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Overgrowth Syndrome

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Introduction

Overgrowth syndromes (OGS) refer to a heterogeneous group of conditions found in many species[1–3], which show a common feature of excessive growth. According to the definitions used in human, OGS can be divided into two categories based on phenotypes, which are generalized OGS and localized/partial OGS[1]. Generalized OGS are often characterized by a 2–3 standard deviations increase in overall growth parameters including body weight, height, and head circumference[4,5]. On the other hand, localized/partial OGS results in overgrowth in to one or few organs or regions of the body[6]. OGS can also be characterized as congenital and/or postnatal according to the age when phenotypes present[4,7–9]. A greater risk of tumorigenesis is a shared feature of many OGS found in human[1].

A generalized congenital OGS in bovine is known as large offspring syndrome (LOS[2]; Figure 1). LOS refers to a group of abnormal phenotypes occurring in bovine and ovine fetuses, placentas and newborns produced by assisted reproductive technologies (ART). There are many ART-induced LOS calf reports from experimental studies[10–14]. Features of LOS include overgrowth, enlarged tongues, umbilical hernias, muscle and skeleton malformation, abnormal organ growth, allantois development defects, abnormal placental vasculature, and even increased early embryo or fetus death rates[15–18]. LOS can affect the dam and cause death of the afflicted animal bringing financial loss to producers. Although there is a lack of published reports providing the incidence of LOS in ART-produced offspring, through personal communications (Rocio M Rivera), this incidence has been reported to being as high as 10%.

Clinical features of LOS

Macrosomia refers to increased body and limbs size, which is the most commonly identified feature of LOS[2,17,18]. This increased size of body and limbs can be two and five times greater than the average size at birth, respectively[17], and the increased body size can be detected as early as the fifth week of gestation in cattle[19]. Increased skeletal lengths have been reported to be coupled with macrosomia[14]. However, calves with macrosomia at birth reach similar mature body weight as control animals[20]. Using the criteria for human, birthweight greater than two times of standard deviation above the mean is defined as macrosomia[21]. Since LOS was coined with overgrowth initially, it is easily taken for granted that macrosomia is a necessary feature. However, LOS is not always characterized by overgrowth, as thus is sometimes referred to as abnormal offspring syndrome (AOS)[16].

Macroglossia (enlarged tongue) is a feature of LOS[22]. Severe macroglossia will cause feeding and breathing difficulties. Abdominal wall defects, including omphalocele and umbilical hernia, have also been observed in LOS fetuses[22]. An omphalocele is the outward protrusion of abdominal organs through the umbilical cord, which these organs are not covered by skin but by membranes (i.e. amnion, peritoneum, and Wharton's jelly;[23]). Omphalocele is a severe defect present at birth and requires immediate corrective surgeries. An umbilical hernia is a bulge of abdominal organs at the umbilicus, which is caused by incomplete closure of umbilical ring and is covered by skin[24].

Organomegaly, the abnormal enlargement of organs, have been observed in heart, liver, and kidney of LOS calve[14,25]. In addition, placentomegaly, an abnormally enlarged placenta, has been found in cow carrying IVF conceived fetuses[18].

Other features including increased incidence of hydrallantois[12,15], increased gestation length[26], increased dystocia rate[27], ataxia/paresis[28,29], and abnormal limbs combined with abnormal spine[15] have also been observed in LOS calves.

Assisted Reproductive Technologies and LOS

In the late 1980's and 1990s clinical epidemiologist Professor David Barker suggested that the gestating maternal environment could have adverse consequences to the well-being of the offspring after birth[30]. The phenomenon which explains this permanent programming of the fetus was named "Fetal Origins of Adult Disease" or the "Barker Hypothesis". The "Developmental Origins of Health and Disease (DOHaD) hypothesis", as the phenomenon is now known, propositions that the inherent developmental (genetic) program of an individual can be influenced by its environment, especially during critical periods of development which can have significant long-term consequences for the wellbeing of the offspring during life. One artificial environment which has received much scientific attention for its potential to cause incorrect developmental programming to the resulting offspring in humans and livestock animals is assisted reproductive technologies (ART).

ART refers to a series of laboratory techniques and procedures used to conceive offspring. ART procedures include oocyte retrieval from ovaries, *in vitro* oocyte maturation, *in vitro* fertilization, embryo culture, and embryo transfer. ART is used in cattle to improve genetic merit of the offspring in a shorted length of time when compared to natural reproduction. Genetic merit is defined as the rank of an animal for its ability to produce superior offspring relative to other selection candidates (Purdue Extension - http://www.nsif.com/factsheets/nsif8.pdf). In addition, ART can be used to produce genetically-manipulated animals with improved production traits[31].

Supplement of serum during *in vitro* embryo culture has been historically used to stimulate blastocyst formation[32]. Two experimental accounts suggest that serum can induce LOS in approximately 25% of ovine and bovine fetuses[33,34]. Adding fetal calf serum and bovine serum albumin during bovine embryo culture accelerate embryo development and improve blastocyst yield by day 6 but decrease embryo survival rate[35,36]. When comparing ovine embryos cultured with or without human serum supplements, bovine serum albumin and amino acid supplements, an increased body weight and gestation length in the human serum group was observed[37]. Co-culture of embryos with various types of cells have also been used to increase blastocyst yield[38]. Similar to what have been found with serum supplementation in sheep, overgrowth[39,40] and increased gestation length[39] have been reported for ovine embryos that were co-cultured with granulosa or oviduct epithelial cells. In addition, the size of the primary muscle fibers (which form during the first wave of myogenesis) and the ratio of secondary to primary fibers of the co-cultured fetuses were also greater than the controls, which indicates that hypertrophy of the primary fibers and hyperplasia of the secondary fibers are associated with the increased body weight observed in these fetuses[40].

A similar OGS occurs in human

In humans, Beckwith-Wiedemann syndrome (BWS, OMIM #130650), a human OGS, has phenotypical and molecular similarities to LOS. The most current report indicates an incidence of BWS in ~1/11,000 natural births[41]. BWS is a heterogeneous condition for which various phenotypic and (epi)genetic defects have been reported. Clinical features of BWS include macroglossia, abdominal wall defects (omphalocele/hernia/diastasis recti), lateralized overgrowth, childhood tumors (Wilms' tumor and hepatoblastoma), neonatal hypoglycemia, macrosomia (large body size), ear malformations (creases/pits), facial nevus simplex (nevus flammeus, port-wine stain), and organomegaly[21]. The use of ART has been reported to increase the incidence of BWS by up to 10.7 times[42,43].

Molecular findings of LOS and BWS

The main molecular defects of BWS occur on human chromosome 11p15 (bovine = chromosome 29) and include defects in DNA methylation, incorrect expression of imprinted genes, changes of chromosomal contents, and gene mutations[8,44–52]. Among them, loss-of-imprinting caused by DNA methylation defects is the most frequently observed. DNA methylation (the addition of a methyl group [CH3] to DNA) is an epigenetic mark involved in the control of gene expression. Genomic imprinting is an epigenetic phenomenon, which regulates parent-specific (i.e. chromosome specific) gene expression of approximately 150 genes (i.e. imprinted genes) in mammals[53–56]. These genes control growth and development of the fetus and the placenta and their expression is tightly regulated by a discreet region of differential DNA methylation known as “imprinting center” (IC)[57]. One of these imprinting centers, namely, Imprinting Center 2 (IC2; also known as KvDMR1) is the most common genomic region affected by DNA methylation defects in BWS and LOS[34]. In the normal situation, the IC2 is methylated on the maternal chromosome and unmethylated on the paternally-inherited chromosome. This methylation state allows for the expression of the gene *KCNQ1OT1* from the paternal allele, which by attracting epigenetic modifiers, silences various flanking imprinted genes including the cell cycle regulator *CDKN1C*[58–60]. The methylated state of the maternal chromosome orchestrates the expression of several genes involved in fetal and placental growth[58–60]. In LOS and BWS, imprinted gene expression of the IC2 loses control as a result of loss-of-methylation of the maternal KvDMR1[34,61–63].

Alterations in Gene Expression

Alterations in imprinted and non-imprinted gene expression as a result of *in vitro* embryo production have been reported in numerous studies in bovine[54,64–73]. Different culture media and supplementation with serum cause transcript abundance changes of several developmentally important genes involved in cell-cell junctions, transport, RNA processing, and stress in bovine embryos[64,65]. The upregulation of several developmentally important genes including the imprinted gene *IGF1R* have been suggested as early markers of LOS for bovine[10]. A two fold increase in expression of the imprinted fetal growth factor *IGF2* transcript can be detected in liver of day 70 bovine fetuses cultured in medium containing estrus cow serum when compared with the serum restricted group[74].

Spontaneous LOS

Although LOS cases in bovine have only been reported to be associated with ART, LOS can occur spontaneously. Spontaneous maternal-fetal disproportion is the predominant cause of dystocia in beef cattle[75]. A number of environmental and genetic factors cause this disparity and it is most commonly associated with first-calf heifers[75,76]. While calves in this scenario may be relatively large to the dam, they may not be oversized in absolute terms of population normals. In the human literature neonates that are large of for gestational age are typically above 97th percentile for birth weight at delivery, although the definition varies slightly by condition[77]. Mechanistically syndromes of overgrowth may be due to increased numbers of cells, hypertrophy, increases in the interstitium (such as fluid accumulation) or a combination of these conditions[77]. In humans there are two broad categories of fetal overgrowth syndromes. The first are those that are driven by the maternal environment such as gestational diabetes, occurring in around 5% of all pregnancies[78]. Conditions such as these predominantly result in symmetric hypertrophy of fetal tissue, particularly adipose tissue. The second category is neonates that are affected by either spontaneous or inherited genetic mutations, such as with BWS, Sotos Syndrome and Proteus syndrome to name a few. While these conditions are rare they are becoming increasing recognized, due to increased utilization of *in vitro* fertilization techniques[79]. Spontaneous fetal oversize syndromes have not been well recognized in food animal species outside of neonates generated by assisted reproductive therapies[2]. For the purposes of this review spontaneous large offspring syndrome can be categorized by conditions associated with prolonged gestation or those of normal gestational length.

Gestational length is relatively constant in cattle within breeds and environmental conditions ranging from 280 to 290 days[80]. Increasing gestational length within the normal range has been associated with larger birth weight[76]. Gestational length is moderately heritable and displays a sex bias with male calves generally having longer gestational lengths than females[76]. A definition for post-term for cattle has not been established, but is generally in excess of 300 days. Prolonged gestation has long been associated with a poor outcome for the resultant neonate[81]. A number of breeds including Ayrshire, Holstein-Friesian, Guernsey, Jersey, Swedish red & white, and Belgian Blue Cattle have been documented with pathologically prolonged gestation[82–84]. Prolonged gestation in these cases is largely secondary a to a dysfunctional hypothalamic-pituitary-adrenal axis with the calf failing to initiate parturition. These conditions have included adenohypohoseal hypolasaia/aplasia, cerebellar hypoplasia and adrenal hypoplasia. A genetic mutation have been suspected in many of these cases, with the mode of inheritance established, but putative genetic mutations not. Infectious cause such as Akabane virus, Bluetongue virus or Bovine Viral Diarrhea virus and toxic causes such ingestion *Veratum californicum* may also result in prolonged gestation due to dysfunction of the hypothalamic-pituitary axis[85]. However, prolonged gestation alone does not always result in fetal oversize with this syndrome only identified in Holstein-Friesian, Swedish red and white and Ayrshire cattle[2,76]. Calves affected by overgrowth, commonly referred to as fetal giants, will have characteristically long teeth, hair coats and toes and otherwise appear to be normal. These calves have been reported to weigh between 59 to 98 kg. Typically these calves are delivered following induction of parturition and almost invariably necessitate caesarean section. The traits that produce prolonged gestation and fetal oversize are largely incompatible with post-natal life and these calves rarely survive for more than 24 hours.

Although rare, fetal giants have also been recognized in calves that are born at normal gestation lengths with the predominant abnormality being absolute oversize. No specific descriptions of these calves have been made, other than Roberts[86] regarding any calf over 59 kg at birth to be a fetal giant. Despite being reported by clinicians and producers there are, to the author’s knowledge, no published descriptions of fetal giants or large offspring syndrome outside that of calves produced by *in-vitro* fertilization.

Spontaneous LOS: Case studies

Three cases of spontaneous LOS are illustrated in Figure 2. The first calf was a purebred male Holstein-Friesian calf that was delivered via caesarean section at 293 days of gestation. The calf weighed 83 kg at birth with the combined weight of the fetal membranes being 12.7 kg. The calf had an appropriate hair coat, erupted teeth and normal eponychium. The calf was proportionate with no obvious musculoskeletal defects. However, the calf did have an enlarged tongue (macroglossia) and large umbilical hernia (omphalocele). The calf was unable to nurse due to the enlarged tongue and was humanely euthanized. Imaging of the brain by MRI and detailed necropsy definitively ruled out a structural alteration of the hypothalamus, pituitary or adrenal glands. The second calf was a female purebred Brown Swiss calf that was delivered at 283 days of gestation. The dam was initially presented due to concern for a hydrops condition with perceived over-distension of the abdomen at approximately 278 days of gestation. Based on palpation and trans-abdominal ultrasound a hydrops condition was considered unlikely; however, the calf appeared to be very large. The calf was delivered by elective caesarean section following induction of parturition with cloprostanol and dexamethasone 40 hr prior to surgery. The viable calf weighed 63 kg at birth, with the fetal membranes unable to be weighed due to retention. The calf had small umbilical hernia and marked carpal contracture, but was otherwise vigorous and healthy. The calf's legs were treated with splints and it was discharged at ten days of age.

Whilst the definitive reason for fetal oversize has yet to be identified in these calves it is strongly suspected that these calves represent spontaneous large offspring syndrome. Following the identification of these two calves, other large for gestational age calves not generated by IVF have been investigated and have been shown to possess the same epi-mutation as IVF generated large offspring calves. This strongly emulates the analogous human condition BWS[79].

Epigenetic conditions should be considered in cases of fetal gigantism where aberrations of gestational length have been excluded. At this time, risk factors have not been established and the occurrence of such calves is sporadic.

Concluding Remarks

The first ART calf was reported by Brackett and colleagues in 1982[87] while the fact that ART can induce the birth of abnormally large calves was first documented in the 1990s[11]. Even though many reports have been published and almost thirty years have passed since the first LOS report, we are not yet able to predict which embryos are molecularly programmed to suffer LOS, as the etiology of the syndrome is not known. Further, as Dr. John F. Hasler states in a recent review of the embryo transfer industry, "*there is a lack of peer-reviewed published data describing the current status of LOS problems in the commercial ET-IVP industry*".[88] Therefore, it is difficult to calculate what is the current incidence of LOS and how much are producers being affected. As mentioned above, off-the record conversations have stated that 10% LOS in some practices is not unusual. For obvious reasons, we do not believe that such numbers will ever be published but we hope to be able to provide information that may be used by ET companies and others using ART embryos in their practices to identify embryos molecularly programmed to suffer LOS prior to transfer.

Perinatal mortality, death occurring prior to, during or within 48 hours of calving, is a recognized problem in the cattle industry[89]. In developed countries, 25–46% of perinatal deaths in cattle are the result of dystocia and in the United State 32% of perinatal deaths are due to unknown causes. One of the main causes of dystocia is fetal-maternal size mismatch. Dystocia has a direct negative impact on calves[89,90], dam survival and reproduction performance[91] and milk production[92]. With our current research, we will determine if similar genetic and epigenetic misregulation is the culprit of spontaneous LOS, a previously uncharacterized syndrome in cattle, and will shed light upon the contribution of spontaneous LOS to the 25–46% rate of perinatal death in cattle resulting from unknown causes and dystocia.

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Key Points:

- Overgrowth syndromes (OGS) refer to a heterogeneous group of conditions found in many species and can be divided into two categories based on phenotypes, namely generalized OGS and localized/partial OGS.
- Large offspring syndrome (also known as abnormal offspring syndrome) is a generalized congenital OGS in bovine most often observed in offspring conceived with the use of assisted reproductive technologies.
- Features of LOS include overgrowth, enlarged tongues, umbilical hernias, muscle and skeleton malformation, abnormal organ growth, allantois development defects, abnormal placental vasculature, and increased embryo or fetus death rates.
- Beckwith-Wiedemann syndrome is a human congenital overgrowth conditions that emulates LOS. Both conditions are the result of epigenetic errors, and have been characterized as loss-of-imprinting conditions.
- Fetal giants have been rarely recognized in naturally-conceived calves that are born at normal gestation lengths with the predominant abnormality being absolute oversize. We propose that these calves represent spontaneous large offspring syndrome.

Synopsis:

Large offspring syndrome (LOS; also known as abnormal offspring syndrome) is a generalized congenital overgrowth syndrome in bovine most often observed in offspring conceived with the use of assisted reproductive technologies. Features of LOS include overgrowth, enlarged tongues, umbilical hernias, muscle and skeleton malformation, abnormal organ growth, allantois development defects, abnormal placental vasculature, and increased embryo or fetus death rates. LOS can affect the dam and cause death of the afflicted animal bringing financial loss to producers. Beckwith-Wiedemann syndrome is a human congenital overgrowth conditions that emulates LOS. Both conditions have been characterized as loss-of-imprinting conditions. Fetal giants have been rarely recognized in naturally-conceived calves that are born at normal gestation lengths with the predominant abnormality being absolute oversize. We propose that these calves represent spontaneous large offspring syndrome. While the molecular etiology and incidence of spontaneous and ART-derived LOS are unknown, current work by the authors is designed to shed light into these questions.

Figure 1. ART Produced LOS.

Large bull calf produced by in-vitro procedures by RMR while at the University of Florida. The picture was taken when the calf was 2 days of age. The calf weighed 98 kg at birth and died at one week of age as a result of complications relating overgrowth, which included inability to stand up to suckle.

Figure 2. Spontaneous LOS.

Case 1 (top)– A post-term 86 Kg (normal birth at birth = 40 to 50 kg) Holstein bull calf was delivered by emergency C-section due to dystocia. The calf was macrosomic, had a marked omphalocoele and macroglossia (right picture). The calf was mentally inappropriate and was euthanized at 1 day of age. Immunohistochemistry of the anterior pituitary and hypothalamus could not demonstrate an aberration that could explain the macrosomia. **Case 2 (middle)** - A pre-term 63 Kg Brown Swiss heifer (normal weight at birth ~ 45 Kg) calf was delivered by planned C-section. The cow was referred for her large size approximately 2 weeks prior to being term. The calf was mentally appropriate at delivery and had an omphalocoelce and bilateral flexural deformities of the front metacarpo-phanalngeal joint. The ompahlocoele was corrected surgically (picture on the right) and the flexural deformities by splints and physical therapy. The calf was discharged in good health and is apparently still performing well. **Case 3 (bottom)** - One day old Holstein-Friesian calf showing typical signs associated with LOS including absolute macrosomia, omphalocele, and asymmetry of the pinna. The calf presented in respiratory distress and was later euthanized.