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Developing Mouse Models for Ovarian Tissue Transplantation and Xenotransplantation: A Review

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Ovarian tissue transplantation (OTT) is the only option for preserving fertility in prepubertal girls and young women who require immediate cancer treatment. Due to ethical constraints and the limited number of clinical cases, human OTT research is challenging. Mouse OTT models serve as valuable preclinical models. This article aims to review the current status of mouse OTT models, including xenotransplantation from humans. We conducted a systematic analysis of original research articles and reviews of mouse OTT models published in PubMed and the China National Knowledge Infrastructure (CNKI). The construction methods included different mouse strains (C57/BL6, Institute of Cancer Research, Naval Medical Research Institute, genetically engineered, and immunodeficient mice), transplantation sites (subcutaneous tissue, sub-renal capsule, back muscle, peritoneum, and ovarian bursa), and transplantation types (xenotransplantation, allogeneic, and autologous transplantation). The evaluation metrics included histological analysis, assessment of neovascularization density, measurement of granulosa cell proliferation activity, and hormonal and estrous cycle monitoring. The choice of metrics should be selected according to the stage after transplantation. To advance the clinical application, mouse OTT models could be improved by developing standardized evaluation criteria and simplified, rapid, noninvasive detection methods to enhance consistency and comparability of research outcomes. Key areas for further research include addressing safety concerns (eg, risk of tumor cell reimplantation), optimizing efficacy evaluations (eg, follicle quality and endocrine function recovery), and improving cost-effectiveness through analysis of mouse strains and transplantation protocols. This review provides valuable insights for future research and clinical applications.

Keywords: Biological Preservation • Fertility Preservation • Experimental Animal Models • Tissue Transplantation • Ovary • Review

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Introduction

Ovarian tissue transplantation (OTT) is a procedure in which ovarian tissue is surgically harvested before gonadotoxic treatment or at the onset of fertility impairment. OTT entails surgical removal of cortical strips of ovarian tissue, cryopreservation, and thawing and transplanting the preserved tissue back into the patient when needed. This technique aims to preserve fertility and restore ovarian endocrine function [1]. Unlike traditional hormone replacement therapy, OTT enables physiological hormone secretion following natural rhythms, while avoiding the inconvenience of long-term exogenous hormone administration and potential damage to liver and kidney function. In 2019, the American Society for Reproductive Medicine published an expert consensus that recommended that oncologists should discuss fertility preservation options with cancer patients of reproductive age [2]. Currently available fertility preservation methods include: (1) embryo cryopreservation (the standard method that requires ovarian stimulation and a male partner or sperm donor); (2) oocyte cryopreservation (suitable for single women but also requires ovarian stimulation); and (3) OTT (suitable for prepubertal female patients who cannot delay cancer treatment). The consensus also stated that OTT should no longer be regarded as an experimental procedure and could be implemented in clinical practice [2]. Among these fertility preservation methods, OTT is the only option for fertility preservation in prepubertal girls and young women who require immediate cancer treatment [3].

In 2020, nearly 900 000 women aged 0-39 years worldwide were diagnosed with cancer [4]. According to global cancer statistics, the overall cancer incidence rate for women was 186.2 per 100 000 in 2022, with approximately 9.658 million new cancer cases globally. The incidence of breast cancer and cervical cancer in young women is increasing [5]. Similarly, the number of young cancer patients is substantial in China, with an increasing incidence of cancer and a shift toward affecting younger individuals [6,7]. Approximately 2.19 million new cases of cancer in female patients were registered in China in 2022 [8]. Consequently, hundreds of thousands of young female patients worldwide have a need for fertility preservation each year. The development and application of OTT technology offer cancer survivors the prospect of having biological offspring, highlighting its clinical importance. Clinical data suggest that the clinical pregnancy rate after OTT is approximately 38%, and more than 200 newborns have been born worldwide following this procedure [9,10], demonstrating that OTT is a safe and effective technique for fertility preservation. In Europe and some developed countries, OTT has become a routine treatment for fertility preservation. However, this technique still faces numerous challenges, including: (1) safety concerns such as risk of tumor cell reimplantation and immune rejection reactions; (2) difficulties in assessing effectiveness, including assessment of follicle quantity/quality and evaluation of fertility restoration; (3) technical challenges in optimization of preservation protocols and surgical techniques; (4) cost-effectiveness considerations including high processing costs and limited health insurance coverage; and (5) other limitations such as significant loss of primordial follicles and short reproductive lifespan after transplantation [11,12]. Therefore, extensive clinical research and basic experiments are required to optimize the steps involved in OTT to maximize fertility preservation. However, ethical and societal constraints limit research on human ovarian tissues.

The mouse model offers a solution to this limitation, serving as an ideal preclinical model for studying OTT. Mouse and human genomes are highly homologous, with 99% of human genes present in mice, and 93% of the mouse genomic regions corresponding to those in humans [13]. Furthermore, the anatomical structure and physiological functions of mouse ovaries are similar to those of human ovaries. Both use primordial follicles as the ovarian reserve unit and share similar oocyte-granulosa cell crosstalk regulatory mechanisms, and a comparable gonadal axis and cyclic ovulation [14]. Research using mouse models can be used to evaluate the risk of malignant tumor cell reimplantation, develop potential biomarkers for outcomes after OTT, optimize transplantation procedures, and explore the use of related assisted reproductive technologies [15,16]. Currently, the modeling methods and criteria for evaluating the efficacy of OTT in mice are not standardized. How well animal model research results replicate those in clinical practice remains to be clarified.

To review the current status of mouse models of ovarian transplantation (including xenotransplantation from humans), we comprehensively evaluated mouse OTT models through systematic analysis of original research articles and reviews published in PubMed and China National Knowledge Infrastructure (CNKI). The keywords used for the English literature search included "ovarian," "ovarian tissue," "transplantation," "autografted," "mice," and "mouse." This review covers both the construction and evaluation of mouse OTT models, as shown in **Figure 1**.

This paper provides a comprehensive review of mouse OTT models worldwide, and aims to summarize current modeling methods and evaluation criteria to guide future research in this field. **Table 1** [15-28] provides an overview of studies that have used mouse models.

Construction of Mouse Models for Ovarian Tissue Transplantation

The sources of ovarian grafts include human and murine ovarian tissues. Based on the relationship between the donor and

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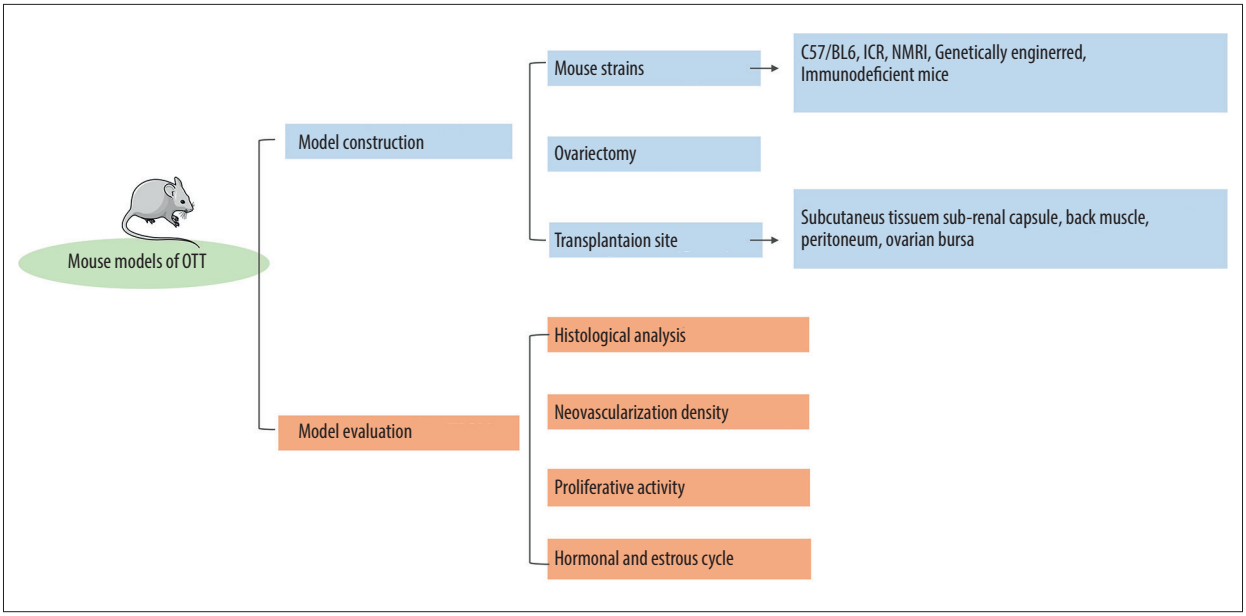

Figure 1. Structure of the review of mouse ovarian tissue transplantation models. OTT – ovarian tissue transplantation.

recipient, transplantation can be categorized as xenotransplantation, allogeneic transplantation, and autologous transplantation. Mouse autologous ovarian transplantation simulates the process of preserving fertility following OTT most closely. Allogeneic transplantation within the same species allows for the analysis and investigation of outcomes associated with OTT at different developmental stages. The xenotransplantation model, involving the transplantation of human ovarian tissue into mice, serves as a preclinical experimental model. This model directly reflects the physiological and pathological changes in human ovarian tissues after transplantation, thus providing reference data for clinical practice. The advantages of this model include: (1) direct evaluation of human ovarian tissue response to transplantation; (2) ability to study human follicle development and activation mechanisms; and (3) assessment of potential therapeutic interventions. The limitations include: (1) immune rejection effects on the grafts; (2) differences in the microenvironment of the murine host transplantation site compared with that of the human body; and (3) variations in hormonal regulation mechanisms between species. To minimize these confounding factors, careful selection of immunodeficient mouse strains and transplantation sites is crucial.

Mouse Strains

Various mouse strains have been used to construct OTT models. These include C57/BL6, Institute of Cancer Research (ICR), Naval Medical Research Institute (NMRI), genetically engineered, and immunodeficient mice. C57/BL6 mice were the first inbred mouse strain to have their genome fully sequenced, offering high homogeneity and a consistent genetic background. This uniformity ensures high reproducibility and consistency in experimental results [29]. ICR and NMRI mice are outbred populations, produced through non-inbred mating. Their advantage lies in consistent population characteristics with inherent genetic heterogeneity, making them better representatives of the genetic diversity seen within the same population [30]. Commonly used immunodeficient mouse strains include nude mice and severe combined immunodeficiency (SCID) mice, which are particularly useful in xenotransplantation models for human ovarian tissues. Nude mice, characterized by a mutation in the *Foxn1* gene, lack body hair and thymic function, resulting in significantly reduced T cell numbers, though they can still produce functional B cells and natural killer cells. SCID mice, with mutations in the *Scid* gene, lack functional T and B cells, conferring a higher degree of immunodeficiency compared with nude mice [31]. Genetically engineered mice are developed through genetic engineering technologies that modify and manipulate specific gene sequences. These mice exhibit phenotypes and physiological characteristics resulting from overexpression or under-expression of target genes. The OTT models using genetically engineered mice enable detection of cells and tissues marked by the target gene, facilitating research on the biological functions and related pathways of these genes. This approach aids in understanding the molecular mechanisms involved in OTT and contributes to the development of protective drugs [17].

Ovariectomy Prior to Transplantation

The endogenous hormone production in mice can potentially affect the survival and growth of transplanted ovarian follicles.

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Table 1. Overview of mouse model studies on ovarian tissue transplantation.

Reference & year	Mouse strains	OTT category	Transplantation site	Key contents
Youm et al (2015) [15]	B6D2F1mice	Autologous transplantation	Muscle, sub-renal capsule, subcutaneous tissue	Evaluate the recovery rate, follicle density, and integrity of grafts at different transplantation sites
Cheng et al (2022) [16]	SCID mice	Xenotransplantation	Sub-renal capsule	Evaluation of the follicle density, apoptosis index, vascular density, ROS, and the expression of hypoxia and oxidative stress-related genes in the graft
Cohen et al (2016) [17]	Nude mice	Xenotransplantation	Muscle	Description of the angiogenic response of the graft and explore the role of endothelial cell Akt1 expression
Terren et al (2022) [18]	SCID mice	Xenotransplantation	Subcutaneous tissue	Evaluation of the follicle count, neoangiogenesis, fibrosis, and Ki-67 expression in the graft
Nascimento et al (2023) [19]	C57BL/6 mice	Autologous transplantation	Subcutaneous tissue	Evaluation of the estrous cycle of mice after transplantation, graft blood perfusion, follicle count, and expression of transcripts
Sanamiri et al (2022, 2023) [20,21]	NMRI mice	Autologous transplantation	Muscle	Evaluation of the condition of ischemia-reperfusion injury in the graft
Ebrahimi et al (2024) [22]	NMRI mice	Autologous transplantation	Muscle	Evaluation of histological parameters, inflammation relative to gene expression, and oxidative status in the graft
Philippart et al (2021) [23]	SCID mice	Xenotransplantation	Inner wall of the peritoneum	Evaluation of the follicular morphology and ultrastructure of the graft
Dolmans et al (2019) [24]	SCID mice	Xenotransplantation	Inner wall of the peritoneum	Evaluation of the oxygen concentration, CD34 endothelial marker, and follicle count in the graft
Yan et al (2020) [25]	C57BL/6 mice	Autologous transplantation	Ovarian bursa	Evaluation of the developmental status of follicles at different stages within the graft and the outcomes of the offspring after transplantation
Ruan et al (2019) [26]	BALB/c mice	Xenotransplantation	Ovarian bursa cavity, subcutaneous thigh, subcutaneous neck	Evaluation follicular growth and survival, and graft recovery
Mahmoudi Asl et al (2021) [27]	BALB/c mice	Autologous transplantation	Subcutaneous tissue	Evaluate the follicular morphology and ultrastructure of the graft, as well as the expression of angiogenic factors and endothelial cell markers
Shojafar et al (2019) [28]	NMRI mice	Autologous transplantation	Muscle	Evaluate the ischemia-reperfusion injury of the grafts

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By performing ovariectomy (bilateral removal of the ovaries), the central gonadal axis inhibition is relieved, promoting follicle-stimulating hormone (FSH) secretion from the hypothalamic-pituitary axis. This procedure also reduces the release of endogenous anti-Müllerian hormone (AMH), a follicle growth inhibitory factor, thereby improving angiogenesis and follicle growth in the grafts [32]. The number of primordial follicles in ovarian grafts is similar in ovariectomized and non-ovariectomized mice, but ovariectomized mice have a greater number of secondary and mature follicles [18]. Additionally, the ovariectomized mouse model more closely replicates the pathological decline in ovarian function observed in patients. Currently, no standardized protocol is available regarding whether to perform ovariectomy prior to OTT in mouse models; however, most related studies include this procedure.

Transplantation Site

Although residual endothelial cells and blood components within the graft can partially sustain early blood supply, the primary blood supply for ovarian grafts in the early stages after transplantation relies primarily on neovascularization and blood perfusion from the surrounding tissues. The ability to rapidly, efficiently, and stably establish new vascular networks is crucial for graft survival. The blood supply status, growth space, and ease of operation at the transplantation site are closely related to the outcomes of ovarian grafts. Common transplantation sites for ovarian tissue include subcutaneous tissue [19,33], the sub-renal capsule [16,20], back muscle [21,22], the inner wall of the peritoneum [23,24], and the ovarian bursa [25,26].

The sub-renal capsule is rich in blood supply and vascular growth factors, which favor the growth of ovarian grafts. However, this site demands a high level of microsurgical skill, and the limited space may constrain the growth of antral follicles in the grafts. Subcutaneous transplantation is easier to perform, minimally invasive, and facilitates data collection and intervention. However, the subcutaneous site has low vascular density, and ovarian grafts in this location are susceptible to external factors such as temperature, pressure, environment, and mouse activity [27]. Studies comparing different transplantation sites, including subcutaneous tissue, fat pads, the sub-renal capsule, and dorsal muscle pouches, have found that grafts in the dorsal muscle group had the highest survival rate, followed by the sub-renal capsule group. Additionally, the follicle apoptosis rate in the dorsal muscle group was lower than that in the sub-renal capsule group [15]. However, during the early stages after transplantation, when the graft has not yet firmly adhered to the surrounding tissue, ovarian grafts in the dorsal muscle may dislodge due to mouse activity, leading to model failure. The fertility potential of follicles within ectopically transplanted ovarian tissue compared with orthotopic transplantation remains unclear. Ruan et al [26] found that the subcutaneous and ovarian bursa groups exhibited similar follicle growth rates in human ovarian tissue grafts, but antral follicles were observed only in the ovarian bursa group. This difference may be attributed to the richer blood supply and a microenvironment more conducive to follicular growth and development in the ovarian bursa. Terren et al [18] proposed a novel model involving ovarian transplantation between the skin and cartilage of the mouse external ear. This site offers high vascularization, which benefits graft vascular reconstruction, reduces post-transplantation fibrosis, promotes follicular growth and development, and the superficial location facilitates observation, drug intervention, and subsequent oocyte retrieval.

The follicular density within a single ovarian tissue fragment varies considerably, making it challenging to compare follicle numbers between ovarian grafts at different sites [34]. Consequently, the optimal site for OTT in mice remains unclear.

Evaluation of Mouse Models for Ovarian Tissue Transplantation

After establishing a mouse model for OTT, objective metrics are essential to determine whether the transplanted ovarian tissue is viable and whether reproductive function has been restored.

Histological Analysis of the Ovarian Graft

Morphological assessment includes the gross appearance of the ovarian graft after transplantation, counting and classifying the types of follicles within the ovarian graft, and examining the morphology of stromal cells [35]. This can be initially assessed through direct visual observation and subsequently through serial tissue sectioning and hematoxylin and eosin staining.

Neovascularization Density

Semi-quantitative analysis using endothelial cell markers such as CD31 and CD34 can be used to assess new blood vessel density [24,36]. Measuring expression levels of angiogenic factors such as angiopoietin-1 (*Ang1*), angiopoietin-2 (*Ang2*), and vascular endothelial growth factor (*Vegf*) mRNA can also be used as biomarkers of neovascularization density [27]. Advanced imaging techniques using laser Doppler blood perfusion imaging and special staining combined with 3D imaging technologies can be used to visually evaluate new blood vessel formation [37].

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Proliferative Activity of Ovarian Granulosa Cells

Assessing the expression of proliferation markers such as Ki-67 in ovarian granulosa cells can be used to gauge cellular activity and regeneration within the graft [38].

Hormonal and Estrous Cycle Monitoring After Transplantation

Measuring changes in sex hormone levels (e.g., estrogen, progesterone) through techniques such as enzymatic immunoassays, and monitoring the restoration of the estrous cycle can be used as indicators of functional recovery of the reproductive system [19,26,28]. Additionally, evaluating follicle development and ovulation function, fertility potential, pregnancy outcomes, and live birth rates are important metrics for assessing the restoration of reproductive function.

Timing of Measurements

Research has documented the initiation and progression of neovascularization following autologous OTT in mice. Within 24 hours after transplantation, nascent blood vessels begin to appear at the periphery of the ovarian graft [19,37]. Revascularization of the graft can occur within 48 hours after transplantation [39]. Initial perfusion of the grafts can be observed as early as 3 days after transplantation in mice, whereas human ovarian tissue xenografts typically require approximately 5 days for vascular reconstruction [40]. Correspondingly, increases in positive cells for CD31 and CD34, along with elevated mRNA expression levels of angiogenic factors such as *Ang1*, *Ang2*, and *Vegf*, are detectable from 3 days after transplantation [24,27,36].

Within the first 2 days after transplantation, the graft has not yet had the opportunity to adhere firmly to the surrounding tissues and so are prone to dislodgement. However, as the time since transplantation increases, the grafts progressively adhere more tightly to the surrounding tissues, and the formation of a new vascular network between the grafts and surrounding tissues becomes visible to the naked eye [15].

Reconstruction of the vascular network within the graft is closely associated with follicle survival. Morphological analyses have shown that ovarian tissue exhibits extensive necrotic regions, significant follicular atresia, and abnormal stromal cell morphology by 2 to 3 days after transplantation [35,41]. By 7 days after transplantation, the ovarian graft cortex shows regenerating stromal cells and the reappearance of follicles at various developmental stages. By 14 to 21 days after transplantation, necrotic regions disappear, and pre-ovulatory follicles and corpora lutea can be observed in the cortex. By 14 days after autologous ovarian transplantation in mice, the ovarian tissue can present four distinct morphological states: (1) hemorrhagic changes in the ovary; (2) ovarian hydrops; (3) degenerative necrosis; and (4) normal, viable ovarian tissue [35].

In the early post-transplantation period, assessing the survival and functionality of ovarian grafts based solely on cellular morphology may be insufficient. Granulosa cells surrounding the follicles are metabolically active, sensitive to microenvironmental changes, and can influence oocyte development and follicular atresia through the exchange of energy and metabolic products. As such, the proliferative activity of granulosa cells may serve as a more sensitive indicator of graft viability compared with morphological assessments alone. Ki-67, a nuclear protein antigen associated with cell proliferation, is expressed throughout all active phases of the cell cycle and can be localized and semi-quantified using immunohistochemical or fluorescence staining techniques [42]. The expression of Ki-67 is closely related to the activation of primordial follicles and follicular growth [16]. In dormant primordial follicles, granulosa cells show negative Ki-67 expression. When primordial follicles are activated or growing follicles survive, their surrounding granulosa cells become proliferative, signified by at least one granulosa cell expressing Ki-67 positively. Manavella et al [38] found that, 7 days after transplanting human ovarian tissue into the mouse peritoneal cavity, the Ki-67 positivity rate in primordial follicle granulosa cells increased, suggesting the onset of granulosa cell proliferation and the activation of primordial follicles into growing follicles. These findings suggest that Ki-67 could be a valuable biomarker for evaluating ovarian graft viability and follicle development, providing insights into the early stages of graft adaptation and function after transplantation.

The restoration of ovarian function is a crucial indicator of successful OTT in mouse models. The endocrine function of the ovaries can be evaluated by monitoring sex hormone levels and the estrous cycle. The estrous cycle in mice is characterized by rhythmic changes in their reproductive organs and sex hormone levels, which can be tracked by observing the changes in cell types in vaginal smears. Studies have shown that the estrous cycle recovery rate in mice is 11.1% at 3 days after OTT, and 100% at 8 days after transplantation [19]. Elham et al [28] observed the recovery of the estrous cycle starting from 9 days after autologous ovarian transplantation in mice, although the length of the cycle was longer than in non-transplanted mice. By 28 days after transplantation, serum levels of progesterone and estrogen in transplanted mice were lower than those in the non-transplanted group. In the context of xenotransplantation of human ovarian tissue into mice, estrogen levels in the transplanted group were similar to those in

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the control group 3 days after transplantation, and significantly higher by 7 days after transplantation [16]. Another study found that 1.5 to 2.5 months after xenotransplantation of human ovarian tissue into mice, the levels of FSH, AMH, and estradiol (E_2) did not differ significantly between the transplanted and non-transplanted groups, suggesting the recovery of ovarian endocrine function after transplantation [26].

To effectively evaluate the model, appropriate metrics should be selected depending on the time since transplantation, as follows:

1) One to 2 weeks after transplantation: The primary focus should be on survival of the graft. The measurement of neovascularization density and granulosa cell proliferative activity should be prioritized to assess the establishment of vascular connections and cellular proliferation.
2) Two to 4 weeks after transplantation: In addition to the metrics mentioned above, histological analysis should be performed to evaluate the structural integrity and development of the graft.
3) Four or more weeks after transplantation: The primary focus should be on the recovery of ovarian endocrine function. Monitoring sex hormone levels and the estrous cycle is crucial to assess the comprehensive functional integration of the graft within the host.

Each evaluation metric for OTT has specific advantages and limitations. Histological analysis is straightforward and intuitive, and is relatively easy to perform. However, it is highly subjective and difficult to quantify. Neovascularization density and granulosa cell proliferative activity can objectively reflect the status of graft survival, but they require specialized staining and imaging techniques, which are relatively complex to execute. Although assessing sex hormone levels and monitoring the estrous cycle provide a comprehensive evaluation of the recovery of ovarian endocrine function, these indicators typically lag behind the early survival state of the graft, and are of limited utility in the early stages after OTT.

By using a combination of these evaluation metrics, a comprehensive and dynamic assessment of both graft survival and functional recovery can be achieved. This multi-faceted approach is crucial for accurately determining the quality of the OTT model in mice, thereby laying a robust foundation for subsequent research endeavors.

Future Directions

Additional, improved mouse OTT models are needed. This could be achieved by establishing standardized evaluation criteria and developing simplified, rapid, noninvasive detection methods. Developing uniform standards for assessing OTT models would enhance the consistency and comparability of research outcomes. Creating methods that rapid, noninvasive evaluation of ovarian grafts would facilitate effective monitoring of transplant status, without imposing additional stress on the animals or harming them. Despite the high genetic homology between mice and humans, the limited genetic heterogeneity in mice compared with humans necessitates careful consideration of interspecies differences when interpreting the research results. Addressing these challenges would improve the reliability and relevance of mouse OTT models and advance the application of OTT in clinical settings.

A scientifically feasible mouse OTT model needs to be established in order to overcome the limitations of current mouse OTT models. Several key aspects require further investigation and optimization. Detailed evaluations of the risk of tumor cell reimplantation using mouse models and assessments of the relative safety of different transplantation sites are required to address safety concerns. To address efficacy, standardized methods for evaluating follicle quantity and quality after transplantation; improved methods for assessing endocrine function recovery; and reliable fertility evaluation metrics are required. Cost-effectiveness considerations must be addressed through an analysis of different mouse strains and transplantation protocols, and optimization strategies are needed to improve transplantation success rates.

Conclusions

OTT is a promising technique for fertility preservation but still faces numerous challenges and difficulties. Research using mouse models aids in optimizing OTT techniques and assessing their safety and efficacy. The reliability of mouse models directly influences the accuracy of the research findings and conclusions. The impact of these differences on research outcomes and the standardization of evaluation criteria remain important challenges.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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