INTRODUCTION

- Polycystic ovary syndrome (PCOS), is a disease of unknown etiology
- It is characterized by a variable elevation and periodicity of LH secretion.
- We previously showed presence & activity of autoantibodies (AAbs) to the second extracellular loop (ECL2) of other group A G-protein receptors (similar to GnRH).

OBJECTIVE

To compare the presence & activity of AAbs directed to the ECL2 of the GnRH receptor (GnRH-R) in PCOS patients compared to ovulatory controls

MATERIAL & METHODS

- Case Cohort Study at an academic fertility clinic 2012-2016
  - Infertile PCOS subjects based on Rotterdam criteria
  - Infertile ovulatory controls
- Stored serum (prior to beginning fertility treatment) was screened by ELISA for AAbs to GnRH-R using a synthetic 28-mer peptide (GenScript, Piscataway, NJ) from the ECL2 of human GnRH-R as coating antigen
- Optical density (OD) values were read at 405 nm at 10 minute intervals for maximal separation
- Activity of GnRH-R AAb in IgG purified from sera of 4 subjects with PCOS & 4 controls was analyzed with a GnRHR-transfected Chem-1 cell-based calcium flux assay (Eurofins, St Charles, MO)
- AAb effect was tested by selective GnRH-R blockade
- Group data are presented as mean ± SD or percent
- Groups were compared using Student t or Pearson chi-squared tests
- OD values were converted to z-scores for analysis, and are reported as such
- A ROC curve was used to assess OD as a diagnostic test for PCOS

RESULTS

- 79 PCOS patients & 73 controls were included
- There were no significant (p>0.05) differences between the groups in age, race, or BMI—TABLE 1
- Standardized OD in PCOS patients (0.53±1.00) was significantly higher (p<0.001) than in ovulatory controls (-0.55±0.62)—FIGURE 1
- Using OD to determine a ROC curve for PCOS the Area Under the Curve was 0.83 (±0.03;p<0.001)
- As a predictor of PCOS, OD alone had 74% sensitivity & 84% specificity for PCOS—FIGURE 2
- There was a significant calcium flux response to IgG isolated from PCOS patients vs controls (67.1±6.4 vs 30.9±1.5, % of maximum response, p<0.01)
- The PCOS (but not control) IgG-induced GnRH-R activation was effectively suppressed by specific GnRHR blockade with cetrorelix (p<0.01)—FIGURE 3

REFERENCES


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DISCUSSION

- Activating AAb to the ECL2 of the GnRH-R is a sensitive & specific biomarker for PCOS
- At the hypothalamic/pituitary level, AAbs will likely be contributive & possibly causative of the menstrual dysfunction & metabolic disturbances demonstrated in PCOS subjects, and may represent the long-desired identifying diagnostic test for PCOS
- Our next steps are
  - Evaluate the association between these AAbs and the PCOS-associated metabolic abnormalities using animal models & humans
  - Evaluate pregnancy outcomes with ovulation induction in patients with & without AAbs to GnRH-R