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R Vigneshwar

Veterinary Officer, Centre for
Stem Cell Research, Christian
Medical College, Vellore, Tamil
Nadu, India

R Divisha

Assistant Professor, Department
of Veterinary Pharmacology &
Toxicology, Veterinary, College
and Research Institute, Theni,
Tamil Nadu Veterinary and
Animal Sciences University,
Tamil Nadu, India

R Madheswaran

Assistant Professor, Department
of Veterinary Pathology,
Veterinary College and Research,
Institute, Udumalpet, Tamil
Nadu Veterinary and Animal
Sciences University, Tamil
Nadu, India

Corresponding Author:

R Vigneshwar

Veterinary Officer, Centre for
Stem Cell Research, Christian
Medical College, Vellore, Tamil
Nadu, India

An observational study on false pregnancy (pseudocyesis) in a laboratory mouse induced by sterile mating

R Vigneshwar, R Divisha and R Madheswaran

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Abstract

Pseudopregnancy, also known as pseudocyesis or false pregnancy, is a condition in which female animals show all the physiological and behavioural signs of pregnancy, despite the absence of a foetus. In rodents, pseudopregnancy can be triggered by vagino-cervical stimulation, whether through mating or other forms of stimulation. This study documents a case of sterile mating-induced pseudopregnancy in an adult FVB/NJ strain female mouse from a laboratory breeding colony. Upon clinical examination, the female mouse exhibited typical signs of pregnancy, including weight gain, mammary gland development, and nest-building behaviour. The male's infertility, caused by nephropathy, led to unsuccessful fertilization, resulting in a false pregnancy.

Keywords: Pseudopregnancy, sterile mating, rodent, FVB/NJ mouse, spontaneous ovulation

Introduction

Pseudopregnancy is a condition observed in non-human mammals, characterized by a progestational state in which the female exhibits endometrial and hormonal changes typical of early pregnancy and lactation, despite the absence of a fertilized embryo. In mice, pseudopregnancy typically occurs after estrus when the female mates with an infertile male, resulting in sterile mating. While mice, like dogs, are spontaneous ovulators, they do not enter pseudopregnancy without mating, as the Corpus Luteum (CL) rapidly regresses in the absence of coital stimulation. However, mating with an infertile male causes the CL to persist, even without embryonic development, thereby inducing pseudopregnancy. During this state, females may develop mammary tissue and exhibit nesting behaviour (Milligan and Khan, 1980) [7]. In laboratory settings, pseudopregnancy is commonly induced to facilitate embryo transfer by creating surrogate dams (Shiotani *et al.*, 1993) [9]. Reports of naturally occurring pseudopregnancy in breeding colonies of laboratory mice are scarce. Therefore, documenting such cases holds significant relevance for laboratory animal veterinarians and facility managers. This study aims to investigate the causes, behavioural patterns, physiological responses, and anatomical changes associated with pseudopregnancy in a laboratory mouse.

Case history

At the Laboratory Animal Facility of Christian Medical College, Vellore, laboratory mice colonies were housed in groups on sterilized bedding within Individually Ventilated Cages (IVCs), in separate rooms designated for breeding, holding, and experimentation. All animal care and maintenance followed the guidelines set by the Committee for the Control and Supervision of Experiments on Animals (CCSEA, India). During a routine examination, a six-month-old female FVB/NJ mouse from the breeding colony (1:1 pair) exhibited signs of pregnancy, including abdominal enlargement and mammary gland development (Fig. 1). While the female tested positive for pregnancy indicators, the male showed decreased activity. Health monitoring tests including oral swabs, urine and faecal cultures, and serological assessments were all negative for microbial infections.

The female mouse was moved to an individual cage equipped with wooden nesting material and an enrichment device (mouse hut). The expected delivery date was recorded on the breeding card. The mouse actively used the nesting material to construct a dome-shaped nest. However, no delivery occurred on the expected date, and the case was noted as prolonged gestation. Five days later, the mouse displayed signs of impending parturition reduced activity, self-isolation, straining, and mild rectal prolapse but still did not give birth, although signs of labor persisted. Differential diagnosis at this stage included foetal mummification or maceration. Due to the mouse's declining condition, including decreased food and water intake and general weakness, surgical intervention (caesarean section) was considered too risky. To alleviate suffering, the animal was humanely euthanized using CO₂ asphyxiation. During necropsy, excessive abdominal fat deposition was observed. The uterus appeared enlarged and showed motility, with prominent vascularization, suggestive of a gravid state (Fig. 2). Corpus luteum was also present. However, upon incision, no foetuses were found, confirming pseudopregnancy.



Fig 1: Enlarged abdomen and prominent mammary glands



Fig 2: Gravid uterine horns with no foetus

The male mouse, which had shown decreased activity in recent days, exhibited clinical signs of discomfort, including back-arching, abdominal pressing, piloerection, reduced urination, and decreased food and water intake. The animal developed abdominal distension and anuria. Elevated serum biomarkers confirmed renal pathology, and the mouse was subsequently euthanized. Necropsy examination revealed haemorrhagic cystitis, characterized by an inflamed bladder containing dark yellowish-red urine, as well as seminal vesiculitis and prostatitis. The kidneys were visibly inflamed and congested (Fig. 3).



Fig 3: Haemorrhagic cystitis and seminal vesiculitis

Materials & Methods

Semen was collected from the tail of the epididymis immediately after euthanasia and examined microscopically (40x) to assess sperm motility. Smears were prepared on clean glass slides, stained with Eosin and Nigrosin to evaluate sperm morphology and viability, and examined under oil immersion (100x). Urine was collected directly from the bladder post-euthanasia and analyzed under low-power magnification (10x), with additional dipstick testing performed using Medi-Test Combi 10 VET urine strips. Tissue samples from the kidneys, urinary bladder, and seminal vesicles were collected, fixed in 10% neutral buffered formalin, dehydrated through graded isopropyl alcohol and xylene, embedded in paraffin, sectioned at 5 µm thickness, and stained with Hematoxylin and Eosin (H&E) for histopathological evaluation under light microscopy.

Results

The male mouse exhibited elevated serum levels of Blood Urea Nitrogen (BUN) and creatinine, measuring 45 mg/dL and 0.8 mg/dL, respectively. These values exceed the normal reference ranges for mice BUN: 20-28 mg/dL and creatinine: 0.1-0.3 mg/dL confirming renal dysfunction. Microscopic examination of the urine sample revealed the presence of red blood cells (RBCs), and a dipstick test was positive for blood, indicating hematuria. Histopathological evaluation showed the loss of brush borders, cellular degeneration, and the presence of eosinophilic secretions in kidney tubules. Additionally, interstitial congestion and infiltration of mononuclear cells were observed in both the interstitium and glomeruli (Fig. 4-A). Microscopic examination of the seminal vesicle revealed several empty tubules and a few tubules containing eosinophilic fluid. The mucosa, lined with tall columnar cells, extended towards the center of the lumen,

which contained eosinophilic fluid along with a few exfoliated cells (Fig. 4-B). Urinary bladder mucosa revealed a multi-layered transitional epithelium extending towards the lumen, surrounded by eosinophilic debris. Foci of mononuclear cells were present in the mucosa, and exfoliated cells were observed within the luminal debris. (Fig. 4-C). Semen analysis revealed poor sperm motility (20%), a high rate of morphological abnormalities (60%), and a significant proportion of non-viable sperm (60%), confirming infertility in the male.

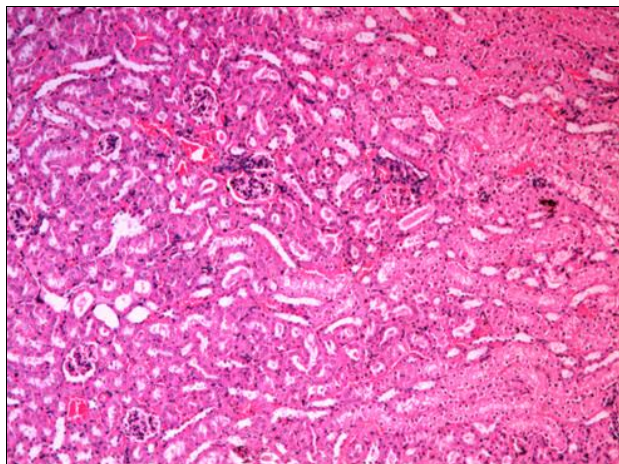


Fig 4-A: Kidney tubules revealed cellular degeneration, and the presence of eosinophilic secretions



Fig 4-B: seminal vesicle showed empty tubules, eosinophilic fluid along with few exfoliated cells

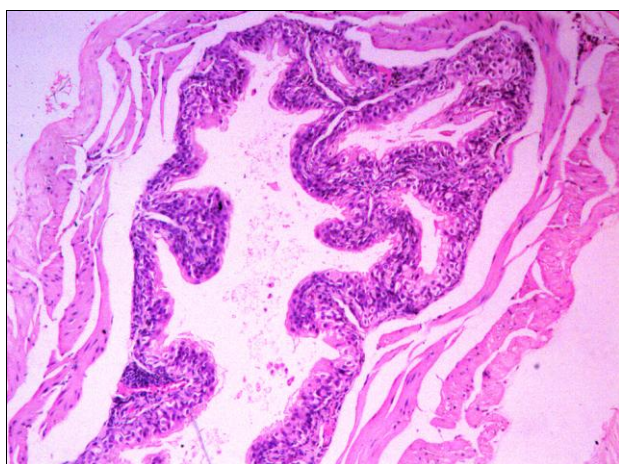


Fig 4-C: Urinary bladder mucosa revealed a multi-layered transitional epithelium with foci of mononuclear cells

Discussion

Renal failure is known to contribute to subfertility or infertility through various mechanisms, including hypogonadism, erectile dysfunction, direct spermatogenic impairment, spermatotoxicity, and late-stage maturation arrest, leading to oligospermia or azospermia (Lundy and Vij, 2019) [6]. End-stage renal disease (ESRD) can result in hormonal imbalances and disrupted spermatogenesis, manifesting as oligoasthenozoospermia and Sertoli cell atrophy (Holley JL, 2004) [5]. The findings of this study are consistent with these established observations.

Rodents are spontaneous ovulators with a short estrous cycle lasting 4-5 days, characterized by an inactive luteal phase and a semi-functional corpus luteum. In the absence of fertilization, progesterone secretion is brief and terminates quickly without a pregnancy-maintaining signal. However, the lifespan of the corpus luteum can be significantly extended, prolonging the luteal phase to approximately 12 days, through neuroendocrine stimulation of the genital tract. In mice, coital vagino-cervical stimulation and in rats, non-coital mechanical stimulation activates neuroendocrine reflexes that lead to sustained, twice-daily surges of pituitary prolactin (Terkel, 1986) [10]. This hormonal response supports the maintenance and function of the corpus luteum, resulting in pseudopregnancy (Yang *et al.*, 2009) [11]. The presence of an active luteal phase and continued progesterone secretion is essential for the development of deciduoma (Finn and Keen, 1963) [3]. In the present case, the anatomical changes in the uterus and ovary were opined with the findings of Ryan KD and Schwartz NB, 1977 [8], who demonstrated pseudopregnancy in group housed and sterile mated female mice.

Sterile mating using vasectomized males is a well-established method for manipulating the reproductive cycle in mice (Behringer *et al.*, 2014; Bermejo-Alvarez *et al.*, 2014) [1,2], and it remains the preferred technique for inducing pseudopregnancy in large numbers of females for embryo transfer procedures. However, naturally occurring pseudopregnancy is uncommon in mice housed within Specific Pathogen-Free (SPF) animal facilities, where animals are routinely monitored for health and diseases, and breeding practices are scientifically managed. Fertility assessment in male rodents poses a challenge, as semen collection is only feasible post-mortem. If a female is paired with an infertile male due to underlying systemic conditions she may enter a pseudopregnant state. In the present case, the male mouse was affected by renal disease, which impaired its fertility and consequently led to pseudopregnancy in the female.

Maternal nest-building behaviour in animals is primarily influenced by the gonadal hormones namely the estradiol, progesterone, and prolactin. However, limited information is available regarding nest-building during naturally occurring events such as pseudopregnancy, which significantly impact the reproductive state in mice. In pseudopregnant animals, this behavior is likely driven by progesterone secretion during the active luteal phase. In the present case, the mouse constructed a well-formed, dome-shaped nest an observation consistent with the findings of Gandelman *et al.*, (1979) [4], who reported that pseudopregnancy alone is sufficient to trigger maternal nest-building behaviour in experimentally induced models.

Conclusion

In conclusion, our observations demonstrate that pseudopregnancy induced by sterile mating can result in significant physiological, anatomical, and behavioural

changes in female mice, while renal disease in male mice can adversely affect fertility. Although infectious diseases are effectively controlled in SPF animal facilities, the presence of systemic non-infectious conditions cannot be readily excluded. Therefore, maintaining and reviewing pedigree records when selecting breeding pairs is strongly recommended to minimize breeding-related complications.

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Conflict of interest

The authors declare no conflict of interest.

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