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Describe role of Submitting/Presenting Trainee in this project (limit 150 words):
Primary contributor to case report, managing patient clinically

Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words

Background:

Type A insulin resistance (IR) is caused by heterozygous mutations in the insulin receptor gene. It presents after puberty with mild acanthosis nigricans, severe IR, and hyperandrogenism in the absence of obesity or lipodystrophy. Treatment aims to improve insulin sensitivity and decrease androgens. Hyperandrogenism in Type A IR likely results from insulin acting as a co-gonadotropin directly increasing androgen synthesis in theca cells via ovarian insulin receptor signaling or indirectly by enhancing GnRH-mediated LH release from the pituitary. Clinical hyperandrogenism represents a serious concern for patients yet there are limited data on treatment options in severe IR syndromes. 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.

Case description:

An adolescent female was evaluated for secondary amenorrhea and prominent hirsutism. She had a normal BMI and laboratories revealed elevated LH to FSH ratio (LH 11.6 mIU/mL, FSH 4.2 mIU/mL), testosterone 96 ng/dL (<50), free testosterone 2.21 ng/dL (<1.09), normal glucose and HbA1c of 5.6%. She was diagnosed with polycystic ovary syndrome (PCOS) and referred to our Multi-Specialty Adolescent PCOS Program. There, oral glucose tolerance test (OGTT) 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 uIU/mL, respectively. Due to hyperandrogenism with severe IR,

dysglycemia and normal lipids, Type A IR was entertained. Genetic testing revealed a novel heterozygous mutation in the insulin receptor gene (c.3095G>A(pGly1032Asp)). After standard treatment for hirsutism and hyperinsulinism failed, the team decided to start leuprolide 11.25 mg/month intramuscular injections to improve hyperandrogenism and potentially see a secondary benefit on insulin resistance. One month after leuprolide-induced LH suppression, dramatic testosterone reduction and hirsutism improvement were noted (13 month follow-up, Table 1). Repeat OGTT still showed impaired glucose tolerance and severe IR along with increased HbA1c (17 month follow-up, Table 1). Ovarian volume had decreased substantially in both ovaries, no longer meeting the definition of polycystic ovarian morphology (17 month follow-up, Table 1).

Conclusion:

We describe a case of an adolescent female with Type A IR whose severe hirsutism and biochemical hyperandrogenism were successfully managed on GnRH agonist therapy, despite extreme hyperinsulinemia. This case allowed us to examine the frequently debated bidirectional relationship between insulin and hyperandrogenism, often deemed independent of gonadotropin activity. It is postulated that excess insulin activates the IGF-1 receptors on the ovary leading to testosterone production. Therefore, in the case of severe IR syndromes, we may expect hyperandrogenism to persist even after the gonadotropin stimulus is suppressed. Contrary to this, 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.
GnRH agonist therapy may be helpful in cases of severe IR syndromes with distressing hirsutism when other modalities are unsuccessful.

Table 1 Clinical and Laboratory Evaluation of an Adolescent Female with a Novel 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
Reproductive Markers								
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 (mcg/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^3)								
Right Ovary		5.0		10.6			4.4	10
Left Ovary		8.9		8.8			5.7	10
Mean OV		7.0		9.7			5.1	-
Follicle Number Per Section								
Right Ovary		7		6			10	9
Left Ovary		8		19			10	9
Mean FNPS		8		13			10	-
Metabolic Markers								
Random cortisol (mcg/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 hr glucose (mg/dL)		199				159	181	<140
OGTT 0 min insulin (uIU/mL)		63.1				397.0	90.9	-
OGTT 2 hr insulin (uIU/mL)		1480				1326	1038	-

Abbreviations: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; 17-OHP, 17-hydroxyprogesterone; LH, luteinizing hormone; FSH, follicle stimulating hormone; OV, ovarian volume; FNPS, follicle number per section; HbA1C, hemoglobin A1c; OGTT, oral glucose tolerance test; mo, month. Reference ranges are reported when available based on internal assays.

Table 1 legend:
Table 1 provides laboratory and pelvic 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 month follow up visit and the following columns to the right (13 month and 17 month follow up visits) she continues on leuprolide treatment.