



Endocrine parameters and ovarian dynamics in Ossabaw miniature swine with metabolic syndrome suggest a model for polycystic ovary syndrome



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INTRODUCTION

- PCOS affects 5-10% of reproductive aged women.
 - PCOS is a complex systemic reproductive and metabolic disorder.
 - Insulin resistance plays a prominent role in PCOS.
 - risk of type II diabetes mellitus (DM) and cardiovascular disease (CVD).
 - Women with PCOS commonly display features of the Metabolic Syndrome (MS), many of which are cardiovascular risk factors.
 - Gynecologic symptoms include hyperandrogenemia, hirsutism, anovulatory infertility, impaired oocyte quality, recurrent pregnancy loss, gestational diabetes and endometrial cancer.
 - The etiology and pathogenesis of the syndrome are unclear, and there is no effective cure.
 - Currently, no comparative animal model of PCOS exists that embodies the complexity of the syndrome.
 - Characterization of a complete animal model will significantly advance the field and provide insight into this multifaceted disease.
- Diagnostic criteria for PCOS include the presence of 2 of the following 3 conditions: 1) oligo- or anovulation; 2) clinical or biochemical signs of hyperandrogenism; and 3) polycystic ovaries, with the exclusion of other etiologies (Rotterdam 2004¹).
- Women with PCOS displaying three of the following five criteria are diagnosed with MS: 1) abdominal obesity; 2) elevated triglycerides; 3) elevated HDL; 4) high blood pressure; and 5) impaired glucose tolerance.

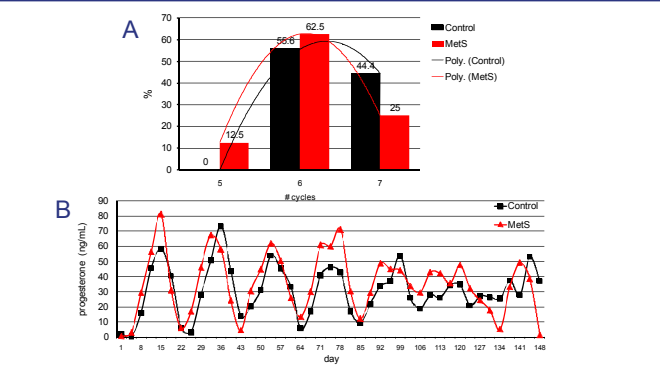


FIGURE 2. Average progesterone values are higher in MetS gilts. Diet significantly ($P < 0.05$) affected average peripheral progesterone concentrations (MetS, 36.14 ± 2.09 vs C, 30.12 ± 1.66). All gilts remained cyclic throughout the trial, although more MetS gilts had only 5 cycles and fewer MetS gilts had 7 cycles when compared to controls (A). (Average # estrous cycles: MetS, 6.13 ± 0.23 ; Control, 6.44 ± 0.18 . Average cycle length: MetS, 20.44 ± 0.28 ; Control, 20.05 ± 0.31). Average progesterone appeared acyclic after the fourth cycle (B), possibly reflective of slightly longer cycles in MetS gilts.

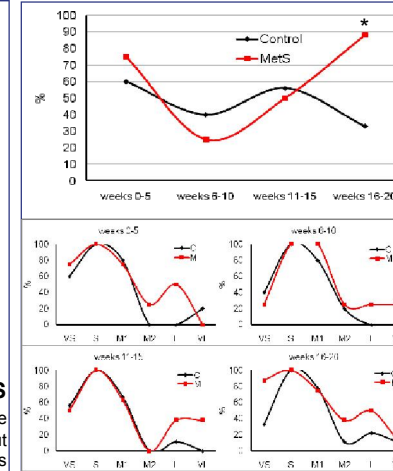


FIGURE 4. Follicular growth is altered in MetS gilts. The percentage of gilts with very small (<1.5 mm) follicles is increased in MetS gilts in the luteal phase of the cycle in the late period of the study, when androstenedione levels are increased (A). The percentage of control and MetS gilts with follicles in each size category over the four periods of the trial (initial, weeks 0-5; early, weeks 6-10; middle, weeks 11-15; late, weeks 16-20) is shown in panel B. MetS gilts consistently have more large follicles, although this does not seem to be affected by time on the diet. (VS, <1.5mm; S, 1.5-2.9mm; M1, 3-4.9mm; M2, 5-6.4mm; L, 6.5-12mm; VL >12mm).

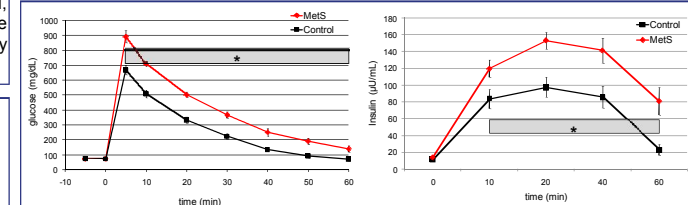


FIGURE 5. MetS gilts develop glucose intolerance and insulin resistance. Blood glucose and insulin response to an intravenous glucose challenge (IVGTT, administered at the completion of the trial) are elevated in MetS gilts.

CONCLUSIONS

- Diet induces hyperandrogenemia in Ossabaw gilts, a primary diagnostic criteria for PCOS in women.
- The normal recruitment of follicles from the growing pool appears to be altered in MetS gilts, resulting in the accumulation very small sized follicles. This is reminiscent of the accumulation of small follicles (2-9 mm), or cysts, in PCOS women. PCO is another diagnostic criteria for PCOS.
- Higher progesterone and slightly longer cycles in MetS gilts suggest that there may be anomalies in the ovulatory mechanism, potentially due to arrested follicular development of very small follicles. Oligo- or anovulation is also a PCOS diagnostic criteria.
- Metabolically, diet induces abdominal obesity, elevated triglycerides (data not shown), and impaired glucose tolerance, thus meeting the diagnostic criteria for metabolic syndrome in the presence of PCOS.
- In summary, these data demonstrate that Ossabaw swine may represent a novel animal model in which to study the interrelated reproductive and metabolic features of PCOS.

REFERENCES

- Rotterdam EA-SPCWG (2004). Revised 2003 consensus on diagnostic criteria and long term health risks related to polycystic ovary syndrome. *Fertility & Sterility* 81, 19-25.

HYPOTHESIS

Obese Ossabaw swine exhibit the complex array of reproductive and metabolic symptoms of PCOS.

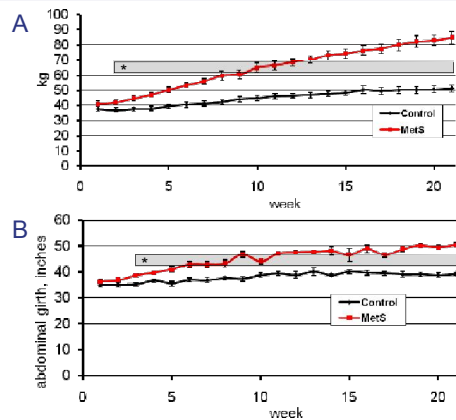


FIGURE 1. Weight and abdominal girth are increased in MetS gilts. Ossabaw gilts were fed a high fat-high fructose diet that induces metabolic syndrome (MetS, n=8), or a control diet (Control, n=9), for 20 weeks. By week 2 ($p < 0.05$) and for each subsequent week ($p < 0.01$), MetS gilts were significantly (*) heavier than controls (A). Abdominal girth measurements were also significantly ($p < 0.01$, *) larger in MetS gilts beginning in week three, and in every subsequent week, than in control gilts (B).

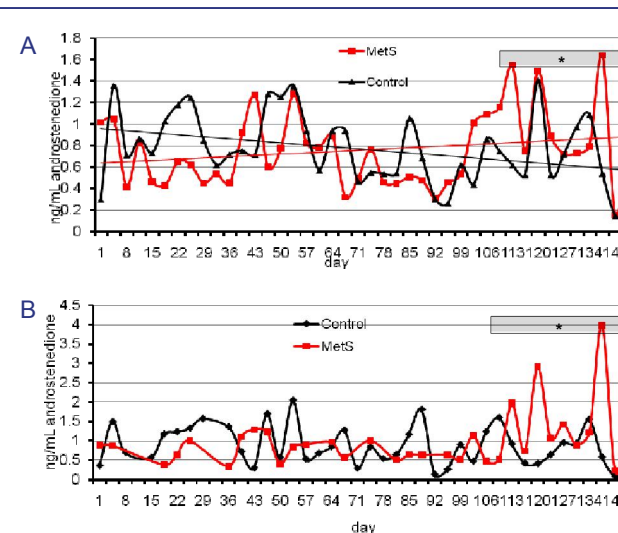


FIGURE 3. MetS gilts develop hyperandrogenemia. The study period was subdivided into initial (d1-36), early (d37-72), middle (73-108) and late (d109-144) periods. MetS gilts had significantly higher androstenedione levels during the late period (A: Control, 0.695 ng/mL; MetS, 0.992 ng/mL, linear trend lines are shown). This difference was even more obvious ($P = 0.02$) in the follicular phase of the cycle (B: MetS, 1.46 ng/mL; Control, 0.84 ng/mL).