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A Prospective Assessment of the Etiology of Murine Dystocia

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Dystocia, a common murine reproductive condition, is classified as either obstructive, a result of fetal factors such as an oversized fetus, or functional, a result of dam factors such as advanced age. Treatment is based on the dam's clinical condition and the underlying etiology, but usually requires euthanasia. A prospective study was conducted to characterize the etiology of murine dystocia to determine if treatment is warranted. The signalment and experimental, clinical, and breeding histories were obtained, and a targeted serum chemistry panel, radiographs, and a gross necropsy were conducted on mice presenting with clinical signs consistent with dystocia. Obstructive dystocia was diagnosed if the pelvic canal width was less than the diameter of the fetal head closest to the cervix or a fetus was lodged in the pelvic canal. Functional dystocia was diagnosed based on clinicopathologic abnormalities. A total of 54 mice were evaluated over 7 mo with 45/54 (83%) confirmed to have dystocia with the remaining 9 (17%) having other reproductive abnormalities. Of the confirmed cases, 27/45 (60%) were C57BL/6 or on a C57BL/6 background, and the average age at presentation was 181 ± 85 d. The number of mice categorized as having an obstructive (*n* = 16) compared with a functional (*n* = 11) dystocia was not significantly different than those in which the definitive category could not be ascertained (*n* = 18). Neither clinical signs nor clinical pathology were significantly different between mice categorized as having an obstructive compared with a functional dystocia. Hunched posture, lethargy, and vaginal discharge were the most common presentation. Azotemia (BUN: 66.6 ± 10.2 mg/dL, mean ± SE), hypoglycemia (96.11 ± 8.5 mg/dL), and hyperglobulinemia (3.13 ± 0.14 mg/dL) were common. Differentiating obstructive from functional dystocia could not be determined cageside with strong confidence.

Abbreviations and Acronyms: MSK, Memorial Sloan Kettering Cancer Center; WCM, Weill Cornell Medicine

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Introduction

Dystocia, defined as difficulty giving birth, is among the most common reproductive conditions in the mouse alongside infertility, congenital deformities (for example, presence of a vaginal septa/imperforate vagina or an incomplete reproductive tract), and clinical conditions affecting the reproductive tract such as cystic endometrial hyperplasia, vaginal or uterine prolapse, and paraphimosis.[4,5,14,18,24] Dystocias are classified as obstructive, when a result of fetal features such as being oversized, abnormal orientation, or having congenital malformations that prevent passage of the fetus through the birth canal, or functional, resulting from maternal factors including uterine inertia (failure of uterus to contract normally), uterine exhaustion (muscular fatigue), an inadequately dilated birth canal, nutritional deficiencies, and advanced age (greater than 6 mo old).[4,14,15,17,22,25] Clinical signs of dystocia include a pup being visibly stuck in the birth canal, protracted labor (contractions without delivery, cessation of contractions, no additional birth within an hour), bloody vaginal discharge, dehydration, immobility/weakness, and pain (including facial grimace).[4] Parturition in the mouse typically lasts 1 to 3 h, often occurring at night, with dystocia usually detected during early morning monitoring.[4] Certain genetically modified mouse strains, such as those deficient in biglycan and decorin (extracellular matrix proteoglycans of reproductive tissues and muscle), NFIL3 (transcription factor), and p53 and FasL (apoptotic factors), are predisposed to dystocia due to gene mutations or loss.[10,19,26] Other risk factors include stress, which can delay parturition or lead to fetal resorption, and nutritional deficiencies such as hypocalcemia and vitamin E deficiency.[3,10,21] Treatment approaches vary based on the dam's condition and the underlying cause (obstructive or functional), although outcomes are often unrewarding, necessitating euthanasia.[22]

Case Series

A retrospective review of mouse health records from our program, with an average daily mouse census of approximately 265,000 mice, revealed an average of 35 mice with presumptive dystocia per month and these mice were typically euthanized. To confirm dystocia, characterize its underlying etiology, and determine whether treatment would be warranted, we conducted a prospective study of 54 mice presenting with clinical signs suggestive of dystocia during a 7-mo period.

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Materials and Methods

Husbandry. Mice (*Mus musculus*) were maintained in individually ventilated polysulfone shoebox cages with stainless steel wire bar lids and filter tops (number 19, Thoren Caging Systems, Hazelton, PA) on autoclaved aspen chip bedding (PWI Industries, Quebec, ON, Canada) at a density of no greater than 5 mice per cage. The individually ventilated caging system was ventilated at approximately 30 air changes per hour. HEPA-filtered room air was supplied to each cage, and the rack effluent was exhausted directly into the building's exhaust system. Each cage was provided with an autoclaved Glatfelter paper bag containing 6 g of crinkled paper strips (EnviroPak, WF Fisher and Son, Branchburg, NJ) and Nestlets for enrichment. Mice were fed a natural ingredient, closed source, flash-autoclaved, gamma-irradiated feed (LabDiet 5053, PMI, St. Louis, MO).[23] All mice received reverse osmosis acidified (pH 2.5 to 2.8 with hydrochloric acid) water ad libitum from polyphenylsulfone bottles with stainless steel caps and sipper tubes (Tecniplast, West Chester, PA). Cages were changed every 7 d in a cage change station (Nuaire NU-S612-400, NuAire, Plymouth, MN). The room was maintained on a 12-h light/12-h dark cycle (0600 on/1800 off), relative humidity of 30% to 70%, and room temperature of 72 ± 2 °F (22 ± 1 °C). The animal care and use program at Memorial Sloan Kettering Cancer Center (MSK) and Weill Cornell Medicine (WCM)/Hospital for Special Surgery are accredited by AAALAC International, and all animals are maintained in accordance with the recommendations provided in the *Guide for the Care and Use of Laboratory Animals* (8th ed.).[12] All investigative animal use was approved by the MSK and WCM/Hospital for Special Surgery IACUCs in agreement with the AALAS position statements on the humane care and use of laboratory animals and alleviating pain and distress in laboratory animals.[1,2]

Mice were free of mouse hepatitis virus, Sendai virus, mouse parvovirus, minute virus of mice, pneumonia virus of mice, Theiler meningoencephalitis virus, mouse rotavirus, murine astrovirus 2, reovirus 3, ectromelia virus, lymphocytic choriomeningitis virus, K-virus, mouse adenovirus 1 and 2, polyoma virus, rodent chaphamaparvovirus 1, mouse cytomegalovirus, mouse thymic virus, hantavirus, *Mycoplasma pulmonis*, *Filobacterium rodentium* (CAR *Bacillus*), *Clostridium piliforme*, *Citrobacter rodentium*, *Salmonella* spp., *Klebsiella pneumoniae/oxytoca*, *Streptococcus pneumoniae*, *Corynebacterium kutscheri*, *Streptobacillus moniliformis*, *Encephalitozoon cuniculi*, *Giardia muris*, fur mites, and pinworms and were potentially infected with mouse norovirus, *Helicobacter* spp., segmented filamentous bacteria, *Demodex musculi*, *Spironucleus muris*, and/or *Chlamydia muridarum.*

Inclusion criteria and case evaluation. Mice presenting with clinical signs consistent with dystocia were included in the study after obtaining investigator permission. Inclusion criteria were 1) mouse appeared pregnant based on a clinical evaluation, including abdominal distention, palpation of pups, visualization of pups, and/or breeding history; and 2) were lethargic/moribund, had a pup visibly stuck in the birth canal, had genital discharge, appeared to be in pain, had palpable fetal structures, and/or the cage contained dead neonates. Presenting clinical signs, which included hunched posture, thin, lethargy, moribund, pallor, piloerection, vaginal discharge, and grimace (Table 1), were assessed and recorded. Signalment and experimental, clinical, and breeding histories were obtained, and the following diagnostic tests were performed: targeted serum chemistry panel, abdominal radiographs for pelvic canal measurements, and a gross necropsy to quantify the number, size (crown to rump length and cranial width), weight, and position of fetuses (that is, breech or malpositioned), and the pelvic canal diameter was determined. Only live mice were included to allow for blood collection.

Classification scheme. Criteria (Table 2) were established to classify individual dystocia cases as either obstructive, functional, or equivocal. Each case was assigned a likelihood rating for each dystocia classification (probable = both conditions from the same classification present; possible = one condition present; or unlikely = no conditions present) and then assigned a final diagnosis based on the most likely cause. If a case was rated probable for one classification and unlikely for the other, then there was a strong confidence for the probable classification. If a mouse was rated probable for one classification and possible for the other, then there was a moderate confidence for the probable classification. Lastly, if a mouse was rated equally for both classifications then it was classified as equivocal.

Clinical pathology. Cardiac puncture blood collection was conducted immediately following CO_2 euthanasia. A targeted serum chemistry panel was performed to rule out a functional dystocia.[3,10,21] For serum chemistry, blood was collected into tubes containing a serum separator and centrifuged (BD Microtainer SST™, Becton, Dickinson and Company, Franklin Lakes, NJ). The serum was then eluted and analysis performed using an automated analyzer (Beckman Coulter AU680, Brea, CA) with the concentration of the following analytes determined: ALP, globulin, glucose, triglycerides, albumin, total protein, BUN, creatinine, total calcium, phosphorus, sodium, potassium, and chloride. Total calcium measured was, to a great extent, protein bound and may not have reflected the status of the biologically active ionized form.[6] Ionized Ca^{2+} was calculated using an ionized calcium calculator that employed the following

Table 1. Clinical signs observed in mice presenting with presumptive dystocia

Clinical sign	Definition
Hunched	Abdomen drawn up and its head down
Thin	Decreased body condition; segmentation of vertebrae column evident, dorsal pelvic bones readily palpable, reduced muscle mass
Lethargic	Decreased spontaneous movement
Moribund	State or condition approaching death; minimal to no provoked movement; lateral recumbency
Pallor	Pale color of the skin, caused by reduced red blood cells in circulation; in hirsute mice, pallor is typically seen on the ears and tail
Piloerection	Erection of hair typically as a result of malaise and/or pain
Vaginal discharge	Bloody, mucous, or purulent discharge originating from the vaginal opening
Grimace[16]	Changes in facial expression associated to pain including orbital tightening, nose bulge, cheek bulge, ear position (rotate outward and/or backward, away from the face), whisker change (either pulled back against the cheek or pulled forward)

Table 2. Dystocia classification scheme

Classification	Condition
Obstructive	Pelvic canal diameter less than fetal head diameter closest to the pelvic canal
Obstructive	Pup stuck in pelvic canal
Functional	Abnormal gross findings outside of reproductive tract
Functional	Abnormal clinical pathologic findings
Equivocal	Equal likelihood of either classification; that is, none of the conditions present or conditions from both classification types present

parameters to determine ionized Ca^{2+}: ALP, triglycerides, albumin, creatinine, total calcium, phosphorus, sodium, potassium, and chloride.[7] Serum chemistry parameters were considered abnormal if the values were outside the reference range for the mouse strain, when available, or for the Laboratory of Comparative Pathology's C57BL/6 reference range.

Radiology. After euthanasia by CO_2 asphyxiation, abdominal radiographs (2 views: lateral and ventrodorsal) were obtained for pelvic canal measurements using a digital specimen radiology system (MX-20 digital Faxitron and software, Faxitron X-Ray, Lincolnshire, IL). Pelvimetry was performed as has been described for other veterinary species.[8] In the ventrodorsal view, the transverse diameter of the pelvis at the narrowest point, at approximately midacetabulum, was recorded. In the lateral view, the distances from the pubis to the sacral promontorium and from the pubis to the first coccygeal vertebra were recorded. The skull diameter of the fetus closest to the pelvic canal obtained at necropsy, excluding any pups that had already been expelled, was used to compare with the radiographic pelvic diameter. Dams with at least one pelvic diameter smaller than the fetal head diameter *and* with gross evidence of a fetus within the pelvic canal at the time of necropsy were considered 'probable' for an obstructive etiology. Dams with at least one pelvic diameter measurement smaller than the fetal head diameter *or* evidence of a fetus within the pelvic canal at time of necropsy was considered 'possible' for an obstructive etiology. Dams with no radiographic measurements smaller than the fetal head diameter measurement and with an empty pelvic canal at time of necropsy were considered unlikely to have an obstructive etiology.

Necropsy. After euthanasia and radiology, a gross necropsy was performed, gross lesions were recorded, and the number, position, crown to rump length, and width (lateral to lateral aspect at its largest dimension) of the fetuses were recorded, and the diameter of the pelvic canal entrance was measured when possible. All tissues including the heart, thymus, lungs, liver, gallbladder, kidneys, pancreas, stomach, duodenum, jejunum, ileum, cecum, colon, lymph nodes (mandibular, mesenteric), salivary glands, skin (trunk and head), urinary bladder, uterus, cervix, vagina, ovaries, oviducts, adrenal glands, spleen, thyroid gland, esophagus, trachea, spinal cord, vertebrae, sternum, femur, tibia, stifle joint, skeletal muscle, nerves, skull, nasal cavity, oral cavity, teeth, ears, eyes, pituitary gland, and brain were fixed in 10% neutral buffered formalin. Bacteriology and/or histopathology of the reproductive tracts were performed in a subset of cases ($n = 3$) in which the uterus exhibited a macroscopic abnormality. Sterile culture swabs (Remel BactiSwab, Thermo Fisher Scientific, Waltham, MA) were used to swab the length of the longest dimension of the abnormal uterus rotating the swab as it was advanced. Swabs were streaked onto agar plates (BBL prepared plated media trypticase soy agar II with 5% sheep blood; BBL chocolate II agar; BBL Columbia CNA agar with 5% sheep blood; BBL MacConkey II agar; and, BL *Brucella* agar with 5% sheep blood, hemin, and vitamin K1, Becton Dickinson, Franklin Lakes, NJ) as well as immersed into thioglycolate broth (BBL fluid thioglycolate medium, Becton Dickinson). The agar and broth media were incubated aerobically or anaerobically at 37 °C with or without 5% CO_2 for up to 7 d. Anaerobic conditions were achieved by promptly placing *Brucella* agar plates into an airtight bag containing an anaerobic incubation sachet after inoculation (BD GasPak EZ container systems, Becton Dickinson). Plates were checked daily and, when present, distinct colonies were speciated by using matrix-assisted laser desorption ionization–time of flight mass spectroscopy (MALDI Biotyper sirius CA system, Bruker, Billerica, MA). After fixation, reproductive tract tissues were then processed in ethanol and xylene in a tissue processor (Leica ASP6025, Leica Biosystems) and subsequently embedded in paraffin. Paraffin blocks were sectioned at 5 µm, stained with hematoxylin and eosin, and examined by a board-certified veterinary pathologist.

Statistical analysis. Comparisons between observed and expected frequencies, that is, having equal frequencies, of functional compared with obstructive compared with equivocal dystocias were compared as well as differences in the frequency of clinical signs between the different dystocia categories and nondystocia cases using χ^2 tests. Differences in clinical chemistry analytes between obstructive compared with functional compared with equivocal dystocias, as well as nondystocia cases, were compared using one-tailed unpaired *t* tests. Correlation of fetal weight and number of fetuses was determined by linear regression analysis. Values of $P \leq 0.05$ were considered statistically significant.

Results

Of the 54 mice included in the study, 45 (83%) met the dystocia criteria while 9 (17%) had unrelated abnormalities including 1 case of neoplasia (lymphoma or histiocytic sarcoma), 1 case of fibrinosuppurative metritis, 1 case of uterine prolapse, 2 cases of early embryonal death, and 4 cases of placental retention (remnant of placental discs, no fetuses in reproductive tract). A single dystocia case presented with a pyometra from which a mixed bacterial culture of *Escherichia coli*, *Rodentibacter heylii*, *Enterococcus gallinarum*, and *Streptococcus thoraltensis* was cultured. The genotype was available for 28 of the 45 (62%) mice with dystocia. Of these, 27 of 28 (96%) were C57BL/6 or on a C57BL/6 background; 16 of the 27 mice (60%) were genetically engineered. Of the mice for which the genotype was unknown, 15 of 17 (88%) had a black coat, while 2 of 17 (12%) were agouti. Breeding configuration was available for 39 of 45 dystocia cases with 20 of 39 (51%) being in a male/female pair, 16 of 39 (41%) in permanent trios (1 male with 2 females), and 3 of 39 (8%) in other configurations.

The average age at presentation for mice meeting the dystocia criteria was 181 ± 85 d. When a breeding history was available, 10 of 29 (35%) were primiparous with an average age of 150 ± 107 d at presentation (Figure 1). The number of fetuses in the uterus correlated positively with the average fetal weight ($R^2 = 0.0959$; $P = 0.04$; Figure 2). The average number of fetuses per litter for all dystocia cases was 5.7 ± 2.6, while for cases whose dams' genotype was C57BL/6 or on a C57BL/6 background it was 5.9 ± 2.6.

Of the 45 mice with dystocia, 16 (36%) were classified with strong or moderate confidence as having an obstructive dystocia, including 3 cases observed with a pup lodged in the birth canal, 11 (24%) as having a functional dystocia, and 18 equivocal cases (40%) in which a classification could not be ascertained

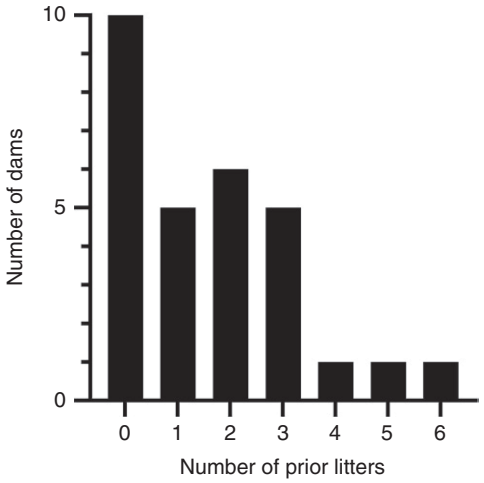

Figure 1. Number of litters prior to presentation with dystocia.

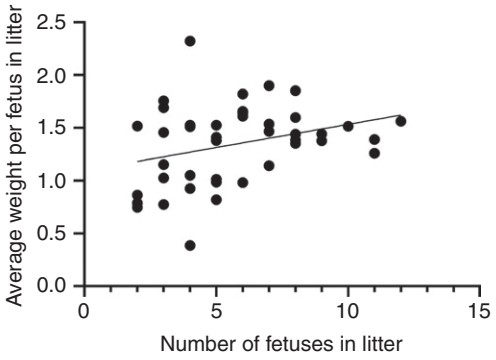

Figure 2. Correlation between number of pups compared with the average weight per pup in the litter of all dystocia cases ($R^2 = 0.0959$; $P = 0.04$).

(Figure 3). The difference in frequencies between these 3 dystocia categories was not significant ($\chi^2 = 1.73$; $P = 0.420$).

Radiographs of obstructive dystocia in which a fetus is lodged in the birth canal are provided in Figure 4. Examples of necropsy findings in obstructive and functional dystocia cases are presented in Figure 5. The 4 cases with a strong confidence of obstructive dystocia included a mouse in which the pup was oriented horizontally in the birth canal and had 5 large fetuses in the uterus, and 3 cases in which the pelvic canal was obstructed with a macerated or normal appearing fetus. Dystocic mice with the largest litters were more likely to have an obstructive etiology; 13 of 16 (81%) of the mice with an obstructive dystocia had more than the median of 5 fetuses at necropsy, which was in contrast to mice diagnosed with a functional (2 of 11 [18%]) or an equivocal (8 of 18 [44%]) etiology. The 5 cases with strong confidence of functional dystocia included a mouse with a pyometra, 2 mice with gross and clinicopathological abnormalities (that is, a mouse with a pale liver, azotemia, hemoperitoneum, subcutaneous edema, and hyperphosphatemia), and a mouse with hemorrhagic placental implantation sites possibly associated with placental defects or a circulatory disturbance. Of the 27 mice with dystocia on a C57BL/6 background or C57BL/6, 7 (26%) were classified with strong or moderate confidence as having an obstructive dystocia, 6 (22%) as having a functional dystocia, and 14 cases (52%) as equivocal; the differences in the frequency between the 3 classifications were not significant ($\chi^2 = 4.22$; $P = 0.12$).

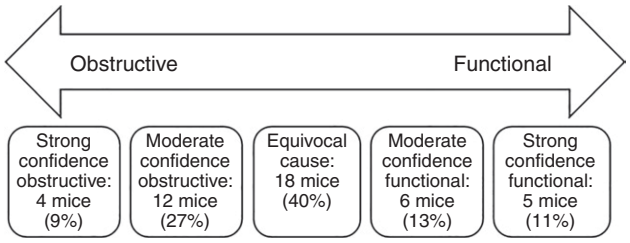

Figure 3. Dystocia classification based on likelihood and confidence level.

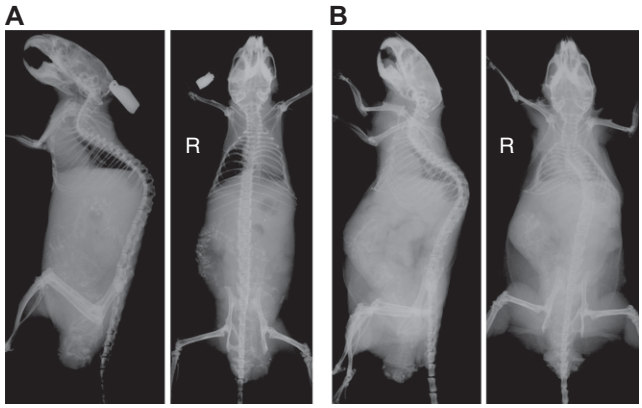

Figure 4. Radiographs of mice with obstructive dystocia. (A) Lateral (left) and ventrodorsal (right) views of a dystocic mouse with a fetus lodged in the pelvic canal. (B) Lateral (left) and ventrodorsal (right) views of a dystocic mouse with a macerated fetus lodged in the pelvic canal. A second macerated fetus can be found in the right uterine horn.

Neither clinical signs nor clinical pathology were significantly different between mice categorized as having an obstructive compared with functional dystocia, or between mice with either an obstructive or functional dystocia and an equivocal classification. However, significant differences were observed in 6 clinical pathology analytes between mice with dystocia ($n = 45$) and those without ($n = 9$). Specifically, ALP (77.38 ± 8.2 compared with 36.0 ± 8.3 U/L, mean ± SEM; $P = 0.0008$), total protein (6.02 ± 0.25 compared with 4.67 ± 0.55 g/dL; $P = 0.02$), albumin (2.99 ± 0.1 compared with 2.33 ± 0.2 g/dL; $P = 0.004$), and globulin (3.13 ± 0.14 compared with 2.34 ± 0.39 g/dL; $P = 0.02$) were significantly higher in mice with dystocia as compared with those presenting for other causes. Conversely, glucose (96.11 ± 8.5 compared with 129.43 ± 18.0 mg/dL; $P = 0.05$) and chloride (105.44 ± 3.76 compared with 121.22 ± 2.72 mEq/L; $P = 0.0008$) were significantly lower. Hunched posture (21 of 45), lethargy (20 of 45), and vaginal discharge (19 of 45) were the most common clinical signs observed in mice with dystocia (Table 3). Out of all the clinical signs observed in mice evaluated in the study, pallor was unique to 3 nondystocia cases that were diagnosed with neoplasia, early embryonal death, or placental retention. Azotemia (elevated BUN) (32 of 45 [71%]; 66.6 ± 10.2 mg/dL), hypoglycemia (38 of 45 [84%]; 96.11 ± 8.5 mg/dL), and hyperglobulinemia (35 of 45 [78%]; 3.13 ± 0.14 mg/dL) were common findings in most dystocic mice.

Discussion

A consistent cageside antemortem method of differentiating obstructive compared with a functional dystocia could not be determined in this study. Ascertaining the etiology of the dystocia is critical before treatment is attempted, as the medical management options available for treating functional dystocia

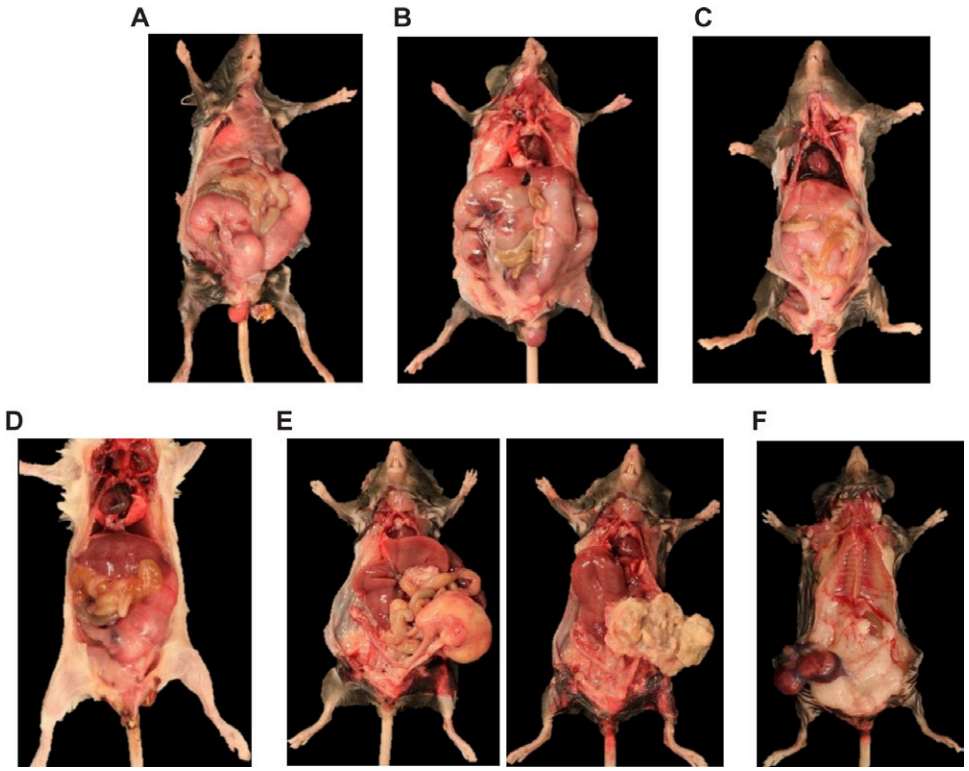

Figure 5. Gross images of dystocic mice classified as obstructive or functional. Note that all mice have perineal hemorrhagic staining. (A) Obstructive dystocia. Uterine horns are markedly distended with pups and a pup is lodged in the birth canal. The cranial half of the lodged pup extends into the left uterine horn. (B) Obstructive dystocia. Pup's rump is observed protruding from the vulva. (C) Obstructive dystocia. The caudal half of a pup is seen extending from the vulva. (D) Obstructive dystocia. Dam with marked vaginal bleeding. Pup hindlimb protruding from the vulva. The other limb was cannibalized. The retained pelvic region of the pup was discolored tan to yellow. (E) Functional dystocia. The proximal aspect of the left uterine horn is markedly distended, soft, and filled with abundant yellow to tan, pasty, friable material (left image, intact left uterine horn; right image, left uterine horn dissected open). Mixed bacterial species were isolated. (F) Functional dystocia. The right uterine horn is distended with multifocal to coalescing dark red areas. The placental implantation sites in the right uterine horn are hemorrhagic. Presumptive placental defects and/or a circulatory disturbance.

Table 3. Presenting clinical signs in mice with functional ($n = 11$), obstructive ($n = 16$), and equivocal ($n = 18$) dystocia and nondystocia ($n = 9$) cases

	Hunched	Lethargic	Vaginal discharge	Thin	Moribund	Grimace	Piloerect	Pallor
Functional	55% (6)	27% (3)	45% (5)	27% (3)	0% (0)	9% (1)	0% (0)	0% (0)
Obstructive	44% (7)	50% (8)	50% (8)	25% (4)	13% (2)	0% (0)	6% (1)	0% (0)
Equivocal	44% (8)	50% (9)	33% (6)	17% (3)	6% (1)	6% (1)	0% (0)	0% (0)
Nondystocia	56% (5)	56% (5)	33% (3)	11% (1)	0% (0)	11% (1)	11% (1)	33% (3)

are contraindicated in cases of obstructive dystocia where fetal abnormalities prevent normal fetal expulsion and, if administered, may negatively impact the health and welfare of the dam.

The average number of fetuses per litter for C57BL/6 mice or on a C57BL/6 background with dystocia was 5.9 ± 2.6, which was lower than reported for the C57BL/6 strain (7.5 ± 1.3 SD).[11] The average age of mice with dystocia at presentation in the cases examined was approximately 6 mo, and primiparous dams were overrepresented. Based on these findings, we recommend pairing breeding animals at 6 to 8 wk of age and avoid breeding females for the first time when over 5 mo of age. In general, female breeders should be retired between 6 and 10 mo of age, as reproductive pathology that occurs as the animal ages can have a negative impact on breeding performance.[18,24] For example, cystic endometrial hyperplasia and secondary bacterial pyometra have been identified as possible causes of dystocia in aged female mice.[18,24] In our study, only one of the mice with dystocia presented with a pyometra from which mixed bacterial species were cultured. Dystocia in primiparous dams may be associated with developmental reproductive tract abnormalities such as the presence of vaginal septa obstructing delivery, although this etiology was not observed in any of the mice we evaluated.[5] Although an inverse relationship between fetal development and litter size has been shown,[13] surprisingly we observed that fetal weights were higher in larger litters. This finding may be associated with intrinsic (for example, strain) or extrinsic (for example, nutritional) factors.[11] It is likely that larger litters with higher fetal weights contributed to dystocia as evidenced by the overrepresentation of obstructive dystocia in this subset of mice.

It is also important to consider the role of the fetus in parturition and whether variation in litter size and/or weight has an impact on the probability of developing dystocia. Although parturition is dependent on a decrease in the concentration of progesterone, it has been proposed that the secretion of surfactant from the fetal lung into the amniotic fluid initiates a sequence of events that leads to parturition.[14,20] Surfactant activates amniotic fluid macrophages, which then migrate

to the maternal uterus, producing cytokines that trigger an inflammatory-like response that results in a decrease of progesterone receptor expression and an increase in uterine contractility and prostaglandin synthesis. This increase in prostaglandins terminates the corpora lutea, decreasing the concentration of progesterone. It is plausible to speculate that differences in litter size, litter weight, and/or dead fetuses may impact this sequence of events or its magnitude.

There were several clinical signs and clinicopathologic findings that were more frequently observed in mice with dystocia, although there was no single clinical sign or serum analyte that could be used to distinguish all of the obstructive from the functional causes of dystocia. However, cases in which a neonate is visibly trapped in the pelvic canal such as the 3 cases observed in this study, lubrication and application of gentle traction to remove the fetus can be considered.[3] In dams that appear stable without a visible obstructive dystocia, medical management may include administration of calcium gluconate, misoprostol, IL1 and IL6, warm subcutaneous fluids, antibiotics, analgesics, uterotonic drugs such as oxytocin, soft diet, extra nesting material, provision of supplemental heat, and/or relocating the cage to a dark quiet location, as well as frequent monitoring.[4,9,18,22] If analgesics are indicated, nonsteroidal antiinflammatory drugs should be avoided because they are tocolytic and inhibit cyclooxygenases, which are involved in the synthesis of prostaglandins, a hormone that is essential to parturition in the mouse.[18] In the case of oxytocin, its use has been debated due to limited evidence of its efficacy in mice with dystocia, can cause pain and distress if administered inappropriately, and its other physiologic and behavioral effects may confound research.[18] Furthermore, oxytocin is not considered essential for parturition in mice, as oxytocin-deficient mice are able to deliver normally, although the process may be lengthened.[14] Treatment should be considered for irreplaceable breeding stocks that may have a functional dystocia and appear healthy. Investigators should be encouraged to engage the veterinary staff at their institution to explore treatment options for valuable breeding mice. For dams in poor condition (for example, moribund, hypothermic, and/or in pain/distress), euthanasia is recommended. If pups are valuable, they can be removed by caesarian section and cross fostered.[4]

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Conflict of Interest

The authors have no conflicts of interest to declare.

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