



# Early Prevention of Polycystic Ovarian Syndrome (PCOS) Risk In Children with Growth Hormone Deficiency

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## ABSTRACT

Polycystic ovarian syndrome (PCOS) is a hormonal disorder and is the leading cause of infertility in women. In 2012, World Health Organization (WHO) stated that around 116 million women around the world were affected by PCOS. The etiology of PCOS has not been fully understood. The most known risk factors are obesity and insulin resistance, usually found in children with growth hormone deficiency (GHD). Growth hormone (GH) therapy can hopefully be the solution to growth disorder and prevent PCOS risks. This article will discuss PCOS and the role of GHD therapy on children in preventing PCOS.

**Keywords:** Growth hormone, growth hormone deficiency, polycystic ovarian syndrome

## ABSTRAK

*Polycystic Ovarian Syndrome* (PCOS) adalah gangguan hormonal yang paling umum ditemukan dan merupakan penyebab utama infertilitas pada perempuan. *World Health Organization* (WHO) pada tahun 2012 menyatakan sekitar 116 juta wanita di seluruh dunia menderita PCOS. Etiologi PCOS belum sepenuhnya dipahami. Namun, faktor risiko yang paling umum diketahui adalah obesitas dan resistensi insulin yang sering didapatkan pada anak-anak dengan *growth hormone deficiency* (GHD). Terapi *growth hormone* (GH) diharapkan dapat mengatasi masalah pertumbuhan dan mencegah risiko PCOS. Artikel ini akan membahas PCOS dan peran terapi GHD dalam pencegahan PCOS pada anak. **Aylicia**. Pencegahan Dini Risiko *Polycystic Ovarian Syndrome* (PCOS) pada Anak dengan Defisiensi *Growth Hormone*.

**Kata kunci:** Defisiensi *growth hormone*, *growth hormone*, *polycystic ovarian syndrome*

### Polycystic Ovarian Syndrome (PCOS)

The Indonesian Obstetrics and Gynecology Association (POGI), through consensus management in 2016, stated that infertility contributes to 90-95% of obstetrics and gynecology patient visits.<sup>1</sup> Polycystic ovarian syndrome (PCOS) is a hormonal disorder generally found and is the leading cause of infertility in women.<sup>2</sup> The symptoms include hyperandrogenism, chronic anovulation, and abnormal metabolic conditions such as obesity, insulin resistance, dyslipidemia, and type II diabetes mellitus.<sup>3</sup> The etiology of PCOS has not been fully understood; genetic factors and lifestyles such as obesity and insulin resistance may have roles.<sup>2</sup>

World Health Organization (WHO) stated that around 116 million women were affected by PCOS in 2012.<sup>4</sup> Wolf, *et al*, claimed that 6-9% of women in productive age in America, several countries in Europe, and Asia are affected by PCOS.<sup>5</sup> The prevalence of PCOS in the USA is

1.6% of 12 million women at the age of 18-45 years which is dominated by the age group 25-34 years and infertility as the main clinical features.<sup>6</sup> Data from Dr. Cipto Mangunkusumo Hospital (RSCM) in Indonesia in 2011 showed that PCOS patients mainly were 26-30-year-old and oligo/amenorrhoea are the main features.<sup>7</sup>

The pathophysiology of PCOS begins with pulsatile GnRH release in the hypothalamus, which causes an increase of luteinizing hormone (LH) production compared to follicle-stimulating hormone (FSH).<sup>1</sup> There is still doubt on whether hypothalamus disorder is the primary or a secondary cause of abnormal steroid feedback.<sup>8</sup> The excessive accumulation of LH will stimulate the production of androgens in the ovaries. At the same time, the relatively reduced amount of FSH causes low aromatase stimulation in granulosa cells, resulting in a decreased conversion of androgens to estradiol estrogens. The increase

of androgens (especially androstenedione) has a role in the patient's abnormal lipid profile, hirsutism, and acne.<sup>9</sup>

The conversion of androgens in the circulation to estrogen estrone mainly occurs in the stromal cells of fatty tissue. In obese PCOS patients, there will be an increase in estrogen production.<sup>9</sup>

Insulin resistance can also occur due to genetic abnormalities and/or an increase in adipose tissue, such as obesity.<sup>9,10</sup> Insulin resistance can cause follicular atresia in the ovaries resulting in impaired follicular development that causes anovulation and then oligomenorrhea or amenorrhea.<sup>8</sup>

PCOS diagnosis used the Rotterdam criteria formulated by the European Society for Human Reproduction, and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) 2003,<sup>11</sup> referred in the PCOS

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management consensus by POGI in 2016.<sup>1</sup> PCOS is diagnosed if there are 2 of the 3 symptoms:<sup>1</sup>

1. Clinical or biochemical signs of hyperandrogenism
2. Chronic ovulation disorders
3. Findings of polycystic ovary morphological features through ultrasonography (USG) tests

Other signs and symptoms in PCOS are menstrual dysfunction (oligomenorrhea to amenorrhoea), hyperandrogenism (hirsutism, acne, androgenic alopecia, and other symptoms), other endocrine disorders (insulin resistance, dyslipidemia, and obesity), obstructive sleep apnea (OSA), metabolic syndrome and cardiovascular disease, endometrial neoplasia, infertility, pregnancy complications including miscarriage, and psychological problems.<sup>1,8</sup>

PCOS clinical manifestations are seen in adolescence, at the onset of puberty. However, the process of PCOS has started since prenatal development. In infants born with low birth weight (LBW) due to maternal malnutrition or placental insufficiency, glucocorticoids are produced. These high levels of glucocorticoids suppress secretions of growth hormone (GH) from pituitary glands.<sup>12,13</sup> The increased glucocorticoids production in infants with LBW is caused by process of survival mechanism by distributing blood flow to vital organs such as the heart, brain and adrenal glands which causes hyperactivity of the hypothalamus - pituitary - adrenal axis and epigenetic modification.<sup>14</sup>

After that, the infant undergoes compensatory growth during the first two years of postnatal life to pursue an appropriate weight target. This triggers metabolic changes such as an increase of body adipose, leading to obesity and insulin resistance.<sup>15,16</sup>

### Growth Hormone Deficiency (GHD)

GH or somatotropin is a single chain 191 amino acid polypeptide produced by somatotrophic cells in the anterior pituitary gland. GH has direct and indirect effect mechanisms. The immediate effect of GH occurs when GH binds to the target cell and stimulates a stimulus-response. Indirect effects mainly occur when insulin-like growth factor-1 (IGF-1) secreted by hepatocytes as a result of increased binding of GH with target cell surface receptors, enter the circulation and have an impact on peripheral tissue growth and its metabolism.<sup>18,19</sup>

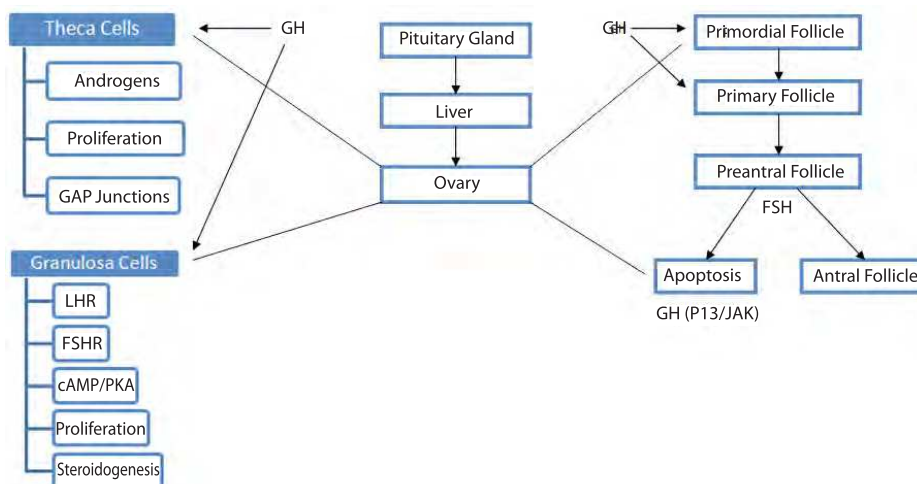
The function of GH on growth is most clearly seen in the cartilages and bones in adolescence. GH activates the mitogen-activated protein (MAP) kinase via the extracellular signal-regulated kinases (ERKs) signal pathway increasing replication of chondrocytes and osteoblasts. The IGF-1 bound to the insulin growth factor 1 receptor (IGF-1R) causes increased metabolism, anabolism, and cellular reproduction and division.<sup>18,19</sup> IGF-1 also works as an inhibitor of cell apoptosis resulting in the prolongation of the age of the existing cells. As the final result, tissue growth occurs and creates a hyperglycemic state in the body. Meanwhile, in the metabolic function, GH performs up-regulating IGF-1, which affects the peripheral cells and basal metabolic

function of organ tissues.<sup>19,20</sup> Fat is processed by stimulation of the triglycerides breakdown and adipocytes oxidation, so it can also be said that GH prevents fat accumulation and can also stimulate lipid mobilization.<sup>17,21</sup>

Growth hormone deficiency (GHD) had an incidence rate of 1:3,500, and 41% of the cases were idiopathic; 35% of the patients were caused by intracranial lesions or radiation treatment, 20% of which were congenital. Risk factors for GHD are a history of head trauma, central nervous system (CNS) radiation, or CNS infection. Neonates with congenital GHD have standard body size at birth. Still, they can have signs suggestive of mixed (multiple) pituitary hormone deficiencies such as micropenis, midline structural defects, prolonged jaundice, or hypoglycemia.<sup>22</sup> GHD in children should be suspected if their growth rate is below average, across the height percentile, and inhibited *bone age*. Thus, children who have GHD usually have fat and short bodies.<sup>23,24</sup> The Indonesian Pediatric Association in its clinical practice guidelines on GHD describe the signs and symptoms that lead to suspicion of GHD.<sup>25</sup>

**Table.** Clinical criteria for growth hormone deficiency in children and adolescents<sup>25</sup>

Height <-2 SD in WHO curve or <P3 in CDC curve
Growth rate <P25 or ≤4 cm per year in the prepubertal phase
The estimated adult height is below the genetic height potential
Other conditions that may be present are intracranial lesions, symptoms and signs of growth hormone deficiency in neonates, and multiple pituitary hormone deficiency (MPHD)
No dysmorphic, bone abnormalities, or specific syndromes



**Figure.** Pathophysiology of PCOS<sup>17</sup>

Laboratory examinations in suspicion of GHD are the measurement of IGF-1, IGF binding protein-3 (IGFBP-3) levels, and GH stimulation test.<sup>26</sup> In children with obesity, normal insulin-like IGF-1 levels were found with reduced GH levels compared to peers with average body weight.<sup>27,28</sup> Conventional measurement of GH levels is not used because GH has pulsatile properties, so the amount measured can vary from undetectable to very high. Meanwhile, the pulsatile properties of GH are dependent on circumstances and environmental stressors. In the GH stimulation test, patients are asked to fast overnight. In the morning, they will be given L-dopa, clonidine, propranolol, glucagon, arginine, or the patient is conditioned to be hypoglycemic using



insulin. The serum GH level will be monitored every hour, and if the GH level does not increase, it can be concluded that the patient has GHD.<sup>18,20</sup>

The main goal of giving GH to GHD patients is to accelerate growth so that the patient has an average height during childhood and can reach the expected size as an adult by the child's genetic potential. A lack of GH levels results in a poor lipid profile in children and can lead to insulin resistance, a risk factor for PCOS. So the provision of GH therapy in children is expected to improve the quality of life by enhancing growth and preventing PCOS in the future.<sup>29,30</sup>

The dose of growth hormone for GHD patients is based on body weight or body surface area (BSA). The recommended starting dose of GH is 0.025 mg/kg/day, and the dosage after that is adjusted to 0.05 mg/kg/day. GH therapy is given subcutaneously for a week and continues for at least in the first four years or until the epiphyseal plate closes. In some patients, higher doses are required. After that, the serum IGF-1 level was measured to determine the response to GH therapy. If the IGF-1 level rises above the average level for the patient's age, the GH dose should be reduced. GH must be given efficiently and effectively because the price is quite high.<sup>25,31</sup>

After initiation and optimization of the dose of GH, a routine check is carried out every 3-6 months to see the growth response and

any side effects of therapy. The examination is done by checking the patient's height every 3-6 months, IGF-1 every three months in the first year, free thyroxine (FT4) and thyroid-stimulating hormone (TSH) every year, and random blood sugar (GDS) every year or more if the patient has risk factors for diabetes mellitus.<sup>25,32</sup>

Furthermore, a study involving more than 4,520 patients with a mean HtSDS of around -1.0 found positive effects on the height standard deviation score (HtSDS) and the psychosocial aspects of patients. These patients received therapy for seven years at an average dose of GH 0.25 mg/kg/week. The difference between adult height standard deviation score (AH SDS) and mid parental height standard deviation score (MPH SDS), which determines the success of the patient to achieve his genetic potential, shows a mean, standard deviation (SD) difference of -0.4 (-2.8 cm) in the SD range -0.2 - 0.6 (-1.4 to -4.2 cm). In contrast, in individuals who did not receive therapy, the mean AH SDS was -4.7, in the SD range of -3.9 to -6. In children and adolescents receiving GH treatment, routine heart examinations, dual X-ray absorptiometry (DXA), and lipid profile examination is recommended.<sup>27,33-34</sup>

Apart from height gain, GH therapy has other positive effects on patients with GHD. The data obtained using DXA show that GHD children have a deficiency in bone mineral density. After one year of GH therapy, normalization

of total body bone mineral density occurred. Body fat percentage also decreased after six months of GH therapy. The target of GH therapy is a growth rate 10 - 12 cm per year in the first year, 7 - 9 cm in the second year, and is equal to or more than 4 cm in subsequent years, or if the bone age is 14-15 years for girls and 16-17 years for boys.<sup>35</sup>

GH administration also has side effects. Acute side effects are such as growth inhibition due to antibody reaction to GH. However, this side effect is rare and only occurs in patients with the deletion of the GH gene. Giving GH to adolescents with fused epiphyseal plates should also be avoided because it can result in acromegaly. Not many long-term side effects have been found. A study in France found a slight increase in the mortality rate in people who had received GH therapy at quite high doses, that is, above 0.05 mg/kg/day. Despite these worrisome findings, increased mortality was not found in a study of 2,800 patients in Sweden, Belgium, and the Netherlands.<sup>36</sup>

### Conclusion

Lack of GH results in a poor lipid profile in children and can lead to insulin resistance, a risk factor for PCOS. GH therapy in children with GHD aims to improve quality of life by achieving optimal height and preventing PCOS risk. GH doses must be administered effectively and efficiently. The patient's response to therapy must always be considered by applicable recommendations to avoid side effects.

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