyte P-5.

Two patients showed hyperprolactinaemia hence received additional cabergoline (Table 8).

Table 8

PCOS in Adolescents-treatment given
G : Gynocare

No	G	G+D	G+P	C
9	1	4	4	2

G+D : Gynocare with Diapal

G+P : Gynocare with Pentaphyte P5

Thy : Thyroxine

C : Cabergoline

Six (83.3%) of them reported regular MC with average flow. Four reported decrease in acne, one reported decrease in hirsutism and weight loss was observed in 3 out of 4 cases, which were on Gynocare with Diapal (Table 9).

Table 9

PCOS in Adolescents-Changes in menstrual cyclicity on follow-up :

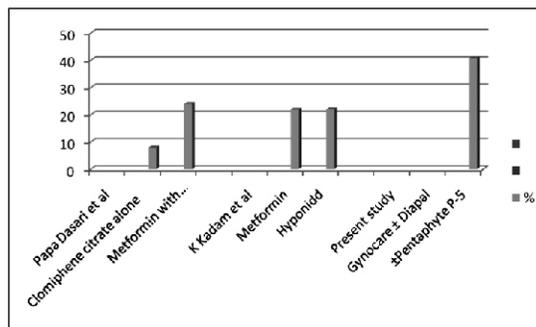
No. of cases	MC regular	MC irregular	Normal flow	Abnormal flow	Acne reduced	Hirsutism reduced	Wt reduced
6	-	6	-	4	1	3	

All nine cases had been diagnosed as PCO on USG. And 6 (83.3%) showed significant reduction in ovarian volume of avg of 4.9 cubic cc. One case however showed increase in volume of unilateral ovary (Table 10).

Table 10

Changes in ovarian volume on follow-up :

No	PCOS on USG	> 6mnths		
		Vol reduced	Vol increased	Vol same
9	9	6	1 (unilat ovary)	2



Discussion

In the present retrospective study, significant number of married women (73.7%) with infertility and (83.3%) adolescents reported regular menstrual cycles after starting treatment with Gynocare alone or in combination with Diapal and Pentaphyte P-5. Reduction in increased ovarian volumes was documented in 25% of the cases with infertility and in 83.3% adolescents. There was significant reduction in acne and weight loss was recorded in 3 out of 4 cases, which were on Gynocare with Diapal. It was not possible to evaluate effect on hirsutism. Oral hormonal contraceptives (OHC) with or without ciproterone acetate (diene) are a treatment of first choice in hyperandrogenic PCOS women, who do not desire conception. But many studies¹⁵ have shown that the beneficial effects are significant only after addition of an insulin sensitizing agent and the role of OCPs in obese adolescents are still under debate.¹⁶ Hence there is scope for alternative medication in the management of this disorder.

Several studies are being conducted to evaluate the efficacy of insulin sensitizers in controlling the metabolic syndrome to enhance success of ovulation induction or spontaneous ovulation. Legro RS *et al*¹⁷ reported that among 626 infertile women with PCOS conception rate while on metformin as 21.7%, with clomiphene as

39.5% and in combination-therapy group it was 46.0%. In India, Papa Dasari *et al*¹⁸ compared the effect of clomiphene citrate (CC) (in 24 subjects) with combination of metformin and CC (16 subjects) and reported 8 % pregnancy rate with CC and 24% with metformin and CC. They also reported that of those who received metformin along with CC, 80% complained of loss of appetite and 24% had nausea and vomiting, though none of them discontinued therapy. In a recent open randomized comparative trial conducted in India¹⁹ workers reported 22% conception rate with herbal preparation Cap Hyponidd and 21.9% with Tab Metformin and 86% ovulation rate with Hyponidd vs 70% with metformin in clomiphene resistant PCOS cases. The conception rates with herbal formulations used in present retrospective study (40.7%) are significantly higher when compared with the results obtained by conventional metformin and other herbal preparation Hyponidd (Bar Chart Graph 1). Animal experiments have shown these are non-toxic herbal alternatives, viz. Gynocare has potent action on ovaries, uterus and adrenal glands. It has been shown to cause the hyperplasia of endometrium. By its action on HPOU axis, it corrects the menstrual cycles. It relieves pain due to its analgesic, anti-inflammatory and antispasmodic action. It improves ovarian steroidogenesis through antioxidant, anti-inflammatory and immuno-modulatory mechanisms. Diapal consisting of number of herbal ingredients that protect beta cells of islets of langerhans, sensitizes tissues to the action of insulin, scavenges free radicals and improves vasodilatation. Pentaphyte P-5 contains phytosteroids which modulate immune and inflammatory reactions in the body beneficially. The

anthroquinolone glycosides contained in it are anti microbial. No side-effects were reported by any of the women taking the above formulations.

Conclusion

The results of this study indicate that Cap. Gynocare alone or in combination with Tab. Diapal and Cap. Pentaphyte P-5 have great potential and can be used as effective alternative therapy in infertile women with PCOS resistant to treatment with conventional OC pills and metformin or metformin and clomiphene. This alternative therapy can be choice therapy in the group of obese adolescents in whom OCPs are controversial because now they are believed to worsen glucose tolerance or cause metabolic dysfunction. What is more significant is that no adverse effects were observed in any of the patients under the study.

A larger randomized double blind placebo controlled trial can confirm the superior efficacy of these herbal medications, which have also been studied in the experimental animals and proved to be non toxic.

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ANTISENSE TECHNOLOGY TO LOWER LDL CHOLESTEROL

A randomised trial of **mipomersen**-an antisense, inhibitor of apolipoprotein B synthesis - as an adjunctive treatment in patients with the rare homozygous form of familial hypercholesterolaemia.

The major finding was that baseline concentrations of LDL cholesterol and apolipoprotein B, reduced substantially in most patients after weekly subcutaneous injections of 200 mg mipomersen for 26 weeks. Lipoprotein(a) concentrations, which are unresponsive to statin therapy, were similarly reduced.

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