

# Polycystic Ovary Syndrome in the Indian Subcontinent

Gautam N. Allahbadia, M.D.,<sup>1,2</sup> and Rubina Merchant, Ph.D.<sup>2</sup>

## ABSTRACT

Polycystic ovary syndrome (PCOS) is a complex, multifaceted, heterogeneous disorder that affects ~5 to 10% of women of reproductive age. It is characterized by hyperandrogenism, polycystic ovaries, and chronic anovulation along with insulin resistance, hyperinsulinemia, abdominal obesity, hypertension, and dyslipidemia as frequent metabolic traits (metabolic syndrome) that culminate in serious long-term consequences such as type 2 diabetes mellitus, endometrial hyperplasia, and coronary artery disease. It is one of the most common causes of anovulatory infertility. However, the heterogeneous clinical features of PCOS may change throughout the life span, starting from adolescence to postmenopausal age, largely influenced by obesity and metabolic alterations, and the phenotype of women with PCOS is variable, depending on the ethnic background.

The etiology of PCOS is yet to be elucidated; however, it is believed that in utero fetal programming may have a significant role in the development of PCOS phenotype in adult life. Though a woman may be genetically predisposed to developing PCOS, it is only the interaction of environmental factors (obesity) with the genetic factors that results in the characteristic metabolic and menstrual disturbances and the final expression of the PCOS phenotype.

Irrespective of geographic locations, a rapidly increasing prevalence of polycystic ovarian insulin resistance syndrome, excess body fat, adverse body fat patterning, hypertriglyceridemia, and obesity-related disease, such as diabetes and cardiovascular disease, have been reported in Asian Indians, suggesting that primary prevention strategies should be initiated early in this ethnic group. In lieu of the epidemic increase in the prevalence of obesity and diabetes mellitus in most industrialized countries including China and India owing to Westernization, urbanization, and mechanization, and evidence suggesting a pathogenetic role of obesity in the development of PCOS and related infertility, active intervention to combat the malice of these disorders is warranted. Pharmacologic therapy is a critical step in the management of patients with metabolic syndrome when lifestyle modifications fail to achieve the therapeutic goals, and studies in China and India have proved to be effective.

**KEYWORDS:** Polycystic ovary syndrome, Indian subcontinent, ethnicity, Asian Indians, India

<sup>1</sup>The Prince Aly Khan Hospital IVF Center and The Aesculap Academy-Asia, Pacific Center For Minimally Invasive Surgery, Training & Research, Mazgaon, Mumbai, India; <sup>2</sup>Rotunda - The Center For Human Reproduction, Bandra, India.

Address for correspondence and reprint requests: Gautam N. Allahbadia, M.D., Medical Director, Rotunda - The Center For Human Reproduction, 672, Kalpak Gulistan, Perry Cross Road, Near Otter's Club, Bandra (W) 400 050, India (e-mail: drallah

@gmail.com).

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Polycystic ovary syndrome (PCOS) may clinically be manifested in young women of reproductive age as oligo-ovulation, biochemical or clinical hyperandrogenism (hirsutism, male pattern balding, acne, acanthosis nigricans), and polycystic ovaries,<sup>1</sup> but PCOS has a long prodrome with detectable abnormalities that present as the metabolic syndrome (hyperinsulinemia, obesity, dyslipidemia [decreased high-density lipoprotein cholesterol and hypertriglyceridemia], hypertension, atherosclerosis, increased risk of development of type 2 diabetes and cardiovascular disease) throughout the life of affected women. There is considerable heterogeneity in the signs and symptoms among women with PCOS, and these may change over time for an individual.<sup>2,3</sup>

PCOS may be diagnosed by the presence of two of three major recommended criteria: (1) oligomenorrhea, (2) any form of hyperandrogenemia, either clinical (hirsutism and acne), or endocrine (the hormonal diagnosis of high androgen levels), and (3) the ultrasound picture of polycystic ovaries, following the exclusion of related disorders, such as Cushing's syndrome, hyperprolactinemia, thyroid dysfunction, androgen-producing tumors, and nonclassic adrenal hyperplasia.<sup>4</sup> Normal ovulatory women with polycystic ovaries (PCO), who exhibit only the ovarian morphology, are not considered to have PCOS. Among different criteria, hyperandrogenemia, specifically elevated bioavailable testosterone, and the recognition of oligo-ovulation are academically conducive in the diagnosis. The presence of either 12 or more follicles, measuring 2 to 9 mm in diameter, or an increased ovarian volume ( $> 10 \text{ cm}^3$ ) are criteria required to define PCO. Polycystic ovaries have been reported in 80 to 100% of women with PCOS. Overall, the ultrasonography (USG) findings are not sufficient for the diagnosis of PCOS as the typical USG findings of PCO are demonstrated in ~20 to 25% of regularly ovulating healthy women. The presence of a single polycystic ovary is sufficient to provide the diagnosis.<sup>5</sup> Estimates of the prevalence of polycystic ovaries in migrant Asian Indians hover around 52%.<sup>6</sup> Zargar et al<sup>7</sup> reported a significantly higher prevalence of ultrasonographically detected PCO (61.0% vs. 36.7%,  $p < 0.003$ ) and PCOS (37.1% vs. 25%,  $p > 0.1$ ) in 105 northern Indian women with diet-treated and/or oral hypoglycemic-treated type 2 diabetes mellitus compared with nondiabetic controls. PCOS has been found to be more prevalent in South Asian women residing in the United Kingdom than in Caucasians.<sup>8</sup>

Significant associations between PCO and menstrual irregularity, infertility, the Ferriman and Gallwey score for body hair distribution, the presence of acanthosis nigricans, and the fasting blood glucose concentration have been reported among Asian Indians.<sup>6</sup> Women with both PCO and non-insulin-dependent diabetes mellitus (NIDDM) had the lowest insulin sensitivity ( $80.5 \pm 30.9 \mu\text{U glucose L}^{-1} \text{ min}^{-1}$ ), but there was no significant difference in insulin sensitivity

between those with PCO but not NIDDM and those with NIDDM but not PCO suggesting that changes in insulin sensitivity in women with PCOS and NIDDM involve different mechanisms and that PCO unlike NIDDM is not associated with a defect in the secretion of insulin.<sup>6</sup>

Menstrual irregularity is the most common gynecologic presentation of PCOS. Oligomenorrhea has been observed in ~85 to 90% of women with PCOS, and as many as 30 to 40% of amenorrheic patients have PCOS.<sup>9</sup> The prevalence of infertility, caused mainly by anovulation in PCOS women, varies between 35% and 94%.<sup>10</sup> South Asians with PCOS present at a younger age ( $26 \pm 4$  years vs.  $30.1 \pm 5$  years, respectively,  $p = 0.005$ ) and have oligomenorrhea commencing at a younger age in comparison with Caucasian women.<sup>8</sup>

Hyperandrogenism is the key endocrine abnormality of PCOS, the prevalence of hirsutism in PCOS women ranging from 17 to 83%. It is recognized that hirsutism is in part ethnically determined, being more common in women with dark skin.<sup>11</sup>

Hirsutism is as common a problem in the Kashmir Valley (India) as elsewhere in the world. In a prospective, randomized study to assess the prevalence of hirsutism and study its etiology in the Kashmir Valley of the Indian subcontinent, Zargar et al<sup>12</sup> studied 5000 women attending various hospitals for reasons unrelated to hirsutism and 150 consecutive women referred for hirsutism. They reported hirsutism in 10.5% of the women studied among who 10.1% had mild (score of 6 to 9) and 0.4% had moderate (score of 10 to 14) hirsutism. PCOS was a common cause of hirsutism in 37.3% of the women as assessed by the Ferriman and Gallwey scoring system and an endocrinologic workup including estimations of gonadotropins, prolactin (PRL), testosterone (T), and 17-hydroxyprogesterone and abdominopelvic ultrasound. Wijeyaratne et al<sup>8</sup> studied ethnic differences in the clinical and biochemical characteristics of South Asian versus Caucasian women with PCOS (47 South Asians, 40 Caucasians) and their ethnically age-matched controls (11 South Asians and 22 Caucasians) in a case-control, cross-sectional observational study. They reported a significantly higher prevalence of hirsutism (Ferriman-Gallwey score 18 vs. 7.5,  $p = 0.0001$ ), acne, acanthosis nigricans, and secondary infertility in South Asians with PCOS.

Insulin resistance (IR) is central to the pathogenesis of PCOS<sup>8</sup> and has been associated with endothelial dysfunction, which is considered the initial step in the process of atherosclerosis.<sup>13</sup> The association between increased IR and PCOS is a consistent finding in all ethnic groups.<sup>14</sup> Jialal et al<sup>15</sup> reported a significant degree of insulin resistance that correlated with the hyperandrogenism in seven normal-weight Indian patients with PCOS with no evidence of acanthosis nigricans. Higher fasting insulin levels ( $89.4 \pm 8.9 \text{ pmol/L}$  vs.  $48.6 \pm 4.8$

pmol/L,  $p = 0.0001$ ), significantly lower serum sex hormone binding globulin (SHBG) ( $35 \pm 3.3$  nmol/L vs.  $55 \pm 9.4$  nmol/L,  $p = 0.02$ ), and lower insulin sensitivity (IS) ( $0.335 \pm 0.005$  vs.  $0.357 \pm 0.002$ ,  $p = 0.0001$ ) have been reported among South Asians with PCOS compared with Caucasians.<sup>8</sup> Sundararaman et al,<sup>16</sup> in a cross-sectional case-control study, assessed insulin resistance and carotid intima medial thickness (IMT) in 40 young women from southern India presenting with hyperandrogenic features of PCOS. Women with PCOS had higher fasting insulin levels ( $36.58 \pm 17.81$   $\mu$ U/mL vs.  $16.60 \pm 3.22$   $\mu$ U/mL in controls,  $p < 0.001$ ), higher insulin resistance (glucose/insulin ratio  $2.81 \pm 1.47$  vs.  $5.47 \pm 1.46$  in controls,  $p < 0.001$ ), and greater IMT ( $0.53 \pm 0.14$  mm vs.  $0.39 \pm 0.06$  mm in controls,  $p < 0.001$ ). The authors concluded that southern Indian women with the reproductive abnormalities of PCOS have greater insulin resistance and IMT, and therefore they must be advised about lowering the risk of future vascular disease.<sup>16</sup> Kaushal et al<sup>17</sup> demonstrated insulin resistance independent of body mass index (BMI) or family history of diabetes in Asian women with PCO (ages 16 to 40 years) and reduced flow mediated dilation (a marker of endothelial function) in women with PCO and a family history of diabetes mellitus (DM). The brothers of women with PCO also had insulin resistance, comparable with that associated with a family history of type 2 DM, and this was associated with elevations of blood pressure, abnormalities in serum lipid concentrations, and impaired endothelial cell function.

Epidemiologic studies confirm a high prevalence of type 2 diabetes<sup>18</sup> that has now reached epidemic levels in Asia.<sup>19</sup> Insulin resistance appears to be the most relevant feature of the metabolic syndrome and is often the precursor of diabetes mellitus.<sup>13</sup> A significantly higher prevalence of obesity, central obesity, hypertension, high triglycerides, and low high-density lipoprotein (HDL) ( $p < 0.01$ ) has been reported in Asian Indians with insulin resistance syndrome (IRS).<sup>20</sup> The increased weight of women with PCOS has been linked to an increased risk of type 2 diabetes, with up to 30% of obese PCOS women having impaired glucose tolerance and 7.5% likely to develop frank diabetes by their forties.<sup>21</sup> Northern Indian diabetic women with PCO are reported to have significantly higher plasma luteinizing hormone (LH), LH/follicle stimulating hormone (FSH) ratio, total testosterone and androstenedione levels, and diabetes of significantly longer duration than those without PCO ( $4.19 \pm 2.0$  years vs.  $2.9 \pm 1.6$  years;  $p < 0.05$ ).<sup>7</sup> Weerakiet et al<sup>22</sup> reported a significantly higher prevalence of hypertensive disorders in pregnancy (HDP) and premature delivery in Asian women with PCOS and a history of gestational diabetes mellitus (GDM) (21.3% and 13.3%) than in the controls (6.4% and 5.4%) but no difference in the prevalence of GDM between the PCOS women and the high-risk group of the controls,

suggesting that PCOS is a risk factor for GDM and HDP with borderline statistical significance.

Obesity is now commonly defined in adults as a BMI  $> 30$  kg/m<sup>2</sup>. Obesity contributes significantly to both insulin resistance and hyperandrogenism in overweight women with and without PCOS,<sup>23</sup> a significant proportion of menstrual disorders in women with PCOS, and worsens the clinical presentation of PCOS.<sup>24</sup> It has been shown to be an independent predictor of conversion of normoglycemia to impaired glucose tolerance or type 2 DM in women with PCOS.<sup>25</sup> Although there are no controlled systematic studies to determine the exact prevalence of obesity, 30 to 50% of PCOS women are obese with perhaps 60% having a BMI greater than 25 kg/m<sup>2</sup> with a tendency for an increased waist-hip ratio or abdominal obesity. Southern Indian women with PCOS are reported to have a higher BMI ( $26.46 \pm 5.24$  vs.  $23.24 \pm 3.05$  in controls,  $p < 0.001$ ), and the differences between PCOS women and controls persisted, even among those who had a BMI of less than 25 kg/m<sup>2</sup>.<sup>16</sup>

The term *metabolic syndrome* refers to the clustering of several cardiovascular risk factors (obesity, hyperinsulinemia, hypertension, atherogenic dyslipidemia [decreased HDL-cholesterol and hypertriglyceridemia], atherosclerosis, and hyperglycemia) believed to be related to insulin resistance.<sup>26</sup> The major risk factors leading to the metabolic syndrome or cardiovascular dysmetabolic syndrome are physical inactivity and an atherogenic diet and the cornerstone clinical feature is abdominal obesity or adiposity. Criteria for the metabolic syndrome in women with PCOS have been defined as abdominal obesity (waist circumference  $> 88$  cm), triglycerides  $\geq 150$  mg/dL, reduced HDL-cholesterol (HDL-C)  $< 50$  mg/dL, elevated blood pressure  $> 130$  mmHg systolic/ $> 85$  mm Hg diastolic, and elevated fasting glucose  $110 \pm 126$  mg/dL. Three out of these five qualify for the syndrome.<sup>27</sup>

Apridonidze et al<sup>28</sup> reported a twofold higher prevalence of metabolic syndrome (MBS) (43%) in women with PCOS compared with age-matched women in the general population. Using Adults Treatment Panel III (ATPIII) criteria, a higher prevalence of metabolic syndrome (15%) has been reported in a cohort of PCOS women with a mean BMI of 25.8 kg/m<sup>2</sup>, which compared with 3.5% prevalence in healthy controls with a mean BMI of 24.6 kg/m<sup>2</sup>. Wijeyaratne et al<sup>29</sup> determined the risk of metabolic syndrome and polycystic ovary syndrome (PCOS) in a cohort of indigenous South Asian women with a recent history of GDM. They reported a larger mean waist circumference ( $90.9 \pm 1.3$  cm vs.  $81.2 \pm 2.8$  cm,  $p = 0.0004$ ), a higher tendency for hypertension (17.6% vs. 7.4%,  $p = 0.001$ ), glucose intolerance (51.7% vs. 10.4%,  $p = 0.00001$ ), hypertriglyceridemia (16.3% vs. 5.9%,  $p = 0.02$ ), and a lower level of HDL (70% vs. 56.7%,  $p = 0.04$ ) in women with a history of GDM compared with controls. Of the

women who had GDM, 49% had metabolic syndrome, 58.5% had polycystic ovaries, and 40% had PCOS, significantly more than the control women, 6%, 13%, and 3%, respectively ( $p = 0.00001$ ). The authors concluded that the prevalence of metabolic syndrome and PCOS in indigenous Sri Lankan women 3 years postpartum is significantly higher in those with previous GDM compared with ethnically matched controls. This confirms an association between GDM and subsequent PCOS and metabolic syndrome. The prevalence of polycystic ovaries in South Asian women (58.5%) with PCOS and a history of GDM<sup>29</sup> was higher than that reported by Kousta et al<sup>30</sup> (52%).

PCOS is associated with a 50% increased risk for CHD compared with age- and BMI-matched women without PCOS.<sup>31</sup> *Hyperhomocysteinemia* varies with ethnicity and is a recognized risk factor for atherosclerosis, particularly among migrant South Asians. It has recently been shown to be correlated positively with the degree of insulin resistance/hyperinsulinemia.<sup>22</sup> Significantly higher homocysteine (Hcy) (SL  $10.2 \pm 1.9$  vs.  $9.0 \pm 3.8$ ,  $p = 0.01$ ; BA  $7.9 \pm 1.9$  vs.  $6.8 \pm 2.5$ ,  $p = 0.001$ ) and fasting insulin concentrations (Sri Lankans  $242.9 \pm 38.9$ ; British Asians  $89.4 \pm 8.9$ ; Caucasians  $48.6 \pm 4.8$  pmol/L;  $p = 0.0003$ ) have been reported in Sri Lankans with PCOS than in British Asians and Europeans with PCOS.<sup>32</sup> High homocysteine in young Sri Lankans with PCOS has major implications for their long-term risk for atherosclerosis.

PCOS appears to be a complex multigenic trait, involving multisystem dysfunctions, namely reproductive, endocrine, and metabolic, in which environmental influences play an important role with abnormal gonadotropin dynamics, excessive androgen production, and insulin resistance presenting as the key features of the disorder. Genomic variants in genes related to the regulation of androgen biosynthesis and function, insulin resistance, and the metabolic syndrome, and proinflammatory genotypes may be involved in the genetic predisposition to functional hyperandrogenism and PCOS.<sup>33</sup> Environmental risk factors (either during prenatal or postnatal life), seem to convert an occult PCOS into a clinically manifest syndrome.<sup>34</sup> The presence of hyperinducible CYP1A1 (T6235C) mutant genotype and its mutants in combination with GSTM1 and GSTT1 null genotypes in southern Indian women with PCO might cause an imbalance between phase I and phase II enzymes and therefore may represent a risk factor for PCO. Alterations in the activities of phase I drug metabolizing enzymes and phase II detoxification enzymes may cause abnormal functioning and formation of follicular cysts in the ovaries thus causing an imbalance in the hormone profiles.<sup>35</sup>

Though the exact etiology of PCOS remains unclear, the facts that the history of weight gain frequently precedes the onset of clinical manifestations,

obese PCOS women have more severe hyperandrogenism,<sup>36</sup> and the presence of anovulatory cycles, oligomenorrhea, and/or hirsutism are significantly higher in obese than in normal-weight women<sup>37</sup> suggest a pathogenetic role of obesity in the development of PCOS and related infertility.<sup>36,37</sup>

In view of the high prevalence of insulin resistance and impaired glucose tolerance among women with PCOS,<sup>21,38</sup> an oral glucose tolerance test, restricted to women who have other risk factors such as obesity (BMI > 30 kg/m<sup>2</sup>) or fasting glucose > 5.5 mmol/L, or a relevant family history and a metabolic screen must be performed for obese women with PCOS.<sup>21,39</sup>

## CLINICAL DISCUSSION

### Management

Treatment goals should include maintaining a normal endometrium, antagonizing the actions of androgens on target tissues, reducing insulin resistance (when present), and correcting anovulation.<sup>40</sup> The selection of therapy for PCOS generally depends on the physical symptoms and patients' desire for childbearing and may be broadly categorized into therapy for (i) symptomatic control, (ii) fertility management where conception is the priority, and (iii) long-term complications of PCOS. For obese women with PCOS, weight loss should be considered as a first option.

### Symptomatic Control

Patients not seeking pregnancy are generally treated with oral contraceptive pills (OCPs), which allow the endometrium to cycle normally (reducing the risks of endometrial cancer and hyperplasia) and alleviate symptoms of hyperandrogenism (acne and hirsutism).

Medical treatment of hirsutism and acne in polycystic ovary syndrome generally aims to reduce androgen levels, attenuate their effects by lowering androgen production, augmenting androgen binding to specific plasma-binding proteins, and blocking androgen action at the level of the target tissue.<sup>41</sup> Treatment to stem worsening hirsutism is likely to be more successful than reversing an already established and prolific hirsutism. Hirsutism can initially, and very dramatically, be alleviated by mechanical methods (shaving, plucking, chemical depilatories, electrolysis), but other general methods, especially in women with PCO, include weight loss, topical treatments, oral contraceptives,<sup>41</sup> antiandrogenic progestational agents<sup>41</sup> such as cyproterone acetate, spironolactone, flutamide, finasteride, and insulin sensitizing agents.

The main mechanism of combined oral contraceptive action is the inhibition of folliculogenesis via suppression of the midcycle surge and secretion of FSH

and LH, and decreased dehydroepiandrosterone sulfate (DHEAS) levels, possibly by way of reducing adrenocorticotrophic hormone (ACTH) levels. Progestins inhibit 5 $\alpha$ -reductase activity, act as antagonists at the androgen receptor, and increase the metabolic clearance rate of both testosterone and dihydrotestosterone (DHT). A daily dose of 30 to 35 mg of ethinyl estradiol guarantees sufficient suppression of ovarian follicular activity as well as effective stimulation of sex hormone binding globulin (SHBG) production.<sup>42</sup>

The mechanism of action of antiandrogens involves blockade of DHT binding to skin androgen receptors, interference with cellular uptake of testosterone and DHT, inhibition of dihydrotestosterone production, inhibition of ovarian and adrenal androgen production, increase in androgen metabolism to inactive compounds, decrease in 5  $\alpha$ -reductase activity, and elevation of SHBG levels, all of which may inhibit the phenotypic expression of androgens. Guido et al<sup>43</sup> reported a significant decrease in the free androgen index, DHEAS, and 17-hydroxyprogesterone after six cycles, a fivefold increase in SHBG in the third cycle, and a decrease in the Ferriman-Gallwey (F-G) score after the use of the estrogen-progestin combination containing drospirenone (DRSP). The first-line pharmacologic treatment for acne should be OCPs, particularly those containing cyproterone acetate, with the inclusion of antiandrogens (spironolactone, flutamide, finasteride) at the lowest effective dose to enhance clinical efficacy; appropriate antibiotic therapy and topical retinoids (tretinoin, adapalene, tazarotene) may also be essential for mild and moderate to severe acne. Antiandrogens overall are more effective than androgen suppression therapy for hirsutism and acne.<sup>44</sup> However, antiandrogens must be used in conjunction with estrogen-progestin to prevent pregnancy because of the risk of the compound causing feminization of a male fetus. According to the Cochrane review published in 2003, spironolactone (100 mg/day) is a more effective treatment than finasteride (5 mg/day) and cyproterone acetate (12.5 mg/day) in reducing hair growth but less effective than flutamide 500 mg/day in reducing F-G scores.<sup>45</sup>

#### INSULIN SENSITIZING DRUGS

Because insulin increases serum total and free testosterone by stimulating ovarian androgen synthesis and lowering circulating SHBG levels, insulin-sensitizing drugs may be effective in ameliorating hirsutism by means of reducing circulating insulin concentrations, leading to both decreased free androgen concentrations and end organ sensitivity to testosterone. Recently, Harborne et al<sup>46</sup> showed that metformin (500 mg, three times daily) treatment, for moderate to severe hirsutism, is potentially effective in women with PCOS. They also suggested that this treatment is more efficacious than the standard Dianette (ethinyl estradiol) (Schering Plough,

Inc, Welwyn Garden City, United Kingdom) 35-mg plus cyproterone acetate (CPA) 2-mg treatment according to the F-G scores and patient self-assessment after 12 months. The authors proposed that the beneficial effect of metformin may be due to a mechanism involving local growth factor action at the dermal papillae due to increased insulin sensitivity. Metformin 1500 mg daily for 12 months also produced improvements in acne scores without much change in the sebum excretion rate.<sup>46</sup> However, Morin-Papunen et al<sup>47</sup> reported no change in the hirsutism score after metformin treatment.

#### Fertility Management

For patients desiring conception, a multidisciplinary, cooperative approach is essential, considering the heterogeneous nature of the clinical presentation.<sup>40</sup>

#### OVULATION INDUCTION

Several nonpharmacologic (exercise, diet modifications, and weight loss) and pharmacologic (clomiphene citrate, aromatase inhibitors, insulin sensitizers [metformin, rosiglitazone, pioglitazone], gonadotropins) approaches, used alone or in combination, may be used to achieve ovulation.

**Clomiphene Citrate** Clomiphene citrate (CC) continues to be the most commonly used drug to induce ovulation in the treatment of normogonadotropic anovulation associated with PCOS, where the main objective is to obtain development of a single follicle and a reduction in multiple pregnancies. The mechanism of action involves depletion of hypothalamic estrogen receptors (ER) at the hypothalamic level that prevents correct interpretation of circulating, estrogen levels. Reduced levels of estrogen act as a negative feedback to trigger normal compensatory mechanisms that alter pulsatile hypothalamic gonadotropin releasing hormone (GnRH) secretion and stimulate increased pituitary gonadotropin release, which in turn, drives ovarian follicular activity.<sup>48</sup>

The beneficial effects and, specifically, the low risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies because of mono-ovulatory cycles<sup>49</sup> makes clomiphene a first-line therapy in PCOS patients. Clomiphene is administered in 50 to 100 mg doses for 5 days from days 3 to 5 of a spontaneous or induced menstrual flow, although daily dosages of 200 mg/day over 5 days can induce ovulation in ~70% of the treated patients. CC treatment generally should be limited to the minimum effective dose and to no more than six ovulatory cycles.<sup>48</sup> It has been shown that ~60 to 85% of the patients ovulate, but only 30 to 40% of them conceive after CC therapy.

Combination therapies involving CC and other agents (metformin, glucocorticoids, exogenous

gonadotropins) may be effective in 20 to 25% of PCOS women who fail to ovulate with incremental doses of CC (clomiphene resistant). In 20 to 25% of PCOS women who do not respond to incremental doses of CC (clomiphene resistant), adjunctive therapies including bromocriptine (in the presence of hyperprolactinemia or galactorrhea), insulin sensitizers (to treat hyperinsulinemia), oral contraceptives (for pretreatment suppression of LH), pulsatile GnRH (to preserve the physiologic interactive feedback)<sup>50</sup> aromatase inhibitors,<sup>51</sup> and, in selected patients, ovarian drilling<sup>48</sup> may be used.

**Insulin Sensitizing Agents** The safety profile of pioglitazone and rosiglitazone remains to be established, hence, metformin must be used as the first-choice insulin sensitizing drug.

#### Metformin

Metformin (Glucophage; Bristol-Myers Squibb, New York, NY), is an oral biguanide antihyperglycemic drug that may be used in women with PCOS for many indications: from infertility to pregnancy outcome, from hirsutism to cycle regulation, and for long-term prevention of undiagnosed and theoretical morbidities. Insulin resistance is an important "upstream" driver for reproductive and metabolic abnormalities in women with PCOS, particularly the obese, and is linked to a spectrum of metabolic abnormalities, including lipid perturbances, hemostatic alterations, low-grade chronic inflammation, high blood pressure, endothelial dysfunction, body fat redistribution, and glucose intolerance, which eventually lead to diabetes and cardiovascular disease. Reproductive data from controlled studies on metformin treatment (usually short-term) indicate modest effects on ovulation either alone or in combination with other fertility-enhancing medications, hirsutism, and, perhaps, benefits in pregnancy complications (gestational diabetes and early pregnancy loss). Reliable data on metabolic changes are sparse but include modest reductions in BMI, insulin, tissue plasminogen activator antigen (t-PA),<sup>52</sup> low-density lipoprotein (LDL)-cholesterol, and C-reactive protein (CRP), with increases in HDL-cholesterol and improved endothelial structure and function.<sup>52</sup> Increased pregnancy rate (particularly in the leaner patients), a decreased risk of early spontaneous miscarriage, 31% decrease in the risk of developing diabetes,<sup>53</sup> and a very important reduction in the rate of OHSS have been reported after metformin treatment.

The most important and promising therapeutic profile of metformin is related to the role of this agent in controlling an important etiologic factor in the pathogenesis of PCOS hyperinsulinemia. Decreased hepatic gluconeogenesis, reduced hyperinsulinemia by a reduction in the activity of the ovarian cytochrome P450c-17 $\alpha$

hydroxylase and reduced hyperandrogenemia independent of changes in body weight, are some of the proposed mechanisms by which metformin achieves its effects.<sup>54</sup>

The restoration of regular menstrual cycles by metformin has been reported in ~60% of the patients and the restoration of ovulation occurred in 78 to 96% of the patients. Recently, Kriplani and Agarwal<sup>55</sup> have shown that a 6-month metformin therapy improved menstrual cyclicity by 85% in oligomenorrheic, hypomenorrheic, amenorrheic, and infertile women with PCOS. In CC-resistant PCOS women with normal glucose tolerance, metformin may markedly restore spontaneous ovulation with no improvement in insulin resistance.<sup>54</sup> In terms of metabolic and anthropometric effects, current evidence supports a reduction in BMI by around 4% over a few months compared with placebo (representing ~2 to 3 kg reduction) in women with PCOS. A combination of diet and metformin for 6 months has been shown to decrease the prevalence of metabolic syndrome in women with PCOS.<sup>56</sup>

#### METFORMIN PLUS CC

Lord et al,<sup>57</sup> alone in a systematic review, found a significant effect of combination treatment on both ovulation and pregnancy rates. Ovulation occurred in 76% of the patients in the combination group but in only 42% of the CC-alone group (OR, 4.41; 95% CI, 2.37 to 8.22;  $p < 0.0001$ ). Similarly, pregnancy rates were found to be four times higher in combination treatment compared with CC-alone group (OR, 4.40; 95% CI, 1.96 to 9.85;  $p = 0.0003$ ). Because patients using metformin achieve spontaneous ovulation without superovulation, it has been proposed that metformin does not confer the same risks of ovarian hyperstimulation and multiple pregnancies as does CC treatment. Moreover, metformin does not have the same negative effects on the cervical mucus and endometrium as does CC.

Polamba et al,<sup>58</sup> in a prospective, randomized, double-blind, double-dummy, controlled clinical trial, reported a significant increase in the cumulative pregnancy rate (68.9% vs. 34.0%, respectively,  $p < 0.001$ ) and a significant decrease in the abortion rate but no significant difference in the ovulation rate (62.9% vs. 67%, respectively,  $p = 0.38$ ) after CC and metformin as the first-line treatment for ovulation induction in 100 non-obese anovulatory women with PCOS when compared with CC alone.

#### METFORMIN PLUS GONADOTROPINS

De Leo et al<sup>59</sup> have shown in their randomized prospective trial that pretreatment with metformin improves FSH-induced ovulation in women with CC-resistant PCOS. The number of dominant follicles,

cycle cancellation rate, and peak estradiol level were significantly lower in cycles treated with FSH and metformin than in those treated with FSH alone. Metformin leads to an orderly FSH-induced ovulation in patients with PCOS. On the contrary, Yarali et al<sup>60</sup> did not find an improvement in insulin resistance, ovulation, and pregnancy rate after metformin treatment during a low-dose step-up protocol using recombinant follicle stimulating hormone (r-FSH).

#### CONTROLLED OVARIAN STIMULATION WITH GONADOTROPINS

The response to gonadotropin stimulation in women with PCOS often differs significantly from the norm, frequently exhibiting an initial slow response, followed by an "explosive" development of a large numbers of follicles, which may be associated with the specific risks of multiple pregnancies and OHSS.<sup>41</sup> Another problem in PCOS patients is tonic hypersecretion of LH that is proposed as one of the major factors responsible for a high miscarriage rate, poor oocyte quality, and a low fertilization and cleavage rate. Therefore, suppression of endogenous LH is important in patients with PCOS who are candidates for in vitro fertilization (IVF).

Conventional gonadotropin protocols commencing with 75 to 150 IU/day gonadotropin with an increased in dose by 75 IU every 5 to 7 days have resulted in a potentially unacceptable multiple pregnancy rate and life-threatening OHSS that reaches a peak level of 12%. Hence, chronic low-dose protocols such as the *chronic low-dose step-up protocol* and the *sequential step-up and step-down protocol* have been proposed to minimize the risk of multiple follicular developments.<sup>41</sup> The chronic low-dose step-up protocol using urinary follicular stimulating hormone (u-FSH) has the advantage of more controlled stimulation, resulting in the development of fewer multiple follicles and therefore a decreased risk of OHSS and multiple pregnancies.<sup>60</sup> The step-up protocol has been found to be approximately twice more effective than the low-dose step-down protocol in obtaining a higher ovulation rate (70% vs. 62%, respectively), monofollicular development (68% vs. 32%, respectively), a lower cancellation rate (15% vs. 38%, respectively), and a decreased rate of OHSS (2% vs. 11%, respectively).<sup>61</sup>

**GnRH-Agonist Treatment** Although PCOS patients respond substantially well to low-dose gonadotropin therapy for ovulation induction, multiple gestation and spontaneous abortion rates are quite high and range from 20 to 35%. A long standard downregulation protocol using gonadotropin releasing hormone agonist (GnRH-a) prior to the initiation of gonadotropin therapy may decrease the likelihood of spontaneous abortions, suppress elevated LH and androgen levels, and prevent the premature LH surge. Homburg et al<sup>62</sup>

found that pregnant women who received only human menopausal gonadotropin (hMG) for superovulation had higher miscarriage rates than did patients who received GnRH-a in addition to hMG (39.1% vs. 17.6%, respectively). Furthermore, patients with PCO who do not receive GnRH-a therapy may have higher cancellation and lower fertilization rates than those in normal patients. Therefore, GnRH-a treatment is required in patients with PCOS who will receive gonadotropins for ovarian stimulation in IVF cycles.

**GnRH Antagonists** GnRH antagonists have several theoretical advantages over the agonists because they act by the mechanism of competitive binding and thus allow a modulation of the degree of hormonal suppression by dose adjustment. Further, antagonists suppress gonadotropin release within a few hours, have no flare-up effect, prevent a premature LH surge, and gonadal functions resume without a delay after their discontinuation. Albeit, there is no real prospective study that shows the superiority of GnRH-antagonist to GnRH-agonist treatment yet. On the contrary, it has been shown that there were significantly fewer clinical pregnancies in patients treated with GnRH antagonists (OR, 0.78; 95% CI, 0.62 to 0.97).<sup>63</sup>

#### ASSISTED REPRODUCTIVE TECHNOLOGY

Women with PCOS are frequently referred for assisted conception treatment, either because of intractable anovulatory problems that are refractory to standard ovulation induction or because of coexisting infertility factors in women with PCOS and tubal factor subfertility.<sup>64</sup> In an observational comparative study, Palep-Singh et al<sup>64</sup> assessed ethnic variations in women with PCOS (Asians: AP = 104; Caucasians: CP = 220) and those with tubal factor infertility (Asians: AC = 84; Caucasians: CC = 200) in response to IVF/intracytoplasmic sperm injection (ICSI) treatment. Six hundred eight fresh IVF or ICSI cycles using long protocol of GnRH-a suppression and resulting in a fresh embryo transfer were compared. South Asian PCOS women presented at a younger age for the management of subfertility and demonstrated a greater sensitivity to gonadotropin stimulation with lower fertilization and ongoing clinical pregnancy rates compared with their Caucasian counterparts. The Caucasian PCOS women had a 2.5-times (95% CI, 1.25 to 5) higher chance of an ongoing clinical pregnancy compared with their Asian counterparts.<sup>64</sup>

#### Management of Long-term Complications

##### LIFESTYLE INTERVENTIONS

Similar to the management of menstrual irregularity of any origin, lifestyle modification with caloric restriction

and exercise is extremely important in the first stage of intervention. This should be considered as active medical therapy and not as an alternative to other medical interventions.<sup>41</sup> A relatively small or modest (2 to 7%) weight loss can improve insulin resistance, hyperandrogenism, menstrual function, and fertility.<sup>8,65</sup> Moreover, weight loss is also important to reduce long-term risks; therefore, weight loss must be a rational and available goal for obese PCOS patients. Two recent, large studies have shown that decreasing insulin resistance through diet, exercise, or metformin can decrease the development of diabetes in individuals at high risk.<sup>53,66</sup>

The latter approach has the potential to be the cheapest and physiologically the best mechanism to decrease the metabolic and vascular risk in this risk population. In the fertility arena, metformin may prove to be of considerable benefit but mainly in association with other forms of treatment.<sup>52</sup> Lifestyle intervention has been shown to be more successful than metformin alone in reducing the risk of diabetes in the Diabetes Prevention Program (DPP). Weight loss as a strategy to reduce hirsutism has been demonstrated to be effective by several authors in PCOS women.<sup>67,68</sup> In women with PCOS, a reduction in BMI of around 5 to 10% by dint of dietary therapy leads to improvements in ovarian function and some metabolic risk factors.<sup>67,69</sup> The most exciting evidence in support of lifestyle modification derives from a non-PCOS population, showing that intensive intervention, with a 7% weight loss and at least 150 minutes of physical activity per week, can substantially reduce (by 58%) the development of diabetes in subjects at risk.<sup>53</sup>

#### MANAGEMENT OF THE METABOLIC SYNDROME

Antiobesity drugs such as sibutramine and orlistat can be tried to reduce weight and central obesity and jointly control the metabolic syndrome components. Weight loss is the single best therapy for the treatment of individual components of the metabolic syndrome. Newer drugs such as the endocannabinoid receptor blocker rimonabant appear promising in this regard. Atherogenic dyslipidemia should be controlled initially with statins if there is an increase in LDL-cholesterol. If there are other lipid abnormalities then combination therapy of statin with fibrates, nicotinic acid, or ezetimibe should be considered. For insulin resistance, drugs such as thiazolidinediones and renin-angiotensin system blockers are available. Available evidence suggests that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may be more beneficial for the treatment of hypertension in patients with metabolic syndrome compared with others as these drugs also prevent development of diabetes. Patients with metabolic syndrome also have elevations in fibrinogen and other coagulation factors leading to a pro-

thrombotic state, and aspirin may be beneficial for primary prevention in these patients. The new developments in the treatment of metabolic syndrome with drugs such as peroxisome proliferator-activated receptor (PPAR) agonists and cannabinoid receptor-1 antagonists will broaden the horizons of the current treatment options. Fixed-dose combination polypharmacy using a single pill is an interesting concept that needs to be evaluated in long-term prospective trials in such patients.<sup>18</sup> Patients with the metabolic syndrome commonly have other less well-defined metabolic abnormalities (e.g., hyperuricemia and raised C-reactive protein levels) that may also be associated with an increased cardiovascular risk. It seems appropriate to manage these abnormalities. Drugs that beneficially affect carbohydrate metabolism and delay or even prevent the onset of DM (e.g., thiazolidinediones or acarbose) could be useful in patients with the metabolic syndrome.<sup>70</sup>

#### ALTERNATE THERAPY

**Ayurvedic Medicine: Hyponidd** Alternative medicines have been reported to be effective in controlling diabetes, but there are very few placebo-controlled, randomized clinical trials. Hyponidd (Charak Pharma Pvt, Ltd, Madanapalas, India) is a herbo-mineral formulation and has 12 blended ingredients including Vijaysar (*Pterocarpus marsupium*), Gurmar (*Gymnema sylvestre*), Jambu Beej (*Syzygium cumene*), Amla (*Emblica officinale*), Haldi (*Curcuma longa*), Neem (*Melia azadirachta*), Trivang Bhasma, and Shilajit. All these agents have been shown to have some antidiabetic action.<sup>71</sup> Antidiabetic drugs could have three sites of action: reducing insulin resistance, increasing insulin secretion, or decreasing the absorption of glucose from the intestine. Most of the Ayurvedic drugs claim to influence all the three sites of action. *Tinospora cordifolia*, a widely used herb in Indian Ayurvedic medicine, has been shown to have antidiabetic and hypolipidemic action.<sup>72</sup> *Gymnema sylvestre* increases insulin secretion probably by regeneration of pancreatic  $\beta$ -cells.<sup>73,74</sup> In vitro trials on experimental models with *Gymnema sylvestre* have proved that this herbal drug increases insulin release by increasing the cell permeability.<sup>75</sup> Vijaysar has been proved to be effective in reducing HbA<sub>1c</sub> levels in newly diagnosed type 2 diabetic patients.<sup>76</sup> *Pterocarpus marsupium* is effective in reducing levels of blood glucose and glycosylated hemoglobin in type 2 diabetic patients.<sup>77</sup> Similarly, *Momordica charantia* seeds have been reported to have insulin-like bioactivity.<sup>78</sup> Jambu Beej and Neem Paan are reported to have hypolipidemic and antidiabetic action.<sup>79,80</sup>

Hyponidd may be used for the treatment of (i) borderline diabetes (impaired glucose tolerance (IGT) and impaired fasting glucose [IFG]), (ii) as an adjunct

therapy with existing hypoglycemic agents in secondary oral hypoglycemic agent (OHA) failure cases to prevent further complications, and (iii) menstrual disorders and infertility in PCOS.

Advantages of Hyponidd treatment include:

1. No clinical hypoglycemia unlike sulfonylureas.
2. Lowers the lipid levels and protects against cardiovascular diseases.
3. Contains natural antioxidants and rejuvenators.
4. Delays the diabetic complications—impotency in males, neuropathy, and retinopathy.
5. Cost-effective for long-term use.
6. Improves quality of life and restores libido.

Babu et al<sup>81</sup> reported significantly lowered levels of blood glucose, a significant increase in levels of hepatic glycogen and total hemoglobin, significant improvement in blood glucose tolerance, decreased levels of glycosylated hemoglobin, and significantly elevated reduced glutathione and vitamin C in rats rendered diabetic by streptozotocin (STZ) (45 mg/kg body weight) and orally treated with Hyponidd (100 mg/kg and 200 mg/kg) for 45 days.

Poongothai et al<sup>71</sup> in a randomized, double-blind, placebo-controlled study to assess the efficacy of Hyponidd in type 2 diabetic patients with secondary failure to OHAs reported a non-significant decrease in fasting plasma glucose in 56% of the drug group by at least 15 mg/dL against 44% in the placebo group and a non-significant decrease in postprandial plasma glucose by at least 15 mg/dL in 63% of the patients in the drug group compared with 44% in the placebo group. This was in agreement with earlier reports. Secondary failure to OHA was diagnosed if the patient had HbA<sub>1c</sub> levels > 8.5% even after supplementation of maximal dose of a combination of a sulfonylurea (15 mg glibenclamide or 160 mg gliclazide or 15 mg glipizide) and metformin 1500 mg/day. Patients with ketosis, diabetes-related complications, hepatic or renal disease, pancreatitis, cardiac problems, uncontrolled hypertension, malnutrition, and severe immune deficiency were excluded from the study. The recommended dose was 2 tablets, 3 times a day for 3 months. The antidiabetic treatment was continued as usual, and other concomitant medications in case of hypertension and hyperlipidemia were also continued unchanged. The slight (but non-significant) increase in both insulin and C-peptide levels suggests that the drug probably works by stimulating  $\beta$ -cells. The hypolipidemic action of Hyponidd has been reported in earlier studies.<sup>82</sup> Hyponidd showed a slight reduction in serum cholesterol levels compared with the placebo. However, One of the limitations of the study was the small sample size (16 drug and 16 placebo), and more studies are clearly needed to determine the efficacy and mechanism of action of Hyponidd in different groups of type

2 diabetic patients. No significant adverse effects for Hyponidd have been reported so far, implying that the drug is safe.

**D-Chiro-Inositol** We<sup>83</sup> studied the efficacy and tolerability of a traditional Indian drug containing D-chiro-inositol versus metformin in hyperinsulinemic PCOS subjects in a prospective, randomized, comparative study. One hundred seventy-three infertile, hyperinsulinemic PCOS women were randomly allocated to metformin 1700 mg daily twice a day (control group,  $n = 123$ ) or the traditional Indian drug containing D-chiro-inositol, 2 tablets twice daily for a period of 6 months (study group,  $n = 50$ ). A significant improvement in the menstrual frequency (34.4 to 33.6 days,  $p < 0.002$  in the control group and 35.7 to 35.1 days,  $p < 0.002$  in the study group) and fasting insulin levels (11.71 IU/mL to 9.46 IU/mL,  $p < 0.000$  in the control group; and 11.48 IU/mL to 9.58 IU/mL,  $p < 0.000$  in the study group) was observed in all the patients during the study. However, there was no significant difference between the groups in either the menstrual frequency ( $p < 0.282$ ) or the fasting insulin levels ( $p < 0.755$ ). There was a significant decrease in the diastolic blood pressure ( $p < 0.001$ ) and the serum testosterone levels ( $p < 0.024$ ) and a better patient compliance in drug therapy in the study group at the end of 6 months in comparison with the control group. Eleven (22%) patients in the study group and 27 (21.9%) patients in the control group conceived with the help of various assisted reproductive technology (ART) procedures at the end of our study. Hence, the traditional Indian drug containing D-chiro-inositol is equally efficacious but with better tolerability and better patient compliance than metformin and its use in hyperinsulinemic PCOS leads to rapid suppression of insulin and androgen levels as well as improved menstrual frequency. The postreceptor insulin mediator signaling process by D-chiro-inositol promotes efficient intracellular glucose utilization and is fundamental to the correction of pathophysiology of PCOS and probable enhancement of pregnancy rate and outcome.<sup>83</sup>

## FUTURE PROSPECTS

Diagnostic criteria in PCOS are at a crossroads between consensus-based guidelines and evidence-based guidelines.<sup>84</sup> Further research into updated diagnostic criteria for the definition of PCOS and proper identification of patients with the disorder is needed. In addition to classic molecular genetic techniques such as linkage analysis in the form of a whole-genome scan and large case-control studies, promising genomic and proteomic approaches will be paramount to our understanding of the pathogenesis of functional hyperandrogenism and PCOS, allowing a more precise prevention, diagnosis,

and treatment of these prevalent disorders.<sup>33</sup> Both male and female first-degree relatives of patients with PCOS should be tested for the underlying molecular defect(s) of this condition, once it is identified.

One of the prime features of PCOS is abnormal primordial-to-primary follicle development, and so far, little attention has been paid to these events with any clinical intervention in PCOS.<sup>52</sup> There is evidence from one study of protracted metformin treatment<sup>85</sup> suggesting that the number of follicles recruited to grow at this earliest stage, may indeed be attenuated by such treatment, which may be related to reduced insulin and/or androgen drive at the earliest stages of development. However, the safety of long-term use of insulin sensitizing drugs must be documented in larger, randomized, controlled trials.

Long-term prospective epidemiologic trials to confirm the hypothesis that the increasing prevalence of obesity among adolescent and young women with PCOS may partly depend on the increasing worldwide epidemic of obesity may have great relevance in preventive medicine and offer the opportunity to expand our still limited knowledge of the genetic and environmental background favoring the development of PCOS.<sup>86</sup> Both PCOS and obesity are independent risk factors for insulin resistance. The strikingly high prevalence of abdominal obesity, diabetes, coronary artery disease (CAD), and metabolic syndrome in Asian Indians provide alarming data for health professionals and policymakers about the extent of these problems in developing countries, many of which are still grappling with malnutrition and micronutrient deficiencies. There is an urgent need to implement coherent, multifaceted strategies and strengthen population-based primary prevention strategies for the prevention of an "epidemic" of obesity and the metabolic syndrome and their life-threatening complications in Asia. Research studies regarding the correct definitions of the metabolic syndrome and genetic and perinatal factors related to insulin resistance must be conducted in South Asians.<sup>87</sup> The proven benefits of exercise in lowering diabetes and vascular risk, together with wider health benefits, suggest that future studies should urgently address how best to enhance physical activity levels in women with PCOS.

Further, obesity may be optimally defined by a lower cutoff of BMI in Asian Indians. The revised criteria for the BMI-based diagnosis in this ethnic group of obesity will lead to a more rational management of dyslipidemia and a more rational application of dietary restriction, lifestyle measures, and use of metformin.<sup>88</sup>

## CONCLUSIONS

PCOS is an entity with a long life span, requiring "control" rather than "cure," and therapies will change

with the stage of life.<sup>40</sup> The complexity and heterogeneous nature of the disorder and its widespread systemic and metabolic ramifications have drawn together professionals from all walks of the scientific community to implement appropriate diagnostic measures and treatment strategies.

Body weight is the major determinant of insulinemia, insulin sensitivity, and ovarian hyperandrogenism, independent of PCOS, and central obesity in association with insulin resistance is a strong predictor of CAD in South Asians. Though mechanisms by which obesity interferes with the pathophysiology and clinical expression of PCOS are complex and not completely understood, the importance of obesity in the pathogenesis of PCOS, the undaunted increase in the prevalence of obesity and its related complications in Asia, and the documented efficacy of lifestyle interventions and weight loss on hyperandrogenism, ovulation, fertility, and additionally metabolic alterations<sup>86</sup> suggest that lifestyle modifications should be used as primary prevention strategy to combat these disorders. Pharmacologic approaches should be used only if such measures fail.

The use of the traditional age-old Indian therapy—Ayurveda—has proved promising in the treatment of the various associated disorders of PCOS. However, larger, randomized, multicentric trials are required to support the documented efficacy of these drugs. Moreover, studies on PCOS in India have only been conducted in individual setups within cities or among Asian migrant populations. There is no multicentric study that is representative of the prevalence and management of PCOS throughout India. Future studies in this direction would help to highlight the magnitude of the problem and its severity in this part of the world.

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