EFFECTS OF SPACEFLIGHT AND ALTERED GRAVITY ON REPRODUCTIVE PROCESSES OF FEMALE MAMMALS

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In recent years, the cadre of female astronauts has grown immensely. NASA's Vision for Space Exploration calls for completing and utilizing the International Space Station (ISS), establishing an extended human presence on the moon, and preparing for the Mission to Mars, all of which require sustained habitation of space. As we move forward with the new space initiative, women are expected to increase their involvement in the Space Program, including their presence on long-duration missions. During extended deep space flight, astronauts will be exposed to a complex environment composed of multiple acute and chronic stressors including radiation hazards posed by chronic low doses of ionizing radiation, altered gravitational fields and physiological stress (Vazquez, 1998). Reproductive disorders and hazards to reproductive health are prominent public health issues (Environmental Protection Agency, Guidelines for Reproductive Toxicity Assessment. Washington, DC, US Environmental Protection Agency, 1996). Thus, in view of these plans, it is vital that we improve our understanding of acute and enduring effects of space travel on the female reproductive system, particularly for women astronauts of childbearing age. Because female astronauts suppress their menstrual cycles during spaceflight (Jennings & Baker, 2000), there is limited knowledge of the effects of space and altered gravity effects on the human female reproductive system. However animal studies have provided some insights into changes that might arise during exposure to altered gravity. In this paper, I describe briefly some findings of reproductive function in female rats, including estrus cycling, ovarian function, conception, pregnancy and postnatal development. Detailed reviews of earlier findings can be found elsewhere (Ronca, 2003; Ronca, 2007; Tou, Ronca, Grindeland, & Wade, 2002).

Female mammals undergo characteristic hormonal and cellular changes during the reproductive cycle. In rats, the estrous cycle averages 4-5 days in length and consists of four identifiable phases: proestrus, estrus, metestrus, and diestrus. Numerous environmental factors can interrupt the estrous cycle, such as stress, sterile mating, mechanical stimulation of the cervix, or continuous illumination. It was previously reported that, when centrifugation was initiated during diestrus, the length of the rat's estrous cycle increased due to prolonged diestrus. Female rats exposed to hind limb unloading to mimic aspects of microgravity exposure showed estrous cycle lengthening due to prolongation of the diestrus phase of the cycle (Tou, Grindeland, & Wade, 2004).

We recently hypothesized that continuous, long-duration (~60 days) exposure to 2-g centrifugation would alter patterns of estrous cycling and delay conception (Ronca, Rushing, Tou, Wade, & Baer, 2005). Sexually mature female and male rats were weight-matched then assigned to either 2-g centrifuged or non-centrifuged (stationary 1-g control) conditions, and to non-breeding or breeding conditions. In non-breeding females, estrous cycles were analyzed by examining vaginal cytology beginning prior to and for 35 days during centrifugation. Females in the breeding condition were time-mated following 7 days of adaptation to centrifugation. Following adaptation to centrifugation, both centrifuged and non-centrifuged breeding females conceived, however centrifuged females took *three-times longer* than controls (CF, 11.0±6.54 days; nCF, 4.14±3.02 days, $p<0.05$) to achieve conception.

The second major goal of our work has been to further our understanding of altered gravity as a chronic stressor in females (Baer, Rushing, Wade, & Ronca, 2005). Stress induced by altered gravity may underlie delayed conception. Previously, our work has incorporated a contemporary perspective in maternal-fetal medicine: '*Prenatal programming*' is a newly emerging field that is revealing astounding insights into the intrauterine origins of adult disease arising from environmental factors (Barker, 1995), including prenatal exposure to stress hormones (Seckl & Meaning, 2004). Adult disease states that have been implicated include metabolic, endocrine, and cardiovascular pathophysiologies. Importantly, our results indicate that 2-g centrifugation beginning prior to conception leads to reduced body weights of neonatal offspring, increased body weights and hormonal alterations in adulthood *even when animals are reared at 1-g*. Mere exposure of the female reproductive system (prior to conception) may be sufficient to induce persistent changes in the health and well-being of offspring. Additional hormonal and neural studies are needed to clarify effects of altered gravity as a chronic stressor,

including both acute and persistent effects on the female reproductive system, and to identify meaningful countermeasures for use in female astronauts. These concerns are vital to our future space endeavors.

Of all of the potential effects of long-duration spaceflight, radiation probably poses the most significant and least reversible. In a recent study of childhood cancer survivors that received pelvic radiation, it was reported that survivors' children were nearly two times more likely to be born preterm than the siblings' children. Compared with the children of survivors who did not receive any radiotherapy, the children of survivors treated with high-dose radiotherapy to the uterus (>500 cGy) had increased risks of being born preterm (50.0% versus 19.6%), low birth weight (36.2% versus 7.6%), and Small for Gestational Age (18.2% versus 7.8%). Increased risks were also apparent at lower uterine radiotherapy doses (starting at 50 cGy for preterm birth and at 250 cGy for low birth weight). These findings indicate that pelvic irradiation increases the risk of residual effects on childbearing, including restricted fetal growth and early births among their offspring. Although radiation doses used in cancer treatment are comprised of high-dose, focused exposures relative to spaceflight, these observations emphasize the importance of evaluating effects of ionizing radiation, similar to that encountered in the space environment, on the female reproductive system.

In summary, these findings provide some preliminary, albeit important, analyses of spaceflight factors (i.e., altered gravity, chronic stress and radiation) on reproductive physiology of the female mammal. Although the short-term effects of altered gravity and spaceflight on female reproductive processes have been studied (Tou et al., 2002; Ronca, 2003; 2007), systematic animal studies are needed to ascertain the consequences of space travel on female reproductive processes. This work needs to commence in advance of long-term space exposures of female astronauts to altered gravity, stress and ionizing radiation. These factors pose significant risk for irreversible changes in reproductive function, and cross-generational transmission of adverse consequences.

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