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Gonadotropin Releasing Hormone (GnRH) Agonist Improves Hyperandrogenism in an Adolescent Female with a Novel Insulin Receptor Gene Mutation

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BACKGROUND

- Type A insulin resistance (IR) is caused by heterozygous mutations in the insulin receptor gene
  - Clinical features include hyperandrogenism and severe IR
- Hyperandrogenism 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 (1,2)
  - In the case of severe IR syndromes, hyperandrogenism could be expected to persist due to severely elevated insulin even after the gonadotropin stimulus is suppressed

CLINICAL CASE

Initial Presentation and Diagnosis

- A 16 year old female (7 years post-menarche) was evaluated for secondary amenorrhea and prominent hirsutism. She had a normal BMI, elevated LH:FSH, testosterone and free testosterone, normal glucose and HbA1c (Table 1)
- She was diagnosed with polycystic ovary syndrome (PCOS) and referred to our Multi-Specialty Adolescent PCOS Program (1 month follow-up, Table 1)
  - Oral glucose tolerance test (OGTT) revealed severe IR and impaired glucose tolerance
  - 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))

Treatment

- Standard treatment (oral contraceptive, metformin, spironolactone) failed due to noncompliance
- Leuprolide 11.25 mg/month was initiated to improve hyperandrogenism and potentially provide a secondary benefit on IR
- After one month of leuprolide, dramatic testosterone reduction and hirsutism improvement were noted (13 month follow-up, Table 1)
  - Repeat OGTT showed persistent impaired glucose tolerance and severe IR along with increased HbA1c
- After 5 months of leuprolide, transabdominal ultrasound showed reduction in ovarian volume (17 month follow-up, Table 1)

CLINICAL CASE

Table 1: Laboratory and pelvic ultrasound values at initial presentation and during treatment

	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	10
Follicle Number Per Section								
Right Ovary		7		6			10	-
Left Ovary		8		19			10	-
Mean FNPS		8		13			10	-
Metabolic Markers								
Random cortisol (mcg/dL)			4.7					-
HbA1c (%)		5.6	5.5	5.4		5.8	6.4	-
Fasting glucose (mg/dL)		80				84	91	-
2 hr $glucose_{OGTT}$ (mg/dL)		199				159	181	-
Fasting insulin (uIU/mL)		63.1				397	90.9	-
2 hr $insulin_{OGTT}$ (uIU/mL)		1480				1326	1038	-

Laboratory and pelvic ultrasound values at initial presentation and throughout treatment. The shaded column demarks initiation of leuprolide at 12 mo follow-up visit and continued treatment at 13 and 17 mo visits. Abbreviations include: 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. Reference ranges are reported where available.

MAIN FINDINGS AND IMPLICATIONS FOR CARE

- GnRH agonist therapy is helpful in cases of severe IR with distressing hirsutism when other modalities are unsuccessful
- Resolution of hyperandrogenism and persistent IR while on GnRH agonist therapy challenges the notion that insulin increases steroidogenesis independently of gonadotropins

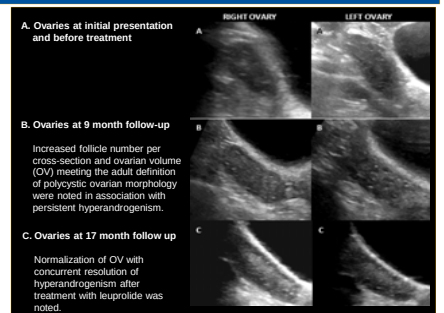

Figure 1: Cross-sectional views of the ovaries using transabdominal ultrasonography before and during leuprolide treatment.

DISCUSSION

- We describe a case of an adolescent female with Type A IR whose severe hirsutism and hyperandrogenism were improved with leuprolide, despite extreme hyperinsulinemia
  - Ovarian volume decreased in association with the resolution of hyperandrogenism, consistent with ovarian size reflecting hyperandrogenism in adolescents (3)
- This case allowed us to examine the frequently debated bidirectional relationship between insulin and hyperandrogenism, often deemed independent of gonadotropin activity

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