Reversible severe ovarian enlargement in an infant with significant insulin resistance

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ABSTRACT

The extent, severity, and radiological findings of ovarian growth in infants with genetic syndromes of insulin resistance have not been fully described. We report a rare case of reversible massive ovarian enlargement in a female infant with a congenital insulin resistance syndrome, likely Rabson-Mendenhall syndrome given the less clinically severe course. The patient presented with neonatal diabetes with hyperinsulinemia and hyperglycemia due to congenital insulin resistance. She developed increasing severe bilateral ovarian enlargement which peaked at 4 months of age, followed by gradual decrease in size of the ovaries following treatment with insulin-sensitizing drugs and improved hyperinsulinemia. The ovarian enlargement is postulated to be secondary to the trophic effects of insulin acting in a gonadotropin-independent mechanism. Hyperinsulinemia in congenital insulin resistance can also result in hypertrophy of other organs. Understanding the pathophysiology behind massive ovarian enlargement in the setting of congenital insulin resistance syndromes can help guide appropriate therapy.

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Introduction

Massive ovarian enlargement, without underlying mass, is a rare finding in neonates. Significant ovarian enlargement has been associated with insulin-resistant states such as polycystic ovarian syndrome (PCOS) and rare congenital syndromes such as leprechaunism, also known as Donohue syndrome [1]. Other entities in the differential diagnosis of severe ovarian enlargement (excluding neoplasm) include ovarian torsion and causes of ovarian hyperstimulation syndrome, such as primary hypothyroidism or elevated human chorionic gonadotropin [1–4]. This report describes the reversible findings of severe bilateral ovarian enlargement in an infant with a congenital insulin resistance syndrome.
Fig. 1 – (a) At 3 weeks of age, transverse sonographic image of the pelvis demonstrates significantly enlarged right and left ovaries containing multiple cystic structures. (b, c) Transverse sonographic images of the pelvis utilizing spectral Doppler demonstrate adequate Doppler flow to both ovaries.
Case report

A 3-week-old female born at 37 weeks via C-section with a history of severe symmetrical intrauterine growth restriction was admitted for hyperglycemia consistent with neonatal diabetes. The patient was subsequently diagnosed with marked insulin resistance secondary to an insulin-receptor (INSR) gene variant detected by focused exome sequencing.

Insulin and proinsulin levels at 3 weeks of age were markedly elevated to 582.3 μIU/mL (normal reference range 2.0–19.6) and 674.3 pmol/L (<18.8), respectively. Glucose levels were markedly elevated at 366 mg/dL. Laboratory evaluation also showed normal thyroid function, low insulin-like growth factor-1 (IGF-1) levels, and pubertal gonadotropin, and estradiol levels. On physical examination, the patient was noted to have abnormal facies with large eyes and upsloping nose, as well as thin extremities. The patient had normal female external genitalia with no signs of puberty to suggest that the ovaries were hormonally active.

Initial pelvic ultrasound at 3 weeks of age demonstrated severe bilateral ovarian enlargement with numerous internal follicles/cysts and preserved color and spectral Doppler flow in both ovaries (Fig. 1). The uterus had a normal prepubertal appearance. Ovarian volumes were 12.8 mL and 8.7 mL on the right and left, respectively. Mean ovarian volume in females between one day to three months of age is 1.06 mL with a standard deviation of 0.96 [5]. This would place this patient’s right and left ovarian volumes at 12.2 and 8.0 standard deviations above the mean for age, respectively.

Her neonatal diabetes was initially treated with high-dose insulin therapy, and subsequently with the addition of insulin-sensitizing agents (metformin and pioglitazone), with slight improvement in glucose control. The patient was also placed on a continuous glucose monitoring device and had a pelvic binder in place to help with the weight of the ovaries.

A computed tomography (CT) scan at 4 months of age performed for abdominal distension and fever showed further increase in the severe enlargement of the ovaries bilaterally, with ovarian volumes of 106 mL and 60 mL on the right and left, respectively (Fig. 2). Insulin levels remained significantly elevated at 625.3 μIU/mL (2.0–19.6). The estradiol level was slightly higher than prepubertal levels and the gonadotropin levels were suppressed, possibly reflecting some degree of mini-puberty.

A follow-up ultrasound at 5 months of age showed interval decrease in size of the ovaries, with volumes of 51 mL and 18 mL on the right and left, respectively (Fig. 3). Another ultrasound performed at 15 months of age demonstrated ovarian volumes of 11 mL on the right and 8 mL on the left, respectively (Fig. 4).

The patient was also found to have borderline left ventricular and septal hypertrophy of the heart, as well as nephrocalcinosis. A presumed diagnosis of Rabson-Mendenhall syndrome (as opposed to Donohue syndrome) was made given the less severe clinical course.

Discussion

We report a case of reversible massive ovarian enlargement in the setting of severe insulin resistance syndrome with resultant significant hyperglycemia, which was unresponsive to insulin but marginally responsive to insulin sensitizers. We postulate that our patient’s massive ovarian enlargement resulted from an insulin-mediated, gonadotropin-independent mechanism, in the setting of severe resistance to the metabolic action of insulin but preserved responsiveness to the anabolic action of insulin. This has been previously suggested in infants with Donohue syndrome and is postulated to be mediated through an intact homologous IGF-1 receptor pathway [6].

Insulin receptor-related severe syndromic insulin resistance comprises a phenotypic spectrum that is a continuum from the severe phenotype of Donohue syndrome (also known as leprechaunism) to the milder phenotype of Rabson-Mendenhall syndrome [7]. Both syndromes are characterized by fluctuations in blood glucose levels in association with hyperinsulinemia. Donohue syndrome is at the extreme end of the spectrum, with death usually before age 1 year due to hypertrophic cardiomyopathy secondary to severe organomegaly [7]. Other manifestations of Donohue syndrome include severe prenatal growth restriction with postnatal growth failure, hypotonia, developmental delay, characteristic facies, and organomegaly [7]. Rabson-Mendenhall syndrome is at the milder end of the spectrum, with complications of longstanding hyperglycemia as the most common cause of death. Other findings may include growth delay, intellectual disability, nephrocalcinosis, and organomegaly [7].
Hyperinsulinemia presumably can produce gonadotropin-independent ovarian enlargement, as well other organomegaly [6,7]. Ovarian tissues express IGF-1 receptors, and insulin and IGF-1 receptors share up to 60% homology [6,7]. Thus, the high serum levels of insulin are thought to transduce anabolic actions through a receptor-effector pathway different from, but homologous to, its natural hormone receptor-effector pathway, that is, via specificity spillover through “promiscuous” (IGF-1) receptors [6].

The ovarian enlargement seen in postpubertal females with PCOS may have a similar insulin-mediated pathogenesis. Severe ovarian enlargement with granulosa-cell proliferation in antral follicles was found in a patient with PCOS and severe insulin resistance, who was on long-term gonadotropin-releasing hormone (GnRH) analogue therapy [4]. This suggests that hyperinsulinemia can act as a granulosa-cell mitogen in the absence of gonadotropin-dependent ovarian function [4]. Indeed, females with type A insulin resistance syndrome, which is on the milder spectrum of inherited severe insulin re-

**Fig. 3** – (a, b) Abdominal/pelvic ultrasound at 5 months of age. Longitudinal sonographic images of the pelvis demonstrate slight interval decreased size of the enlarged ovaries, with volumes of 51 mL and 18 mL on the right and left, respectively.
Fig. 4 – (a, b) Pelvic ultrasound at 15 months of age: Longitudinal sonographic images of the pelvis demonstrate decreased size of the now mildly enlarged bilateral ovaries with volumes of 11 mL and 8 mL on the right and left, respectively.

sistance syndromes, also develop PCOS and enlarged ovaries [8]. Ovarian cysts have also been seen in non-insulin-resistant hyperinsulinemic infants of diabetic mothers, which further suggests that high circulating insulin levels may act in the trophic manner typical of gonadotropic hormones [6].

Overall, this is a unique case of massive ovarian enlargement in the setting of a severe insulin resistance syndrome, with resolution of the severe ovarian enlargement postulated to be secondary to reduction in insulin resistance and hyperinsulinemia after insulin-sensitizer therapy.

Conclusion

Massive ovarian enlargement in the neonate is rarely encountered by the radiology community.

Presumably increased levels of insulin can drive ovarian enlargement by a gonadotropin-independent mechanism of action. We explored insulin receptor-related insulin resistance syndromes, which can result in severe ovarian enlargement.
Patient consent statement

We have obtained written, informed consent for publication of this case from the patient’s parents.

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Disclosures

Dr. Ryabets-Lienhard - Principal Investigator for clinical trials with Amgen, Ultradyn, Shire, and Ascendis. Dr. Geffner - Principal Investigator for a clinical trial with NovoNordisk; Advisory Board member/Consultant for Adrenas, Daiichi Sankyo, Gilead, Pfizer, QED, and Spruce Biosciences; member of a Data Safety Monitoring Board for Ascendis; and recipient of royalties from UpToDate and McGraw-Hill. The authors are requesting co-first authorship for Dr. Lillian Lai and Dr. Amir Mikhchi given equal contribution to this work.

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