Review Article

Intraperitoneal Injection of Sesame Oil as Vehicle Induces Decidual Reaction in Female Rats: A Review of In-House Data

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Abstract

This review investigates the incidences of decidual reactions and associated microscopic changes in Sprague-Dawley rats comparing dual-route (intravenous-IV + intraperitoneal-IP) to IV-only preclinical studies of nonimplant medical devices at Syngene International Ltd. Data from 132 rats in 14 dual-route studies and 120 rats in 12 IV-only studies were analyzed retrospectively. Sesame oil and normal saline were used as the vehicle for intraperitoneal and intravenous administration, respectively. The dual-route studies showed higher incidences of decidual reactions (9.8%) compared with IV-only studies (0.8%). Associated microscopic changes included increased mucification in the cervix (3.8% vs 0.8%) and vagina (6.1% vs 2.5%), and mammary gland hyperplasia (12.9% vs 4.2%), indicative of pseudopregnancy. The findings suggest that intraperitoneal administration of sesame oil, in presence of pseudopregnancy, significantly contributes to these effects. This review highlights the importance of understanding the potential effects of the vehicle and route of administration while interpreting the results in preclinical studies.

Keywords

decidual reaction, intraperitoneal injection, Sprague Dawley rats, sesame oil, pseudopregnancy

Introduction

Decidual reaction (sometimes called Deciduoma), a proliferative, nonneoplastic change seen in the uterus is an uncommon finding in rats, particularly in young females in 30-day subacute studies.[3] Background lesion data from National Toxicology Program's (NTP's) 90-day studies in Fischer-344 rats showed an incidence of 1.3% (2/159).[4] Elcock et al[7] described 5 incidences of spontaneous decidual reaction out of 12,000 Sprague Dawley rats. However, we observed higher incidence of decidual reactions following intraperitoneal administration of sesame oil in dual-route toxicity (IV+IP route) studies meant for the safety evaluation of medical devices. Although decidual reactions have been experimentally induced in mice following intraperitoneal injection of various vegetable oils, we could not find any literature on the incidences of decidual reactions in the context of preclinical toxicity studies.[9] A decidual reaction mimics the decidual implantation formed during pregnancy.[5] Recognizing such background changes is critical for the accurate interpretation of the histopathological findings in preclinical toxicology studies. For this reason, we decided to investigate the incidences of decidual reaction observed in 30-day dual-route studies conducted over the past 5 years at Syngene International Limited, Bengaluru, India.

In this review, we describe the incidence and possible mechanisms underlying the induction of decidual reactions in female Sprague-Dawley rats, from 30-day studies involving concurrent intraperitoneal and intravenous administration (dual-route). We compare these results with studies involving only intravenous administration (IV-only) to assess any effects of sesame oil used as a vehicle intraperitoneally. These studies were part of the safety evaluation of nonimplantable medical devices. Data only from vehicle control groups has been used in this review.

Safety Assessment of Medical Devices

Medical devices include a wide range of materials that are used in the management of human health conditions. ISO 10993-1 provides an overview of the definition and classification of

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Table 1. Dosing details of dual-route and IV-only studies.

Study type	Dual-route studies		IV-only studies
Route	IP	IV	IV
Vehicle	Sesame oil	Saline	Saline
Volume	5 mL/kg	10-20 mL/kg	10-20 mL/kg
Dosage	Once every 3 days, for 30 days	Once daily for 30 days	Once daily for 30 days

medical devices.[20] These devices, however, may pose potential biological risks in humans, owing to their leachates and therefore need to be evaluated for safety. Safety assessment of medical devices involves the use of in-vitro, in-vivo and ex-vivo models. For subacute/subchronic toxicity testing, implantable devices are best assessed via implantation, but nonimplantable devices can be evaluated through dosing of their extracts.[20]

Intraperitoneal route is required for the safety assessment of nonimplantable medical devices that come into direct contact with the peritoneal cavity or where the extracts of medical devices cannot be given intravenously due to their particulate nature.[22] The examples for nonimplantable devices include the components used in dialysis, including transfer sets, ethyl vinyl acetate (EVA) bags, and dialyzer gaskets.

The whole medical device or selected representative portions of medical devices are extracted in vehicles.[23] Concurrent administration of polar and nonpolar extracts can simulate clinical exposure, with both types injected into the same animal to assess total extractables toxicity. Hence, preclinical evaluation of the systemic toxicity potential of nonimplantable medical devices requires the administration of test item extracts through intravenous (IV) and intraperitoneal (IP) routes to the same animal.[22] Polar and nonpolar extracts are used for IV and IP administration, respectively. Vegetable oils such as corn oil, sesame oil, olive oil, and mineral oils have been commonly used as nonpolar extract vehicles.[17]

Methods

The studies considered for this review were conducted in the Department of Safety Assessment at Syngene International Limited, Bengaluru, India from 2018 to 2024 in compliance with Good Laboratory Practice (GLP). The data were retrospectively evaluated from vehicle control-rats of all 30-day dual-route and IV-only studies conducted for the evaluation of nonimplantable medical devices. For dual-route studies, data from 132 female rats across 14 studies were used. For IV-only studies, data from 120 female rats across 12 studies were used.

All animals were handled humanely with due regard for their welfare. Every effort was made to minimize and eliminate the pain and suffering of animals in the study. Care of animals complied with the recommendations of the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) and the Committee for Control and Supervision of Experiments on Animals (CCSEA), Government of India. The study was designed to use the minimum number of animals possible as per the guideline ISO 10993-2.[21] The "Form B" for conducting animal experimentation was reviewed and approved by the Institutional Animal Ethics Committee.

Animals

Hsd:Sprague Dawley rats, sourced from Envigo, Netherlands, were used in all the studies. The rats were nulliparous, nonpregnant and 6 to 8 weeks old at the start of the dosing phase.

Animal Housing

The rats were acclimatized for at least 5 days prior to the start of dosing. On the last day of acclimatization, the rats were randomized into vehicle control and test item-treated groups based on their body weight. Rats were pair-housed sex-wise in clean, sterilized, solid-bottom polycarbonate rat cages covered with stainless steel grill tops. The experimental rooms were maintained at a temperature range of 22°C ± 3°C, relative humidity of 30% to 70%, and a light/dark cycle of 12 hours each with at least 15 fresh air changes per hour. Animals were fed ad libitum with certified Rodent Pellet feed. Potable water was provided ad libitum throughout the in-life phase of the study.

Vehicle

The vehicles for IV and IP administration were normal saline and sesame oil (Sigma-Aldrich, Mexico, Product no. S3547), respectively.

Dosing and Restraining

The dose selection was based on the guideline ISO 10993-11:2017.[22] The vehicle control rats were administered only the vehicle (sesame oil or normal saline), without the test item extracts. For dual-route studies, a dose volume of 10 to 20 mL/kg body weight for intravenous infusion and 5 mL/kg body weight for intraperitoneal route were maintained (Table 1). For IV-only studies, a dose volume of 10 to 20 mL/kg body weight for intravenous infusion was used. The rats were dosed intravenously once daily as a slow infusion at 1 mL/min, whereas the intraperitoneal injections were administered as slow boluses once every 3 days. The individual dose volumes were calculated based on the most recent body weights. The animals were held in restrainers during intravenous infusion, and the infusion was performed at the lateral tail vein using an infusion syringe

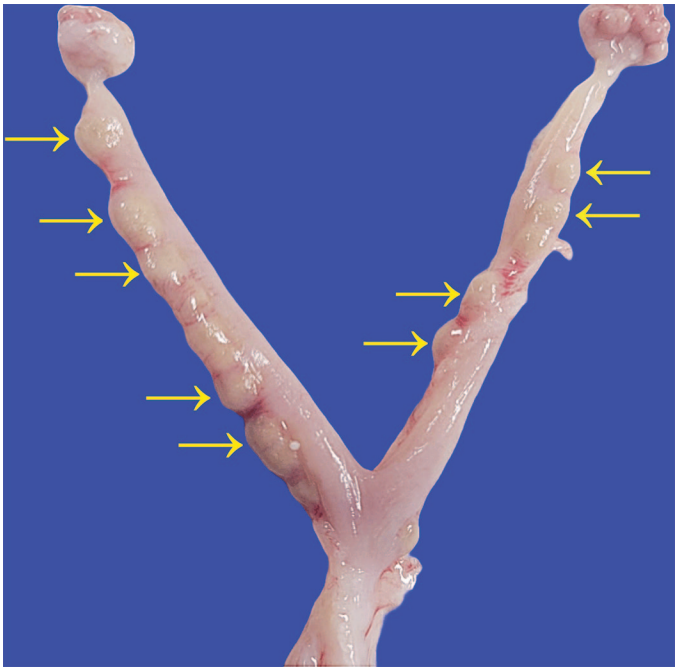

Figure 1. Uterus showing multiple raised foci (arrows) on the horns.

pump. For intraperitoneal injections, the rats were restrained by hand, and the injections were performed at the lower right quadrant of the abdomen.

Clinical Observation

All animals were observed daily for clinical signs, at least once after dosing, and on the day of their scheduled necropsy.

Necropsy, Gross Observation, Organ Collection, and Slide Preparation

At the end of the dosing phase, the animals were euthanized by exsanguination under deep isoflurane anesthesia and examined for gross changes. The protocol specified organs, including the ovary, oviduct, uterus, cervix, vagina, and mammary gland were collected, preserved in 10% neutral buffered formalin, processed, sectioned (4-5 µm thickness), and stained with hematoxylin and eosin. The oviducts were not collected and/or evaluated in 4/14 dual-route studies.

Histopathology Evaluation

The slides were evaluated using a light microscope by a pathologist and a contemporaneous peer review was performed by a board-certified pathologist for all the studies.

Data Compilation

The gross and microscopic finding data from the vehicle control female rats were compiled from the studies. This review discusses only the findings noted in the female reproductive system and mammary gland.

Table 2. Comparison of incidences of gross changes in dual-route and IV-only studies.

Type of study		30-day IV+IP	30-Day IV
No. of studies		14	12
No. of female animals		132	120
Organ	Gross findings	Incidence (percentage)	
Uterus	Cyst	1/132 (0.75%)	Nil
	Focus, raised	14/132 (10.60%)	1/120 (0.83%)

Statistical Analysis

Statistical comparisons were performed to assess the microscopic incidences of decidual reaction and associated findings between dual-route and intravenous (IV-only) administration groups. Fisher's exact test and the Pearson chi-square test were employed. All analyses were two-sided and performed at an α significance level of .05.

Results

Clinical Observations

There were no in-life observations noted in any of the rats.

Gross Changes

In dual-route studies, gross changes in the uterus included raised foci (n=14, 10.60%) (Figure 1) and cysts (n=1, 0.75%) on the uterine horns. In IV-only studies, raised foci (n=1, 0.83%) was noted grossly in a rat (Table 2).

The distribution of raised foci in the uterus was multifocal and was present in one or both uterine horns. The raised foci in the uterus noted grossly were correlated with microscopic findings of decidual reaction.

Microscopic Changes

In dual-route studies, microscopic changes included decidual reaction (n=13/132, 9.84%) in the uterus, increased cervical mucification (n=5/132, 3.78%), increased vaginal mucification (n=8/132, 6.06%), and lobuloalveolar hyperplasia of the mammary gland (n=17/132, 12.87%) (Table 3). Among the rats with decidual reaction, 12/13 rats showed at least one of the above-mentioned microscopic findings in the cervix, vagina, and mammary gland.

Additionally, foreign body granulomatous inflammation was noted in the ovary (n=54/132, 41%), oviduct (n=17/92, 18%) and uterus (2/132, 2%). Among the rats with decidual reaction, foreign body granulomatous inflammation was noted in the ovary of 6/13 rats, oviduct of 1/8 rats, and the uterus of

Table 3. Comparison of incidences of light microscopic changes in dual-route and IV-only studies.

Type of study		30-day dual-route	30-day IV-only
No. of studies		14	12
No. of female rats		132	120
Organ	Microscopic findings	Incidence (percentage)	
Uterus	Decidual reaction	13/132 (9.84%)*	1/120 (0.83%)
Cervix	Mucification, increased	5/132 (3.78%)	1/120 (0.86%)
Vagina	Mucification, increased	8/132 (6.06%)	3/120 (2.5%)
Mammary gland	Hyperplasia, lobuloalveolar	17/132 (12.87%)*	5/120 (4.16%)

*Significantly higher than IV-only group, $P \leq .05$.

1/13 rats. In addition, foreign body granulomatous inflammation was noted in liver, diaphragm, spleen, kidney, mesentery and other organs in the abdominal cavity.

In IV-only studies, microscopic changes included a single incidence of decidual reaction (n=1, 0.83%) in the uterus, increased cervical mucification (n=1, 0.83%), increased vaginal mucification (n=3, 2.5%), and lobuloalveolar hyperplasia of the mammary gland (n=5, 4.16%). The single rat with decidual reaction showed the above-mentioned microscopic changes in the cervix, vagina, and mammary gland.

Microscopically, in dual-route studies, the decidual reactions showed multifocal distribution and were present in one or both uterine horns. The decidual reaction was characterized by nodular proliferation of large eosinophilic stromal or mesenchymal cells with prominent nuclei in the endometrium and myometrium of the uterus (Figure 2A and 2B). In some cases, a clear distinction between the mesometrial and antimesometrial regions of the decidual reaction was noted (Figure 3A). The cells in the antimesometrial region were densely packed (Figure 3B), whereas the ones in the mesometrial region had long cytoplasmic processes with cytoplasmic vacuolation (Figure 3D). A transitional region was present between the mesometrial and antimesometrial region, which contained spindle shaped cells with vacuolar cytoplasm (Figure 3C). Some decidual reactions showed degenerative changes with eosinophilic material and cell debris (Figure 4). In addition, increased mucification of the cervical and vaginal epithelium, and diffuse lobuloalveolar hyperplasia of the mammary gland were noted in most of the rats with decidual reactions (Figures 5 and 6).

Other microscopic changes in the female reproductive system included the presence of foreign body granulomatous inflammation on the serosa/surface of the ovary (54/132), oviduct (17/92), and occasionally in the uterus (2/132). This change was characterized by the presence of clear vacuoles of varying sizes surrounded by inflammatory cells, particularly mononuclear cells and multinucleated giant cells, accompanied by fibroblasts and fibrous connective tissue (Figure 7). This is likely due to the inflammatory response against the injected

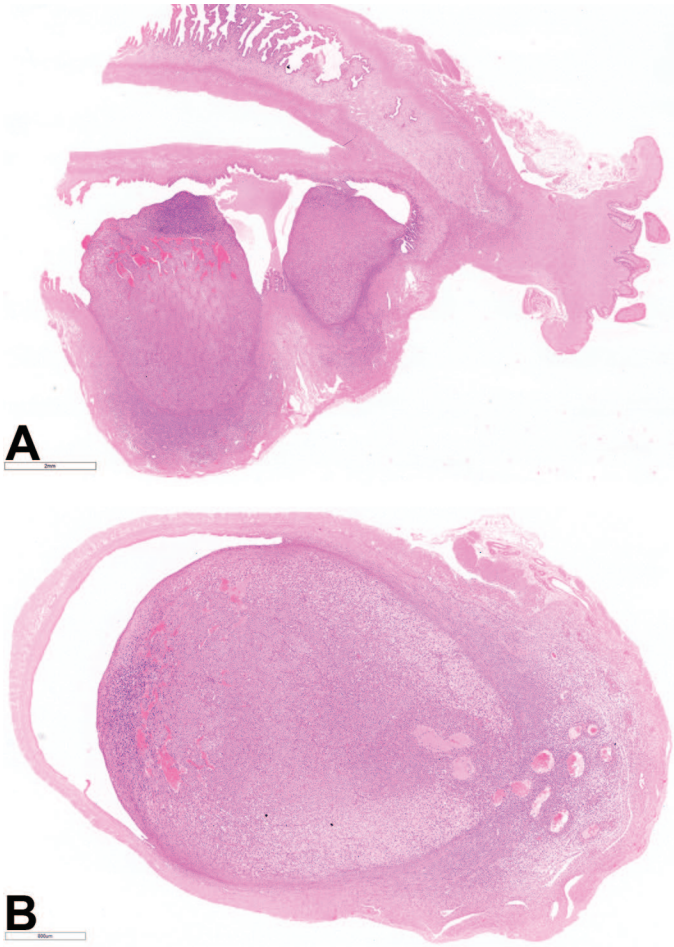

Figure 2. Microscopic images of decidual reactions in rat uterus. (A) Longitudinal section (Original scan 1.3X) and (B) Cross section (Original scan 2.8X). H&E stain.

sesame oil in the peritoneal cavity.[15] The injection of these oils into the peritoneal cavity causes an inflammatory reaction owing to their irritant nature. It has been widely reported that the intraperitoneal injection of vegetable and mineral oils induces lipogranulomas in the serosa or capsule of several organs within the peritoneal cavity.[1,15] However, no sesame oil-induced granulomatous inflammation was noted in the uterine lumen. No other microscopic changes were noted in the ovaries, including changes in the size or number of follicles/corpora lutea.

Decidual reaction was noted in 11/14 dual-route studies, but only in 1/12 IV-only studies. The data from these studies showed statistically significant, higher incidences of decidual reactions and mammary gland hyperplasia in Sprague Dawley rats administered sesame oil in dual-route studies, compared with those in IV-only studies. Fisher's exact test yielded a *P*-value of **.0016** and a chi-square test produced a χ^2 value of 8.09 ($df = 1$, $P \approx$ **.0044**) for decidual reaction. For mammary gland hyperplasia, the Fisher's test showed a *P*-value of **.0236** and chi-square test produced a χ^2 value of 4.94 ($df = 1$, $P \approx$ **.0262**). Results consistently indicated a significantly higher

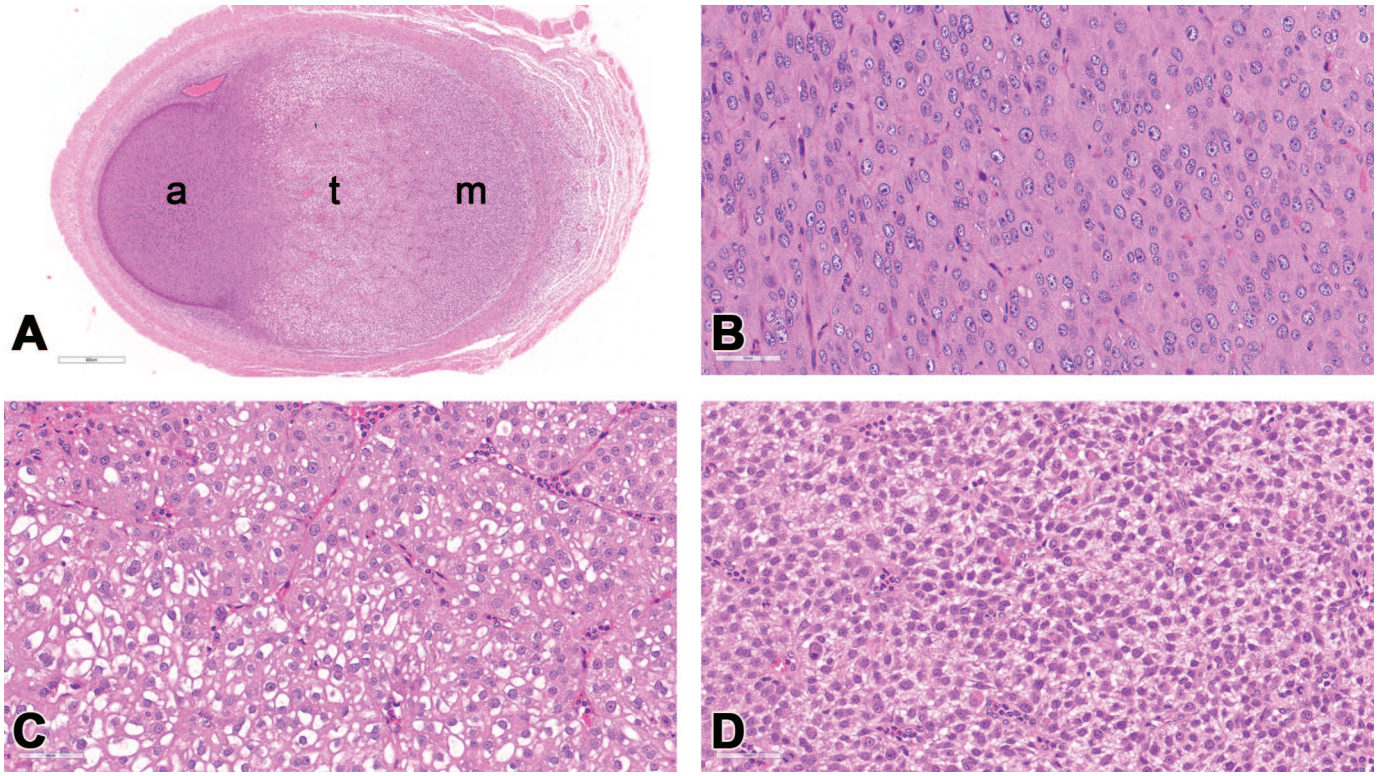

Figure 3. (A) Microscopic image of decidual reaction showing different regions—antimesometrial region (a), transitional region (t), and mesometrial region (m) (Original scan 4X). (B) The antimesometrial region shows densely packed epithelial-like cells (Original scan 40X). (C) The transitional region shows spindle shaped cells with vacuolar cytoplasm (Original scan 40X). (D) The mesometrial region shows cells with long cytoplasmic processes with cytoplasmic vacuolation (Original scan 40X). H&E stain.

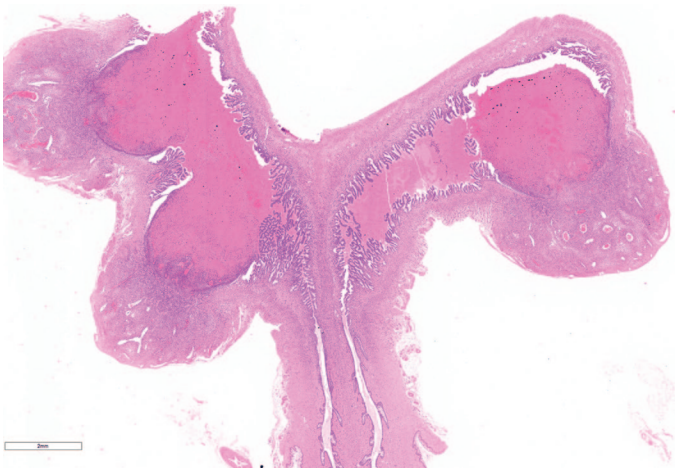

Figure 4. Degenerating decidual reaction in rat uterus (Original scan 1.1X). H&E stain.

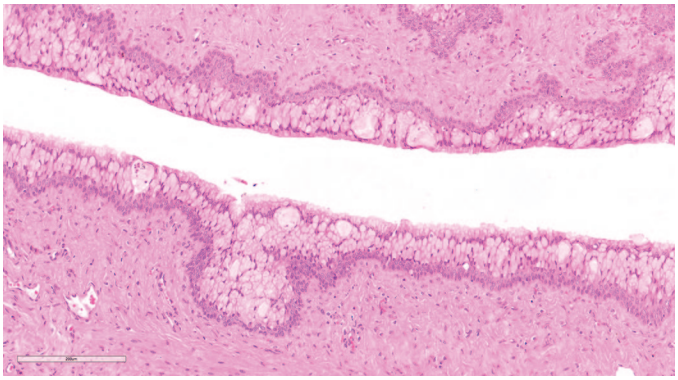

Figure 5. Increased mucification in the vaginal epithelium (Original scan 20X). H&E stain.

incidence of decidual reaction and mammary gland hyperplasia in the dual-route group (Table 3).

Microscopic changes typically associated with pseudopregnancies, such as increased mucification of the cervical and vaginal epithelium, and lobuloalveolar hyperplasia of the mammary glands, were observed in both the dual-route and IV-only studies.[12] However, the incidences of these changes were lower in the IV-only group, reinforcing the idea that intraperitoneal administration of sesame oil plays a significant role in eliciting these effects.

Discussion

Sesame oil and other vegetable oils, such as corn, peanut, and olive oils, have been shown to induce decidual reactions in pseudopregnant rats and mice following intraperitoneal or intrauterine administration.[2,9] This property of vegetable oils

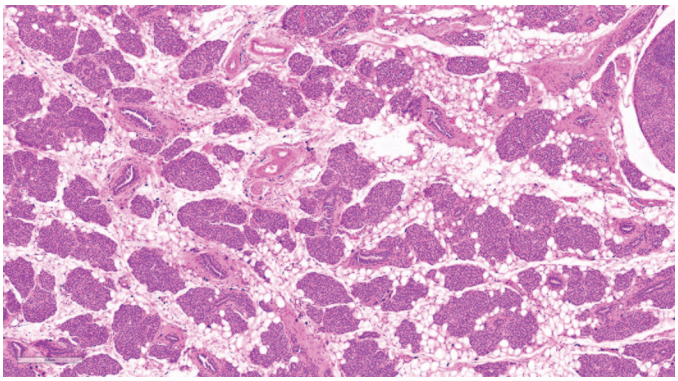

Figure 6. Lobuloalveolar hyperplasia of Mammary gland acini (Original scan 8X). H&E stain.

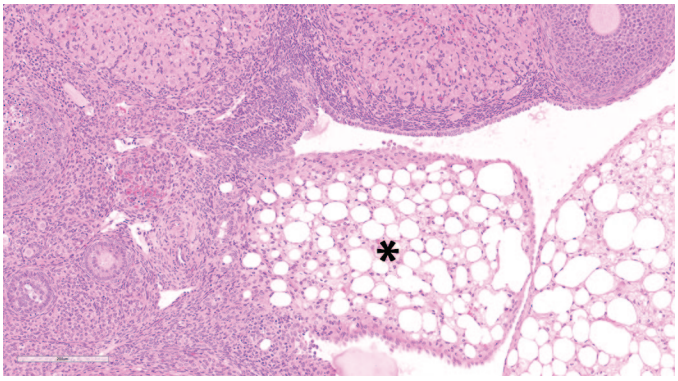

Figure 7. Ovary showing foreign body granulomatous inflammation (*) (Original scan 16.8X).

has been utilized in experimental settings to artificially induce decidual reactions through intrauterine instillation.[8,9,11] These effects were not observed with intraperitoneal administration of mineral oil or oral corn oil administration, suggesting that the decidual response is specific to certain oils, including sesame oil.[9] These oils appear to stimulate decidualization upon migration into the uterine lumen.[9]

Migration of Sesame Oil?

One hypothesis that may explain the decidual reaction in the dual-route studies is the migration of sesame oil into uterine lumen from the peritoneal cavity. Although rats possess a complete ovarian bursa, it contains small pores that may serve as channels between the uterine lumen and the peritoneal cavity.[13,14] Following intraperitoneal injection, sesame oil could likely migrate through the ovarian bursa and fallopian tube into the uterine lumen.[9] However, no direct evidence supporting this hypothesis was identified.

Mechanism of Action

The exact mechanism by which intraperitoneal administration of oils induces decidual reactions remains incompletely understood. The effect of sesame oil could likely be a direct effect on the uterine lumen, rather than an induction of dominant-lethal mutations or chromosomal alterations leading to the decidual reaction.[9]

Intrauterine instillation of sesame oil was shown to promote the expression of the stathmin gene in the uterus of pseudopregnant rats and mice.[18] Stathmin is a cytosolic phosphoprotein highly expressed at embryo implantation sites. A more recent study demonstrated that the administration of sesame oil into the uterine lumen increased the expression of calreticulin (CALR), a highly conserved chaperone protein associated with decidualization.[25] The enhanced CALR expression, confirmed by immunostaining and immunoblot analysis, was observed during deciduoma development without blastocysts. Additionally, CALR was preferentially expressed at blastocyst implantation sites, indicating its role in the progression of decidualization. This suggests that sesame oil may promote decidualization through enhanced expression of proteins like stathmin and calreticulin, which play a key role in the process.

Role of Pseudopregnancy

Pseudopregnancy is a physiological condition observed in female rats, more commonly in mature and older rats. While spontaneous occurrence in young rats is rare and not well-documented, it can be experimentally induced through cervical stimulation, such as mating with sterile males or mechanical methods.[12] Pseudopregnancy has been shown to predispose rats and mice to decidual reactions[10,11,24] and has been linked to a surge in pituitary prolactin (PRL) levels in female rats.[16,19] In dual-route studies, repeated physical restraining of rats for vehicle or test item administration leads to stress, which in turn could promote PRL surge in these rats.[6] In addition, stimulation of female genitalia accidentally during repeated restraining of animals may lead to pseudopregnancy, which in turn can predispose them to decidual reactions.

Spontaneously occurring decidual reactions are rare and typically associated with pseudopregnancy, and their precise causes are not always clear. These reactions generally occur during days 3 and 4 of pseudopregnancy, requiring at least 48 hours of progesterone exposure followed by small amounts of estrogen. These reactions follow a defined course, ultimately ending in the degeneration of decidual cells and spontaneous regression within approximately 12 days.[5]

The microscopic changes observed in these studies, such as increased mucification of the cervical and vaginal epithelium, and lobuloalveolar hyperplasia of the mammary glands, are consistent with pseudopregnancy, further suggesting its role in facilitating the decidual reaction.[26,12]

The role of sesame oil in inducing these reactions is unclear. Migration of the sesame oil from the peritoneal cavity into the uterine lumen where it promotes decidualization is a possibility, but the hypothesis lacks evidence at the moment. Additionally, the presence of pseudopregnancy, which predisposes animals to decidual reactions, may have primed the uterus for such reactions. Further research is required to establish the exact mechanism by which sesame oil injected into the peritoneal cavity can result in decidual reaction in rats. This review underscores the

importance of accounting vehicle-related effects in preclinical toxicity studies.

Author Contributions

Anikethana Ramesh: Conceptualization; Investigation; Writing—original draft; Writing—review & editing; Data curation; Supervision.
Rajesh Karunanithi: Writing—review & editing; Data curation; Supervision; Investigation.
Manohar M. Deshmukh: Supervision; Writing—review & editing.
Smitha A Thilak: Writing—review & editing; Supervision.
Kumar Krishnachari: Supervision; Writing—review & editing.
Kiran H. Jayaram: Writing—review & editing; Supervision.
Mohan Krishnappa: Writing—review & editing; Supervision.
Kalaiselvan Ponnusamy: Conceptualization; Investigation; Writing—review & editing; Supervision.

Declaration of Conflicting Interests

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References

1. Alsina-Sanchis E, Mülfarth R, Moll I, Mogler C, Rodriguez-Vita J, Fischer A. Intraperitoneal oil application causes local inflammation with depletion of resident peritoneal macrophages. *Mol Cancer Res*. 2020;19(2):288-300. doi:10.1158/1541-7786.mcr-20-0650.
2. Chelich AM, Edmonds ES. Pseudopregnancy and the decidual response in the obese Zucker rat: a reexamination. *Biol Reprod*. 1986;34(5):805-808. doi:10.1095/biolreprod34.5.805.
3. Dixon D, Alison R, Bach U, et al. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol*. 2014;27(suppl 3-4):1S-107S. doi:10.1293/tox.27.1S.
4. Dixon D, Heider K, Elwell MR. Incidence of nonneoplastic lesions in historical control male and female Fischer-344 rats from 90-day toxicity studies. *Toxicol Pathol*. 1995;23(3):338-348. doi:10.1177/019262339502300310.
5. Dixon D, Vidal JD, Leininger JR, Jokinen MP. Oviduct, Uterus, and Vagina. In: Bradley A, Suttie AW, Boorman GA, et al., eds. *Boorman's Pathology of the Rat*. Amsterdam: Elsevier; 2017:537-559. doi:10.1016/b978-0-12-391448-4.00027-7.
6. Drago F, Spadaro F, D'Agata V, et al. Role of prolactin in stress-induced biological modifications in animals. In: Puglisi-Allegra S and Oliverio A, eds. *Psychobiology of Stress*. Dordrecht: Springer; 1990:125-133. doi:10.1007/978-94-009-1990-7_10.
7. Elcock LH, Stuart BP, Mueller RE, Hoss HE. Deciduoma, uterus, rat. In: Jones TC, Mohr U, Hunt RD, eds. *Monographs on Pathology of Laboratory Animals: Genital System*. Berlin: Springer-Verlag; 1987:140-145.
8. Finn CA, Keen PM. The induction of deciduomata in the rat. *J Embryol Exp Morphol*. 1963;11:673-682. doi:10.1242/dev.11.4.673.
9. Generoso WM, Cain KT, Hoskins JA, Washington WJ, Rutledge JC. Pseudo dominant-lethal response in female mice treated with plant oils. *Mutat Res*. 1984;129(2):235-241. doi:10.1016/0027-5107(84)90156-8.
10. Herington JL, Underwood T, McConaha M, Bany BM. Paracrine signals from the mouse conceptus are not required for the normal progression of decidualization. *Endocrinology*. 2009;150(9):4404-4413. doi:10.1210/en.2009-0036.
11. Hetherington CM. The development of deciduomata induced by two non-traumatic methods in the mouse. *Reproduction*. 1968;17(2):391-393. doi:10.1530/jrf.0.0170391.
12. Hvid H, Thorup I, Sjögren I, Oleksiewicz MB, Jensen HE. Mammary gland proliferation in female rats: effects of the estrous cycle, pseudo-pregnancy, and age. *Exp Toxicol Pathol*. 2012;64(4):321-332. doi:10.1016/j.etp.2010.09.005.
13. Kellogg MP. The development of the periovarial sac in the white rat. *Anat Rec* 1941;79(4):465-477. doi:10.1002/ar.1090790406.
14. Martin GG, Sack M, Talbot P. Structure of bursae ovaricae surrounding the ovaries of golden hamster. *Anat Rec*. 1981;201(3):485-498. doi:10.1002/ar.1092010306.
15. Ramot Y, Ben-Eliahu S, Kagan L, Ezov N, Nyska A. Subcutaneous and intraperitoneal lipogranulomas following subcutaneous injection of olive oil in Sprague-Dawley rats. *Toxicol Pathol*. 2009;37(7):882-886. doi:10.1177/0192623309347911.
16. Smith MS, McLean BK, Neill JD. Prolactin: the initial luteotropic stimulus of pseudopregnancy in the rat. *Endocrinology*. 1976;98(6):1370-1377. doi:10.1210/endo-98-6-1370.
17. Strickley RG. Solubilizing excipients in oral and injectable formulations. *Pharm Res*. 2004;21(2):201-230. doi:10.1023/b:pham.0000016235.32639.23.
18. Tamura K, Hara T, Yoshie M, Irie S, Sobel A, Kogo H. Enhanced expression of uterine stathmin during the process of implantation and decidualization in rats. *Endocrinology*. 2003;144(4):1464-1473. doi:10.1210/en.2002-220834.
19. Terkel J. Neuroendocrine processes in the establishment of pregnancy and pseudopregnancy in rats. *Psychoneuroendocrinology*. 1988;13(1-2):5-28. doi:10.1016/0306-4530(88)90004-2.
20. The International Organization for Standardization (ISO). *Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing Within a Risk Management Process* (ISO 10993-1:2018). Geneva: ISO.
21. The International Organization for Standardization (ISO). *Biological Evaluation of Medical Devices—Part 2: Animal Welfare Requirements* (ISO 10993-2:2022). Geneva: ISO.
22. The International Organization for Standardization (ISO). *Biological Evaluation of Medical Devices—Part 11: TESTS for Systemic Toxicity* (ISO 10993-11:2017). Geneva: ISO.
23. The International Organization for Standardization (ISO). *Biological Evaluation of Medical Devices—Part 12: Sample Preparation and Reference Materials* (ISO 10993-12:2021). Geneva: ISO.
24. Velardo JT, Dawson AB, Olsen AG, Hisaw FL. Sequence of histological changes in the uterus and vagina of the rat during prolongation of pseudopregnancy associated with the presence of deciduomata. *Am J Anat*. 1953;93(2):272-305. doi:10.1002/aja.1000930205.
25. Yoshie M, Kusama K, Tanaka R, et al. Possible roles of calreticulin in uterine decidualization and receptivity in rats and humans. *Int J Mol Sci*. 2021;22(19):10505. doi:10.3390/ijms221910505.
26. Yoshie M, Tamura K, Hara T, Kogo H. Expression of stathmin family genes in the murine uterus during early pregnancy. *Mol Reprod Dev*. 2006;73(2):164-172. doi:10.1002/mrd.20408.