Review Article

A Comparative Review of Preclinical Infertility Models

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ABSTRACT

Current animal models of infertility in female rats fail to adequately recapitulate transitions like fluctuations in hormonal changes and other complications. androgen-induced infertility rodent model is cause PCO and a new rodent model of Accelerated ovarian failure (AOF) successfully replicate the human perimenopause and postmenopause also it including estrus acyclicity and undetectable estrogen levels .This models not only for menopause it is also useful method for various other infertility models, to develop this model various chemicals are used but in that all models 4- Vinyl cyclohexene diepoxide (VCD) novel chemical which is used for induction of menopause in female rodents. Along with menopause it can also used for other infertility and gynecological complications. In this study other infertility models were compared with androgen induced infertility rodent model, VCD model and our aim to use this animal models to elucidate novel perspective and interventions for maintaining a high quality of life in women and to potentially decrease the negative health consequences associated with these changes during age and other gynecological, neurological complications.

Keywords: Infertility, gynecological complications, VCD model, PCO, infertility.

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INTRODUCTION

Motherhood is the very important role in life of a woman but according to World Health Organization the Reproductive age (15-49 years) at risk of becoming pregnant (not pregnant, sexually active, not using contraception and not lactating) WHO report trying successfully for a pregnancy for two years or more[1]. Infertility is defined as the inability to conceive naturally after one year of regular unprotected intercourse. Most of the time, infertility is some degree of Subfertility in which 1 in 7 couples need specialist help to conceive.

Subfertility can be either primary or secondary. Primary subfertility is delay for a couple who have had no previous pregnancies; and, secondary subfertility is a delay for a couple who have conceived previously, although the pregnancy may not have been successful for example, miscarriage, and ectopic pregnancy[2]. To minimize the clinical compliance researchers' have developed various well characterized laboratory animal models are used to evaluate effects of different hormones and aging, including non-human primates and rodents because of their genetic, behavioral and reproductive system which are similar to humans[3] shown in figure-1.

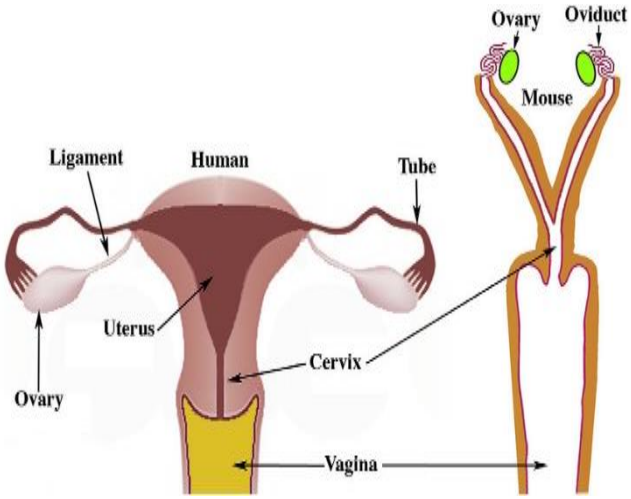

Figure 1: Similarity between female reproductive system of human and rodents

Rodent models, especially laboratory rats and mice, are particularly useful because of their well-defined aging trajectories and thoroughly studied brain and reproductive systems, as well as their approximate two to three year lifespan[4]. This review focuses on these rodent models, comparing and contrasting the benefits and drawbacks of rodent models of reproductive senescence, and discussing the utility of the rodent model for infertility complications[3]. Although the current rodent models of menopause have and will continue to inform our understanding the role of both estrogen and hormone replacement therapy in the menopause transition, they fail adequately to recapitulate perimenopause. The intact aging model fails to achieve very low estrogen levels, and the ovariectomized model lacks a transition to

perimenopause[5]. A new rodent model of Accelerated Ovarian Failure (AOF) successfully replicates human perimenopause and postmenopause, including estrous acyclicity and fluctuating, followed by undetectable, estrogen levels, and allows for the dissociation of the effects of hormone levels from the effects of aging[6, 7]. The AOF menopause model will generate new insights into women's health particularly in determining the critical periods during perimenopause for restoring ovarian hormones for the most efficacious effect on memory and mood disorders[5] and also this model is very useful for detection and evaluation of various infertility complications in females.

ANIMAL MODELS OF FEMALE INFERTILITY

Intact Aging Model

Intact aging model was naturally occurring health compliances in rodents. Like women animals also experience natural hormonal fluctuations in middle age, during this situation we can observe variations in their hormonal secretions like estrogen levels are very low or undetectable, progesterone levels decrease, and follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels are elevated[8, 9]. At the middle age (9-12 months) rodents began to exhibit acyclicity, usually characterized by additional days of diestrus-I within the normal cycle, resulting in prolonged cycles[10]. During this presumptive perimenopause, there is an attenuation and delay of the LH surge and a decrease in fertility, similar to humans[11, 12]. Rats, more often than mice, will also pass through a phase of repetitive pseudopregnancy prior to transitioning into an anestrous state, or they may stay in a pseudopregnant state for their remaining lifespan, wherein they ovulate irregularly (and sometimes supraovulate), resulting in corpora lutea that are maintained for an extended period of time producing high progesterone levels[13, 14]. Eventually, as aging progresses to about 16-18 months, rodent's transition into an acyclic, anestrous state, in which persistent estrus is observed, ovulation ceases and estrogen as well as other ovarian hormone levels decline from pre-estropausal levels[15]. Whereas rats retain a larger number of primary follicles, mice have complete follicular exhaustion at 24 months of age and demonstrate a greater decrease in estrogen levels than rats in estropause[16] in this condition there is no change estrogen and progesterone levels. In this model vaginal cytology monitoring is easy way to monitor estrous cycle in figure-2, this vaginal cytology can become unpredictable in middle age due to dysregulation of hypothalamic pituitary-gonodal axis activity. Some stocks or strains of laboratory rodents are considered better models than others for aging research. One example is the National Institute on Aging's (NIA) recommendation to use the Fischer-344 (F344) inbred strain for aging research due to their longevity and well defined aging patterns. Sprague Dawley and Long Evans are also commonly utilized rat strains in aging research.[3]. This model usually used to evaluate the clinical compliances like estrogen activities, menopause, other infertility complications and spacial memory.

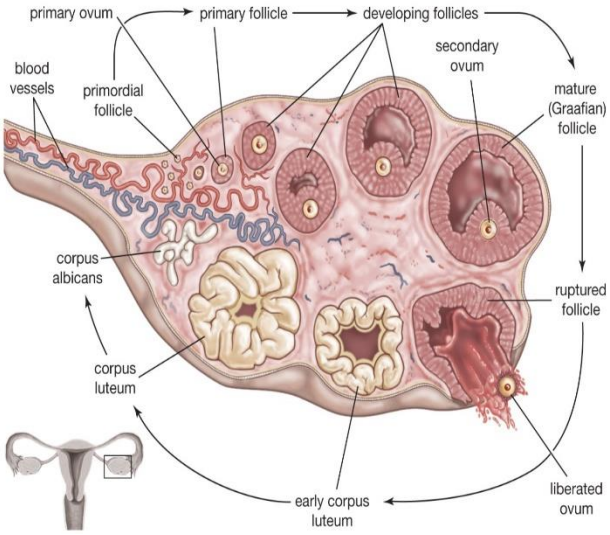

Figure 2: Estrous cycle

Ovariectemy Model

Ovariectomy was done to create a new rodent model to perform preclinical studies for evaluating estrogen activities and other hormone effects in female rodents; generally ovariectomy model was denoted with OVX. This OVX model is well established in the field of aging[17]. Ovaries of the rodents were surgically removed in aseptic conditions. The anatomy of the rodents is differs from women in that rodents have a bifurcated uterus, called the uterine horn, which accommodates large litters (Figure). In this model, rodents may be OVXed at ages correlating with different life stages. For example, rodents may be OVXed at 2-6 months with regular estrous cycles, 11 months at the beginning of acyclicity, or 18 months at the beginning of constant estrous to model specific aspects of aging[16]. The standard OVX procedure is to bilaterally excise the ovaries, oviducts (i.e., the fallopian tubes) shown in figure-3, and tips of the uterine horn from the peritoneal cavity, leaving the ligated uterine horns intact. After recovering the OVX rodents are allowed to participate in respective study. Usually this model is used to determine the treatment for various complications which occurs in women irrespective of age, mostly disturbances in estrogen cycles, gonodal hormone deprivation, and menopause. During the OVX model studies animal were continuously administrated with endogenous estrogen replacement in the form of 17β-estradiol along with other steroids..Compares intact aging model this model was less time taking, even in young animal we can observe the similar hormonal variations. Along with the benefits this models having various drawbacks those are 1. This is not naturally occurring model, 2. Nearly 90% the women are having their ovaries. 3. Along with ovarian hormones other gonodal alteration can observe. 4. Causing pain to animals.

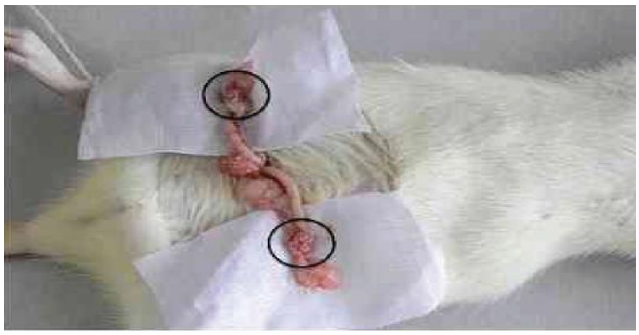

Figure 3: Ovariectomy in rodents

Androgen Induced Infertility Model

Androgen induced infertility model advanced method when compares to intact aging model and ovariectomy. Androgens are the substrates for production of estradiol (E2) which plays a important role in ovary functions and follicle development. Increase androgen secretions can cause the poly cystic ovaries (PCO) showed in figure-4. Because of this PCO this animal model is used to evaluate the polycystic ovary syndrome (PCOS) in humans which is associated with excess androgens, obesity and infertility.

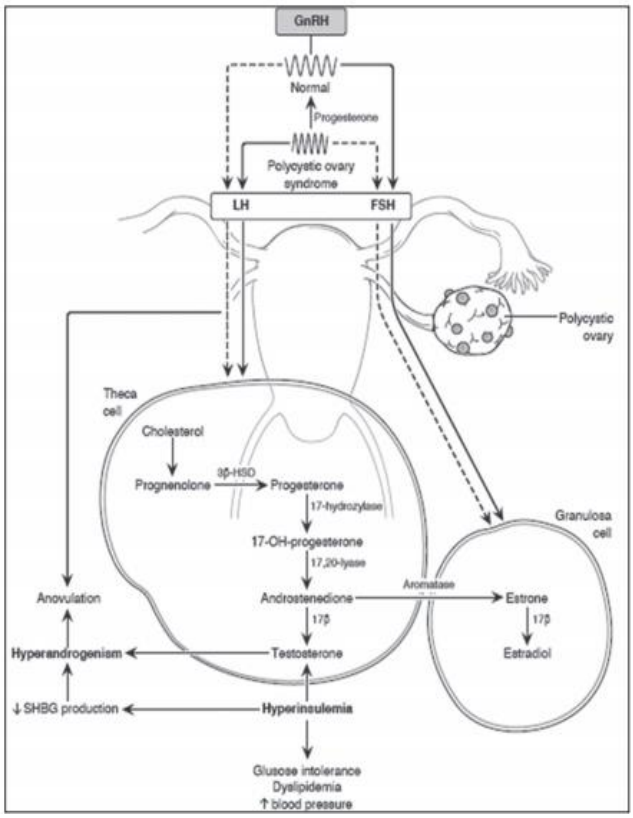

Figure 4: PCO ovaris due to excess androgens

Androgen receptors are present on oocyets, glandular and thecal cells of follicle, are highest in small follicles and expression is developmentally regulated during follicle development being down-regulated by FSH and LH[18]. Various chemicals and androgen molecules are available to create these type model (PCOS) like testosterone, letrozole, DHEA (Dehydro epiandrosterone)[19] etc.., these are casing PCO in rodents which is mimics human reproductive pathophysiology. Follicle population is depends on the stag of follicle development and ratio of androgens converted in to E2 Compares to intact aging, ovariectomy models animals retain their ovaries, but we can observe interrupted follicles development and forming water bubble like structures in between the follicles[20]. Compares to ovariectomy animals weren't having pain. The main drawbacks are more number of follicle cells were damaged, and there may be chance of complete damaged ovaries then intact aging model and very low production of FSH, LH levels were observed.

Acceleratory Ovarian Failure

Acceleratory ovarian follicles (AOF) model is a innovative method which is similar to human menopause, in this ovarian failure was induced by 4-vinylcyclohexene diepoxide (4-VCD) which is a chemical used in commercial industries like rubber, insecticides, antioxidant, flame retardants and plasticizers. 4-VCD is a liquid compound, soluble in water i.e 35.2 g/L at 25°C maximum solubility can achieve, structure shown figure- 5

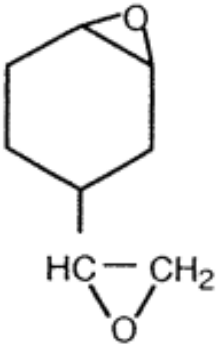

Figure- 5: 4-vinylcyclohexene diepoxide

In this AOF model 4-VCD injected to the rodents to selectively accelerate the natural loss of immature follicle cells due to the involvement of involvement of f phosphatidylinositol-3 kinase (PI3) signaling in the initiation of VCD-induced ovotoxicity. A recent publication suggests that the direct molecular target of VCD may be a post-translational PI3 signaling pathway in the oocyte itself, as evidenced by changes to the signaling cascade occurring prior to follicular loss[21] which is called as atersia (apoptosis of follicle cells) and the bioactive form of 4-VCD i.e 4-VCH (4-vinylchohexene) in rat and mouse ovary contain epoxide hydrolase, glutathione S-transferases, and cytochrome P-450, which metabolize known ovarian toxicants including VCH and VCD[22], resulting changes in cycling process and increase androgen secretions cause damage to only small and primary follicle but no effect matured ovaries, remaining tissue toxic free. Usually 4-VCD injected in the doses of 160 mg/ Kg IP for three times per week ; for total 15 days this dose can cause the activation of Bax protein which is responsible for apoptosis of the immature follicle cells called "atersia" which is similar to human menopausal condition but there is no changes in the Bcl-2 protein (Pro-oncogene protein). According to this mechanism accelerated ovarian failures achieve in rodents. Compares to previous methods animals

retain ovaries, animals wont experience pain (in ovariectomy) very rapidly achieve the pathological state than intact aging model, and no need of injecting the excess androgens to the animals, this model can used to evaluate various clinical compliances like menopause, spatial memory studies, estrogen activities and other infertility complications, toxicology studies etc..

CONCLUSION

According to all the above models androgen induced model and acceleratory ovarian models are best preclinical models for understanding and evaluation of female reproductive system and its complications along with other neurological complications which are occurs due to changes in ovarian hormones, depletion of ovarian follicles and exogenous hormonal therapy. To provide direction and potential treatment for women to lower risk factors for diseases and to maintain quality of life.

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