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# GnRH Agonist Improves Hyperandrogenism in an Adolescent Girl With an Insulin Receptor Gene Mutation

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Type A insulin resistance (IR) is caused by heterozygous mutations in the insulin receptor gene. It presents with mild acanthosis nigricans, severe IR, and hyperandrogenism in the absence of obesity or lipodystrophy. Treatment aims to improve insulin sensitivity and decrease androgens. An adolescent girl was evaluated for secondary amenorrhea and prominent hirsutism. She had a normal body mass index, and laboratory testing revealed an elevated LH to FSH ratio (LH 11.6 mIU/mL, FSH 4.2 mIU/mL), testosterone 96 ng/dL (reference range <50 ng/dL), free testosterone 2.21 ng/dL (reference range <1.09 ng/dL), normal glucose, and HbA1c of 5.6%. She received a diagnosis of polycystic ovary syndrome (PCOS) and was referred to our Multi-Specialty Adolescent PCOS Program. There, oral glucose tolerance test showed fasting glucose and insulin of 80 mg/dL and 63.1 mIU/mL, respectively. The 2-hour glucose and insulin were 199 mg/dL and 1480  $\mu$ IU/mL, respectively. Because of hyperandrogenism with severe IR, dysglycemia, and normal lipids, type A IR was considered. Genetic testing revealed a heterozygous mutation in the insulin receptor gene [c.3095G>A(pGly1032Asp)]. After standard treatment of hirsutism and hyperinsulinism failed, a trial of GnRH agonist therapy improved hyperandrogenism and reduced ovarian size while severe IR persisted. We describe an adolescent with type A IR who experienced resolution of clinical and biochemical hyperandrogenism during GnRH agonist treatment. Given the patient's marked reduction in testosterone and hirsutism despite persistent hyperinsulinism, this case challenges the idea that insulin increases steroidogenesis independently of gonadotropin effect. GnRH agonist therapy should be considered in the treatment of hyperandrogenism in severe cases of IR.

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**Freeform/Key Words:** adolescent, GnRH, hyperandrogenism, insulin resistance, leuprolide

Type A insulin resistance (IR) is severe IR caused by heterozygous mutations in the insulin receptor gene. It presents after puberty with acanthosis nigricans, IR, and hyperandrogenism [1]. Hyperandrogenism in type A IR may result from insulin acting as a co-gonadotropin directly increasing androgen synthesis in theca cells via ovarian insulin receptor signaling [2] or indirectly by increasing GnRH-mediated LH release from the pituitary [3]. Clinical hyperandrogenism is a concern for patients, yet there are limited data on treatment options in severe IR syndromes. In a recently published case of type B insulin resistance masquerading as ovarian hyperthecosis, GnRH agonist treatment curtailed hyperandrogenism without ameliorating diabetes [4]. Similarly, we describe an adolescent patient with type A IR who demonstrated resolution of hyperandrogenism during GnRH agonist treatment while severe IR persisted. This case challenges the notion that insulin increases steroidogenesis independently of gonadotropins.

Abbreviations: BMI, body mass index; IGT, impaired glucose tolerance; IR, insulin resistance; OCP, oral contraceptive pill; OGTT, oral glucose tolerance test; PCOM, polycystic ovarian morphology; PCOS, polycystic ovary syndrome.

**Table 1. Clinical and Laboratory Evaluation of an Adolescent Girl With an Insulin Receptor Gene Mutation**

|                                 | Initial Presentation | 1-mo Follow-Up | 5-mo Follow-Up | 9-mo Follow-Up | 12-mo Leuprolide Initiated | 13-mo Follow-Up | 17-mo Follow-Up | Reference Range |
|---------------------------------|----------------------|----------------|----------------|----------------|----------------------------|-----------------|-----------------|-----------------|
| <b>Reproductive markers</b>     |                      |                |                |                |                            |                 |                 |                 |
| Total testosterone, ng/dL       | 96                   | 142            | 99             | 139            |                            | 7               | 22              | <50             |
| Free testosterone, ng/dL        | 2.2                  | 3.6            | 2.7            | 3.1            |                            | 0.2             |                 | <1.09           |
| Androstenedione, ng/dL          |                      |                | 258            |                |                            |                 |                 | 80–240          |
| DHEA, ng/dL                     | 415                  |                |                |                |                            |                 |                 | 39–481          |
| DHEAS, µg/dL                    |                      |                | 133            |                |                            |                 |                 | 50–540          |
| 17-OHP, ng/dL                   | 178                  |                | 146            |                |                            |                 |                 | 20–265          |
| LH, mIU/mL                      | 11.6                 | 12.1           | 9.4            | 12.7           |                            | 0.3             | 1.0             | —               |
| FSH mIU/mL                      | 4.2                  | 4.1            | 4.2            | 4.5            |                            | 2.0             |                 | —               |
| Ovarian volume, cm <sup>3</sup> |                      |                |                |                |                            |                 |                 |                 |
| Right ovary                     |                      | 5.0            |                | 10.6           |                            |                 | 4.4             | 10              |
| Left ovary                      |                      | 8.9            |                | 8.8            |                            |                 | 5.7             | 10              |
| Follicle number per ovary       |                      |                |                |                |                            |                 |                 |                 |
| Right ovary                     |                      | 18             |                |                |                            |                 | 26              | —               |
| Left ovary                      |                      | 20             |                |                |                            |                 | 18              | —               |
| Follicle number per section     |                      |                |                |                |                            |                 |                 |                 |
| Right ovary                     |                      | 7              |                | 6              |                            |                 | 10              | 9               |
| Left ovary                      |                      | 8              |                | 19             |                            |                 | 10              | 9               |
| Endometrial thickness, cm       |                      | 0.6            |                | 0.7            |                            |                 | 0.6             | 1.0             |
| <b>Metabolic markers</b>        |                      |                |                |                |                            |                 |                 |                 |
| Random cortisol, µg/dL          |                      |                | 4.7            |                |                            |                 |                 | —               |
| HbA1c, %                        |                      | 5.6            | 5.5            | 5.4            |                            | 5.8             | 6.4             | <6              |
| OGTT 0-min glucose, mg/dL       |                      | 80             |                |                |                            | 84              | 91              | <100            |
| OGTT 2-h glucose, mg/dL         |                      | 199            |                |                |                            | 159             | 181             | <140            |
| OGTT 0-min insulin, µIU/mL      |                      | 63.1           |                |                |                            | 397.0           | 90.9            | —               |
| OGTT 2-h insulin, µIU/mL        |                      | 1480           |                |                |                            | 1326            | 1038            | —               |

Table provides laboratory and transabdominal ultrasound results for the patient at initial presentation and throughout the treatment course at each of her follow-up visits. The shaded column demonstrates the initiation of leuprolide at the patient's 12-mo follow-up visit, and in the columns to the right (13-mo and 17-mo follow-up visits) she continues on leuprolide treatment. Reference ranges are reported when available based on internal assays.

Abbreviations: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; 17-OHP, 17-hydroxyprogesterone.

## 1. Case Presentation

A 16-year-old Hispanic–African American girl presented with secondary amenorrhea and hirsutism. She attained menarche at age nine with normal cycles until age 13, when menstrual cycles ceased. At age 14, she noticed increased facial hair necessitating daily waxing of her upper lip and chin. Measurements revealed a normal body mass index (BMI) of 23.7 kg/m<sup>2</sup>. Physical examination was unremarkable except for an elevated Ferriman-Gallwey hirsutism score of 24 and mild acanthosis nigricans. After exclusion of other endocrinopathies, elevated testosterone (Table 1) and secondary amenorrhea led to the diagnosis of polycystic ovary syndrome (PCOS). The patient was subsequently evaluated at the multispecialty adolescent PCOS program 1 month later. Her testosterone levels continued to rise, and a transabdominal ultrasound revealed normal ovarian morphology (based on adult criteria) and no evidence of malignancy. Oral glucose tolerance test (OGTT) showed impaired glucose tolerance (IGT) and a substantially elevated 2-hour insulin level of 1480  $\mu$ IU/mL (Table 1). Despite prominent IR, her lipid profile was favorable. She was prescribed metformin and a course of medroxyprogesterone to induce withdrawal bleeding.

Because of hyperandrogenism with severe IR, dysglycemia, and favorable lipid profile, type A and type B IR syndromes were considered. Genetic testing revealed a heterozygous mutation in the insulin receptor gene for a missense variant designated c.3095G>A(pGly1032Asp), pointing toward the diagnosis of type A IR.

Five months from initial presentation, the patient reported variable metformin adherence. The medroxyprogesterone challenge had triggered vaginal bleeding for 1 week, but no further cycles had occurred. Facial hair returned by noon after her morning shave and depilation, so spironolactone was added to her treatment. Elevated LH and testosterone levels persisted, and additional androgen levels were measured to rule out other endocrinopathies (Table 1).

Nine months after the initial presentation, she still was nonadherent to metformin, had not started spironolactone, and was on her second month of oral contraceptive pill (OCP), which had been started by her primary care physician to induce cyclic bleeding. Hirsutism remained a major concern, and the patient's mood had worsened to prominent depression. Laboratories showed prominent hyperandrogenemia despite OCP therapy (Table 1). Repeat transabdominal ultrasound revealed an unchanged left ovary and a substantial increase in right ovarian size that was not attributed to a dominant follicle, recent ovulation, or ovarian mass. Sonographic findings related to ovarian size (Table 1) now met the definition of polycystic ovarian morphology (PCOM) based on the recent international guidelines for PCOS in adults [5]. Twelve months after the initial presentation, the team decided to start leuprolide 11.25 mg/mo intramuscular injections to improve treatment adherence and hyperandrogenism while potentially yielding a secondary benefit on insulin resistance.

One month after leuprolide-induced LH suppression (13-month follow-up, Table 1), dramatic testosterone reduction and hirsutism improvement were noted, but the patient complained of hot flashes, so OCP was restarted. Seventeen months from initial presentation (5 months after leuprolide was started), repeat OGTT still showed IGT and severe IR along with increased HbA1c (Table 1). Ovarian size had decreased substantially in both ovaries, no longer meeting the definition of PCOM (Table 1). Endometrial thickness was normal and unchanged (<1.0 cm, Table 1). Of note, the patient had discontinued OCP after only 1 month.

## 2. Discussion

We describe a case of an adolescent girl with type A IR whose severe hirsutism and biochemical hyperandrogenism were successfully managed on GnRH agonist therapy, despite extreme hyperinsulinemia. Our patient's dysglycemia and extreme hyperinsulinemia led to genetic testing, which revealed a mutation in the insulin receptor gene [c.3095G>A(pGly1032Asp)]. Although the direct causality cannot be proven, we suspect the mutation is pathogenic because it fits the patient's clinical picture of type A IR and was not present in the asymptomatic mother's genetic testing (asymptomatic father not available for testing). The

amino acid residue pGly1032 is highly conserved during evolution, and no missense variants at this codon have previously been reported. Yet other heterozygous missense variants in this domain have been reported pathogenic in severe IR [6].

This case allowed us to examine the frequently debated bidirectional relationship between insulin and hyperandrogenism, often deemed independent of gonadotropin activity. Insulin can act directly on theca cells to drive testosterone production [3]. Even in patients with insulin receptor defects, ovarian sensitivity to insulin remains conserved. It is postulated that excess insulin activates the similarly structured IGF-1 receptors, leading to ovarian hyperandrogenism [7]. Therefore, in the case of severe IR syndromes, we may expect hyperandrogenism to persist even after the gonadotropin stimulus is suppressed. However, our case showed clinical and biochemical hyperandrogenism that responded dramatically to leuprolide despite persistent hyperinsulinism. Our case suggests that LH is necessary to facilitate insulin's action on steroidogenesis even in severe IR due to a defective insulin receptor. A similar conclusion was drawn in the aforementioned case by Brown *et al.* [4], which demonstrated the permissive effect of LH in a patient with autoimmune type B IR. Hyperandrogenemia itself can lead to IR, but data are inconsistent on the impact of decreasing androgens in improving insulin sensitivity [3]. Some patients with PCOS and mild IR have shown modest improvements in insulin sensitivity during androgen suppression with GnRH agonists [8]. In our case, prominent IR persisted after marked testosterone suppression.

Of note, our patient's diagnosis of severe IR would have been missed if OGTT had not been performed. OGTT is not routinely performed in the setting of normal HbA1c, fasting glycemia, and BMI. Supported by previous findings of abnormal glucose tolerance in nonobese adolescents with hyperandrogenism [9], we argue OGTT should be considered in all patients with hyperandrogenism.

The utility of transabdominal ultrasound for the evaluation of adolescent reproductive health is controversial [5]. There has been some support for use of ovarian size measurement (reviewed in 10]). However, the relevance of follicle counts has remained questionable because of a lack of normative data during adolescence as gathered via modern ultrasound technology. We observed an increase in ovarian volume meeting the adult definition of PCOM in association with persistent hyperandrogenism. Normalization of ovarian volume occurred with resolution of hyperandrogenism. This observation is consistent with ovarian size reflecting hyperandrogenism in adolescents [10]. Transabdominal ultrasound may be helpful in monitoring progression or resolution of hyperandrogenism, particularly in cases where access to reliable biochemical assays is limited.

In conclusion, we present a case of an adolescent with a mutation in the insulin receptor gene whose hyperandrogenism responded to GnRH agonist therapy. Her persistent, severe IR brings into question the mechanism of insulin causing hyperandrogenism independently of LH. GnRH agonist therapy may be helpful in cases of severe IR syndromes with distressing hirsutism when other modalities are unsuccessful.

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**Disclosure Summary:** The authors have nothing to disclose.

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