Ovarian Follicular Dysplasia (OFD) in Florida beef herds and beyond.

John F Roberts[1], Julie Gard[2], Fernando Biase[3], Owen Rae[4], Timothy Braden[1]

[1]Department of Anatomy, Physiology and Pharmacology, College of Veterinary Medicine, Auburn University, Auburn AL, [2]Department of Clinical Sciences, [3] Department of Animal Sciences, Auburn University, AL, [4] Dept of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL

Beef operations in many sections of the United States often have a yearly production rate less than 80% live calves in per bull exposed female. This lower efficiency is often blamed on infectious disease of the uterus while minimal consideration is given to ovum production and hormonal regulation in the ovary. Non-infectious and degenerative diseases of the ovary are difficult to diagnose and post mortem microscopic examination is needed to accurately confirm these lesions. For years a small group of Florida bovine practitioners have suspected a high incidence of ovarian pathology using palpation and in recent years these veterinarians have further utilized ultrasound to characterize degenerative ovarian disease. In post-mortem studies of repeat-breeder and open cows sponsored by the Florida Cattleman's Association ovarian follicular dysplasia (OFD) was by far the most common reproductive disease diagnosed in reproductive cull cows. OFD has also been recognized in cull cows processed in South Carolina and in randomly sampled cows submitted to the diagnostic system in Alabama.

OFD is a slowly progressive bilateral disease manifested by evident dysplasia of follicular granulosa cells and in advanced cases progresses to Sertoli-type granulosa-thecal cell tumors (GTCT). The average of age of cows diagnosed with OFD at slaughter is 7-8 years but early stages of the disease have been observed in heifers. Cows with early stages of OFD are capable of conceiving but this ability appears to diminish as the disease progresses. We have observed early and mid gestation abortions and mummified fetuses in OFD cows and hormonal maintenance of pregnancy has been questioned. Because OFD has been recognized in Florida, producers and veterinarians are quick to implicate the presence of *Bos indicus*, genetics, common in the Southeastern United States, as a predisposing factor for this disease. Literature on ovary dysplasia and Sertoli-type GTCT does not support this hypothesis. A 2004 study conducted in Estonian dairy cattle describes some microscopic characteristics present in OFD including small cystic degeneration of follicles, dysplasia of follicles, hyperplasia of cortical stroma, hyperplasia of the rete ovarii and preneoplastic changes in granulosa cells. (Kübar) In a 1969 study of ovarian tumors in *Bos tarus* two types of granulosa-thecal cell tumors (GTCT) were identified; classic large granulosa cell tumors, often associated with nymphomania and a second lesser known type of benign Sertoli-type GTCT. (Norris) Dr. McEntee, Cornell University, examined thousands of bovine reproductive tracts over a 30 period and concluded that cows commonly have small benign tumors that are often not noticed by routine by USDA inspection. (McEntee) It is our observation that early OFD associated changes in granulosa cells resemble a morphological shift towards testicular Sertoli cells. This is entirely plausible since granulosa cells and testicular Sertoli cells have a common embryologic origin: gonadal precursor cells. (Piprek) For these reasons we believe OFD to have always been present since at least the 1960's and may possibly affect cattle on multiple continents.

We developed a microscopic grading system (I-IV) for the severity of OFD ranging from mild (Grade I) to Sertoli-type GTCT (Grade IV). Grade II through IV may have dystrophic mineralization of dysplastic follicles and these mineral densities create shadows on ultrasound images. Therefore in some cases of OFD it is possible to visualize increased hyperechogenicity and decreased number of fluid filled follicles

on ultrasound. These changes are not difficult to see in Grade III and IV OFD while changes in Grade I and II are difficult, if not impossible to visualize by ultrasound.

Since culling of early OFD cows would improve herd efficiency and an early ante-mortem diagnostic method is needed. We are just beginning to explore variations in gene expressed demonstrated in OFD. At present, we have compared the ovary cortex transcriptome from five OFD and five non-OFD females originating from ranches with high incidence of OFD. Approximately 13,400 commonly expressed genes were identified in each ovary and 44 genes had variable expression between the two selected groups. Thirty-eight of these genes had been previously characterized in at least one species of animal and six genes were non-annotated. Ten of these genes were over expressed and thirty four were under expressed. A review of literature that cited annotated genes identified in our study identified 13/38 involved in cancer pathogenesis (ATP4B (Raja), CCL21 (Bohm), CDH5 (Bekes, Wang), CHGA (Wu), CLMN (Garritano), ECEL (Davidson), FAM43A (Chen), FLI1 (Tang), FLT4 (Decio), KAT2A (Sun), MECAM (Dutta), NISCH (Li), TCF4(Yoshioka), 9/38 associated with vascular endothelial function (ASB5 (Boengler), CD300LG (Umemoto), CDH5(Bekes), ECE2(Choi), FLT4 (Ortega), PECAM (Caruso), CDC42EP1 (Liu), CLEC14A(Mura), KDR(Roberts) and 4/38 involved in testicular function (BCL6B (Caines), CLGN (Taketo, Lin), PECAM (Caruso), SOX18(Pula). One of the up-regulated genes (FAM189A2) is also a marker for gonadal dysgenesis in humans. (Norling) One of the down regulated genes (TCF4) is associated with polycystic ovary syndrome in humans. (Gammoh) Expression profiles of 2/6 non-annotated genes showed good potential as markers for OFD. Our goal is to identify a genetic marker present in blood or body fluids that could be used to identify sub-fertile females. We are also hopeful that variations in ovarian gene expression may reveal cellular pathologic processes leading to discovery of the OFD etiology.

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