Editorial

Animal models closer to intrauterine adhesive pathology

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Although the true incidence of intrauterine adhesion (IUA) is uncertain, the prevalence of IUA after curettage is reported to be between 15% and 40% (1). IUA may cause menstrual disorders as well as adverse reproductive outcomes such as subfertility, infertility and recurrent miscarriage. Among the aforementioned, IUA was found in 4.6% of infertile women, and 21.8% in those with recurrent pregnancy loss (2,3). Endometrial factor is much more difficult to treat than other infertility factors such as anovulation, and tubal and male factors.

Currently the treatment of choice for IUA is mainly mechanical removal of fibrotic and damaged endometrial tissue using hysteroscopic surgery. Such procedure may provide restoration of anatomical structure without the functional recovery, which leads to limited efficacy in the treatment of infertility caused by repeated embryonic implantation failure. Therefore, development of novel strategies such as the use of biological scaffolds and stem cell therapies are necessary for the treatment of refractory damaged endometrium. However, trials of various potential therapies may raise safety issues when clinically applied. It is also difficult to compare the therapeutic effects among various experimental approaches due to the lack of standardized assessment scales in currently available animal models (*Table 1*). Hence, the establishment of more compatible animal model to human disease is an essential component of translational research on the recovery of endometrial damage after cell therapy with or without scaffold material (22).

Recently, Xu *et al.* reported a successful establishment of IUA animal model which used pregnant rats. To date, animal models of IUA have been developed using various methods including chemical and/or mechanical injury in non-pregnant animals. The most important cause of IUA seems to be postpartum curettage due to their relationship with this procedure (24). The timing of endometrial trauma in relation to puerperium is considered as one of the most important factors, and this corresponds to the fact that endometrium is recovered within 3 days after curettage in non-pregnant rat models because the hormonal changes associated with pregnancy play a role in inhibiting the regeneration of epithelial cells and promoting fibrosis of interstitial tissue. Therefore, the animal model simulating human IUA using pregnant rats has a great advantage in terms of the similarity of actual pathophysiology of IUA clinically observed.

When establishing IUA animal model in pregnant rats, the procedure of removing multiple embryos in bilateral uterus is added. The shorter the duration of anesthesia is, the better stability and efficiency was shown in production of an IUA animal model (4). Therefore, it would be informative to evaluate how much time was spent by carrying out the procedure of incision, removing embryos and curettage. Also, mechanical methods using curettage were found to show inconsistent degree of damage compared to chemical methods. In this regard, it is necessary to standardize the most efficient protocol of establishing animal models.

Conclusively, since a recent study described a successful establishment of novel IUA animal model, promising results can be expected in regard to the development of more efficient strategy using this animal model.

Table 1 Currently available animal models with different strain, age, weight, methods for damage, and pregnant status

Reference	Strain	Age	Weight	Anesthesia	Category	Method for damage	Time of damage	Pregnant status
Okazaki M, 2005 (4)	BDF1, TNF-R p55-deficient mouse, C57BL/6	6–10 W	–	Sodium pentobarbital	–	Clamping the uterine horn and uterine artery	5–30 min	Non-pregnant
Buhimschi CS, 2010 (5)	MRL/Mpj (+/+), C57Bl/6	9 W	–	Ketamine, Xylazine	Incision	Uterine incision	–	Non-pregnant
Li X, 2011 (6)	Sprague–Dawley Rat	–	250–300 g	Ketamine and diazepam	Mechanical	Collagen scaffolds	–	Non-pregnant
Lin N, 2012 (7)	Sprague–Dawley Rat	–	250–300 g	Ketamine and diazepam	Incision	Partial of rat uterine horn was excised and left for scar formation	–	Non-pregnant
Hamon E, 2012 (8)	SD Rat	–	–	–	–	95% alcohol injection	5 min	Non-pregnant
Du H, 2012 (9)	C57Bl/6	–	–	–	–	Lower uterine horn and uterine artery using atraumatic vascular clips	30 min	Non-pregnant
Keskin HL, 2013 (10)	Wistar albino rat	–	180–230 g	Ketamin hydrochloride, Xylazine hydrochloride	Electrocautery	Monopolar electrocautery	3–5 sec	Non-pregnant
Micili SC, 2013 (11)	Wistar albino rat	–	200–230 g	Ketamine, Xylazine	Incision	Full thickness defect by incising a segment	–	Non-pregnant
Ding L, 2014 (12)	Sprague–Dawley Rat	–	250–300 g	–	Mechanical	Partial full thickness uterine excision and Collagen scaffolds	–	Non-pregnant
Miyazaki K, 2014 (13)	Fischer Rat	10–12 W	–	3% inhaled isoflurane	Incision	Uterine horn excision	–	Non-pregnant
Zhang W, 2014 (14)	BALB/c	8–10 W	–	–	–	i.p. injection	–	Non-pregnant
Song T, 2015 (15)	Sprague–Dawley Rat	–	200–250 g	Ketamine and diazepam	Mechanical	Collagen scaffolds	–	Non-pregnant
Zhang XH, 2015 (16)	Kunming mouse	–	25–30 g		Mechanical	Scratched with a blunt syringe on the right uterine horn or both	–	Non-pregnant
Rinaldi SF, 2015 (17)	C57BL/6	D9–D11	–	Isoflurane	Chemical	Intrauterine LPS injection or intravaginal LPS administration	–	Non-pregnant
Agostino M, 2015 (18)	Kunming mouse	8 W	–	Inhaled anesthetics	Mechanical	Intrauterine adhesions using mechanical injury	–	Non-pregnant
Zhang Y, 2016 (19)	ICR mouse	6–7 W	–	8% Chloral hydrate (0.1 mL/10 g), i.p.	Electrocautery	Electrocoagulation	3 sec	Non-pregnant
Wang Y, 2017 (20)	ICR mouse	–	–	–	Mechanical and electrocautery	Curettage and coagulation	–	Non-pregnant
Sahin Ersoy G, 2017 (21)	C57Bl/6 J	8 W	–	Isoflurane	–	Intrauterine injection	–	Non-pregnant
Kim YY, 2019 (22)	C57BL/6	8 W	–	Zoletil, Rompun	–	50% ethanol was infusion	5 min	Non-pregnant
Feng Q, 2020 (23)	Sprague-Dawley	10 W	400–450 g	Chloral hydrate	–	Embryos were removed and the rat endometrium was scraped with a curette in 4 different directions	–	13- to 15-day pregnant

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Footnote

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