Polycystic ovary syndrome (PCOS), one of the most common female endocrine disorders and one of the leading causes of female infertility, affects approximately 5-10% of women of reproductive age (12-45 years of age). Although a multiplicity of clinical presentations existed for polycystic ovarian disease earlier; in 1935, Stein and Leventhal reported the classic symptomatology of amenorrhea, infertility, hirsutism and enlarged polycystic ovaries in a group of women. High serum concentrations of androgenic hormones, such as testosterone, androstenedione and dehydroepiandrosterone sulfate (DHEA-S), may be observed in these patients. However, individual variation is considerable, and some patients may even have normal androgen levels. Profound insulin resistance, prevalence of impaired glucose tolerance (IGT) (31-35%), type 2 diabetes mellitus (75-100%), lipid abnormalities, cardiovascular disease and endometrial carcinoma are observed in patients with PCOS.

A proposed mechanism for anovulation and elevated androgen levels suggests that, under the increased stimulatory effect of luteinizing hormone (LH) secreted by the anterior pituitary, stimulation of the ovarian theca cells is increased. In turn, these cells increase the production of androgens (e.g., testosterone and androstenedione). Also, a decreased follicle-stimulating hormone (FSH) level relative to LH results in decreased estrogen levels and, consequently, anovulation. Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) may also augment the effect on ovarian function.

Patients with PCOS may present with various clinical features such as menstrual abnormalities, hyperandrogenism, infertility, obesity and metabolic syndrome. Abnormal menstruation patterns attributed to chronic anovulation are observed. In some patients, oligomenorrhea or secondary amenorrhea is present. Hyperandrogenism clinically manifests as excess terminal body hair in a male distribution pattern. Some patients have acne and/or male-pattern hair loss (androgenic alopecia). Most women with PCOS...
ovulate intermittently, and a subset of women with the syndrome is infertile. Conception may take longer as compared to other women. Obesity is present in nearly half of all the women with PCOS. 

Approximately 10% of women with PCOS have type 2 diabetes mellitus and 30-40% have IGT by the age of 40 years. Many women with PCOS have obstructive sleep apnea syndrome. These patients have excessive daytime somnolence and have apnea/hypopnea episodes during sleep. In women, metabolic syndrome is characterized by abdominal obesity (waist circumference >35 inches), dyslipidemia (triglyceride >150 mg/dl, high-density lipoprotein cholesterol [HDL-C] < 50 mg/dl), elevated blood pressure, a proinflammatory state characterized by an elevated C-reactive protein level and a prothrombotic state characterized by elevated PAI-1 (plasminogen activator inhibitor type 1) and fibrinogen levels.

The European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine recommend that at least two of the following three features should be present to diagnose PCOS:

- Oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea.
- Hyperandrogenism (clinical evidence of androgen excess) or hyperandrogenemia (biochemical evidence of androgen excess).
- Polycystic ovaries (as defined by ultrasonography).

Polycystic ovaries are defined as ≥12 follicles in at least one ovary measuring 2-9 mm in diameter or a total ovarian volume of >10 cm³.

Samples for laboratory studies should be drawn early in the morning, with the patient in a fasting state and, in women with regular menses, between Days 5 and 9 of the menstrual cycle. Androgen excess can be tested by measuring total and free testosterone or a free androgen index. An elevated free testosterone level is a sensitive indicator of androgen excess.

Due to the high prevalence of IGT and type 2 diabetes mellitus in women with PCOS, a 75-g oral glucose tolerance test can be performed. A 2-hour postload glucose value <140 mg/dl indicates normal glucose tolerance, a value of 140-199 mg/dl indicates IGT and a value of ≥200 mg/dl indicates diabetes mellitus.

Drugs used in the treatment of PCOS include metformin, spironolactone, eflornithine (topical cream to treat hirsutism) and oral contraceptives.

In the present study, Evecare® syrup, a polyherbal formulation, is evaluated for its efficacy and safety in women suffering from infertility due to PCOS. The principal herbal ingredients of Evecare® syrup, such as Saraca indica, Symplocos racemosa, Cyperus rotundus, Tinospora cordifolia, and Aloe vera, are known to possess potent uterine tonic effect and normalize the hormonal and ovarian cycle.

Aim of the Study

The aim of the study was to evaluate the efficacy and short- and long-term safety of Evecare® syrup in the management of female infertility due to PCOS.

Material and Methods

Study Design

A double-blind placebo-controlled study was conducted in the Dept. of Gynecology and Obstetrics, Gauhati Medical College between June 2007 and September 2008 in accordance with the Declaration of Helsinki and GCP Guidelines issued by the Ministry of Health, Government of India, to evaluate the clinical efficacy and safety of Evecare® syrup in women suffering from infertility due to PCOS. The study was approved by the Ethics Committee of the institution and all the patients signed the written informed consent before enrolment.

In order to ensure appropriate and consistent quality of medicinal plant/herbal substances, Good Agricultural and Collection Practice (GACP) was followed while collecting, manufacturing, processing and packaging of the herbal formulation. Botanical identification and Ayurvedic criteria of the desired quality were in accordance with the guidelines of Pharmacopoeial standards of Ayurvedic formulations (1987).

Inclusion Criteria

Women aged above 18 years suffering from infertility (who had not conceived for more than one year after stopping contraception) due to PCOS presenting with symptoms such as hirsutism, acne and obesity, and proven with laboratory investigations (ultrasonography or hormonal assay) were included in the study provided they were willing to sign the written informed consent and comply with the study procedure.

Exclusion Criteria

Women aged above 45 years, who had tubal obstruction with anatomical defects in the reproductive system and had a history of significant pelvic inflammation
were excluded from the study. Individuals with any associated liver, kidney or cardiac diseases, and who were not willing to sign the written informed consent and comply with the study procedures were also excluded from the study.

**Study Procedure**

Hundred women suffering from infertility due to PCOS were included in the study. They were randomly divided into Evecare® and placebo groups of 50 patients each; their heights and weights were measured to calculate their body mass indices (BMIs). A detailed history was taken based on the findings of polycystic ovary appearance on ultrasound, oligomenorrhea, hirsutism, acne and elevated serum testosterone. Clinical examination included vaginal and cervical smear examinations. Pelvic examination was performed to check for fibroids or ovarian cyst, and tenderness to rule out endometriosis. Laboratory investigations included estimation of blood sugar, cholesterol and testosterone levels. Ultrasonographic examination was performed to examine the ovarian follicles in the ovaries. Other endocrine investigations were carried out to confirm the absence of hyperprolactinemia. VDRL, HBsAg and HIV tests were also conducted after obtaining informed consent from the individuals. If tested positive for the above tests, they were excluded from the trial. All the patients received either Evecare® syrup at a dosage of 2-3 teaspoonfuls, twice-daily or a similar looking placebo at the same dosage for a period of six months. Normal sexual intercourse was advised to influence conception. Pregnancy test was done in females who missed the menstrual cycle. Confirmation of pregnancy was done by checking urine HCG levels or by ultrasonography scan. The mean age, body weight, BMI, duration of infertility and other associated clinical (acne, hirsutism, obesity) and hormonal (testosterone, LH and FSH) characteristics of the patients are summarized in Table 1. The parameters in both Evecare® and placebo groups were comparable.

The incidence and type of adverse events reported by various studies were also tabulated separately. All adverse events, either reported or observed by patients, were recorded with information about severity, duration and action taken regarding the study drug. Relation of adverse events to study medication was pre-defined as ‘Unrelated’ (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), ‘Possible’ (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), ‘Probable’ (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state) and ‘Certain’ (the adverse events must have definitive relationship to the study drug, which cannot be explained by concurrent disease or any other agent).

**Primary and Secondary Outcome Measures**

Primary predefined outcomes were restoration of fertility, clinical recovery of PCOS, hirsutism, acne, lowering of blood sugar and cholesterol levels, and normalization of menstrual cycles and hormonal levels. Secondary endpoints were safety and compliance to Evecare® syrup.

**Statistical Analysis**

Parametric analysis was done by repeated measures of ANOVA followed by Dunnett’s multiple comparison test; nonparametric analysis was done by repeated measures of ANOVA using Friedman’s test followed by Dunnett’s multiple comparison test. The incidence of fertility with respect to treatment (Evecare®) and placebo groups was analyzed statistically using Fisher’s exact test. Values are expressed as mean ± SD or as incidences of patients with or without symptoms. The minimum level of significance was fixed at 95% confidence limit and a two-sided p < 0.05 was considered significant. Statistical analysis was performed using GraphPad Prism Software, Version 4.03 for Windows (Graph-Pad Software, San Diego, California, United States).
Results
A significant reduction in BMI was noted from second week onward till the end of the treatment (p < 0.0001) with Evecare® syrup. Acne score reduced from 1.28 ± 1.11 (at entry) to 0.54 ± 0.76 (at the end of treatment) (p < 0.001). The acne score started reducing from the second week but significance was observed only from the fourth month onward and continued till the end of the study. Hirsutism score decreased significantly from 1.78 ± 0.93 (at entry) to 0.80 ± 0.81 (at the end of treatment) (p < 0.001). Obesity score reduced from 1.76 ± 0.94 (at entry) to 0.76 ± 0.80 (at the end of treatment) (p < 0.001). Oligomenorrhea score showed improvement with Evecare® syrup but was not significant. No such changes were observed in the placebo group (Table 2).

Table 2. Effect of Evecare® Syrup on BMI and Various Clinical Parameters

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Evecare® syrup (n = 50)</th>
<th>Placebo (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At entry</td>
<td>2 months</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.86 ± 4.00</td>
<td>28.42 ± 3.83</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>1.78 ± 0.93</td>
<td>1.48 ± 0.93</td>
</tr>
<tr>
<td>Acne</td>
<td>1.28 ± 1.11</td>
<td>1.08 ± 0.99</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.76 ± 0.94</td>
<td>1.46 ± 0.93</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>0.66 ± 1.06</td>
<td>0.52 ± 0.81</td>
</tr>
</tbody>
</table>

Statistical analysis: Parametric analysis was performed by repeated measures of ANOVA followed by Dunnett’s multiple comparison test. Nonparametric analysis was performed by repeated measures of ANOVA using Friedman’s test followed by Dunnett’s multiple comparison test.

Table 3. Effect of Evecare® Syrup on Investigational Parameters of Patients Suffering from Infertility due to PCOS

<table>
<thead>
<tr>
<th>Investigational parameters</th>
<th>Evecare® syrup (n = 50)</th>
<th>Placebo (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At entry</td>
<td>2 months</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.16 ± 0.54</td>
<td>11.13 ± 0.49</td>
</tr>
<tr>
<td>Packed cell volume (%)</td>
<td>23.26 ± 1.79</td>
<td>27.08 ± 1.65</td>
</tr>
<tr>
<td>Biochemical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean cholesterol (mg/dl)</td>
<td>213.8 ± 18.4</td>
<td>210.8 ± 19.2</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>112.9 ± 17.5</td>
<td>112.6 ± 16.9</td>
</tr>
<tr>
<td>Hormonal parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (ng/ml)</td>
<td>2.06 ± 0.39</td>
<td>1.98 ± 0.41</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>1.98 ± 0.17</td>
<td>1.78 ± 0.28</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>1.22 ± 0.17</td>
<td>1.71 ± 0.35</td>
</tr>
</tbody>
</table>

Statistical analysis: Parametric analysis was performed using repeated measures of ANOVA followed by Dunnett’s multiple comparison test.

a compared to initial at entry values; b compared to values at 2 months; c compared to values at 4 months.
In the Evecare® group, hemoglobin and packed cell volume improved significantly from 10.16 ± 0.54 and 23.26 ± 11.79 (at entry) to 12.66 ± 0.60 and 34.42 ± 1.23 (at the end of study), respectively (p < 0.001). All the other hematological parameters improved from the second month onward. In the placebo group, no improvements were observed in the hematological parameters (Table 3). Cholesterol levels also reduced from second month onward till the end of the treatment (p < 0.0001) with Evecare® syrup. Testosterone levels reduced from 2.06 ± 0.39 (at entry) to 1.83 ± 0.38 (at the end of the study). Also, there was a significant improvement in the LH and FSH levels from the second month till the end of the study. However, no significant difference was observed in the fasting blood sugar levels. In the placebo group, no improvements were observed in any of the above-mentioned parameters (Table 3).

Size as well as the number of ovarian follicles decreased with Evecare® treatment from second month onward to the end of the study, as examined by ultrasonography (Table 4).

Four women, who were treated with Evecare® syrup, were pregnant at the 2-month follow-up, as diagnosed by urine HCG and ultrasonography. At the end of four months, 11 women conceived (p < 0.0005); at the end of six months, 18 women conceived (p < 0.0001) (Table 5).

### Discussion

According to the World Health Organization (WHO), worldwide, 2-10% of couples are unable to conceive primarily, about 60-80 million couples are infertile, and an estimated 10% of normally fertile couples fail to conceive within their first year of attempt. Among these couples, the causative factors are found in women in 30-40% of the cases and in males in 10-30% of cases. In 15-30% of the cases, both the partners have detectable abnormalities. The most common cause of female infertility is ovulatory disorder, characterized by anovulation or by infrequent and/or irregular ovulation. Hormonal balance between estrogen, progesterone, FSH and LH is important to induce and promote fertility. PCOS is a heterogeneous disorder characterized by menstrual irregularities, clinical and/or biochemical hyperandrogenism, and hyperinsulinemia secondary to reduced insulin sensitivity.

The principal herbal ingredients of Evecare® syrup, such as S. indica, S. racemosa, C. rotundus, T. cordifolia, and A. vera, are known to possess various beneficial activities. S. indica has a stimulatory effect on the ovarian tissue, which may produce an estrogen-like activity that enhances repair of the endometrium and stops bleeding. It is found to be effective in menorrhagia and dysmenorrhea. S. racemosa has been used since ancient times to treat menorrhagia and other uterine
disorders.\textsuperscript{18} It exhibits relaxant and antispasmodic effects on several spasmogens on uterine smooth muscles, attributing favorable actions in dysmenorrhea.\textsuperscript{19} The ethanolic extract of \textit{Boerhaavia diffusa} is found to halt intrauterine contraceptive device-induced bleeding in monkeys. This herb is also known for its anti-inflammatory and analgesic properties, which are comparable to that of ibuprofen. It has also proved useful as a hematonic.\textsuperscript{20} \textit{C. rotundus} possesses high levels of iron and is useful in treating general weakness and anemia.\textsuperscript{21} \textit{T. cordifolia} is well-known for its immunomodulatory effect and thus, helps in boosting the immune system, which indirectly increases the feeling of well-being. \textit{A. vera} regulates female hormones and improves fertility. It also possesses oxytocic property.\textsuperscript{22} \textit{Adhatoda vasica} has antihemorrhagic activities, which are beneficial in DUB. The herb is especially used as a uterine hemostatic in menorrhagia and metrorrhagia.\textsuperscript{23} \textit{T. cordifolia} and \textit{Solanum nigrum} are known to possess adaptogenic activity.\textsuperscript{24,25} The synergistic actions of all these herbs help in ovulation, conception and proper implantation, which result in normal pregnancy.

\textbf{Conclusion}

This study indicated a significant improvement in the clinical presentations of PCOS in Evecare\textsuperscript{®} syrup treatment group, which was further substantiated by hormonal evaluation tests. After Evecare\textsuperscript{®} treatment for six months, 18 of the 50 cases conceived showing a significant effect on fertility. Hemoglobin and cholesterol levels also showed a significant improvement. In addition, the number and size of the follicles significantly reduced as shown by ultrasonography. No adverse effects were reported or observed during the entire study period. Therefore, from the above findings it can be concluded that Evecare\textsuperscript{®} syrup is safe and effective in women suffering from infertility due to PCOS.

\textbf{References}