

Chemotherapy-induced Ovarian Damage At birth, the ovary contains a finite number of oocytes that are surrounded by a single layer of pregranulosa cells to form primordial follicles. It is therefore, of paramount importance to understand the mechanisms by which chemotherapy injures the follicular stockpile to develop ways to improve fertility post anticancer drug exposure. Clinically, patients may suffer from complete ovarian failure resulting in amenorrhea, climacteric symptoms, an increase in gonadotropins, and low estradiol levels.³ Histologic studies show that the end stage effects of chemotherapy are ovarian atrophy, a depletion of the primordial follicle stockpile, diminished ovarian weight, and stromal fibrosis.⁸ Alternatively, chemotherapy's effects may be partial and patients may experience a reduction in their primordial follicle stockpiles, menstrual irregularities, and hormonal disturbances, but may still be able to maintain menses posttreatment. In a recent study, the first model of human ovarian reserve from conception to menopause that best fits the combined histologic evidence has been described.⁷ This model suggests that 81% of the variance in primordial follicle population is exclusively owing to age and analysis showed that 95% of the fluctuation in follicular reserves is owing to age alone for ages up to 25 years. In mice, chemotherapy causes the destruction of growing follicles.⁹ Chemotherapy also results in diminished primordial follicle stockpiles in mice in a dose-dependent manner¹⁰ and has been correlated to a reduction in primordial follicles in the rhesus macaque.¹¹ Chemotherapy has differential effects on primordial, dormant follicles and growing, larger ovarian follicles. Even low doses of chemotherapy can wipe out the population of maturing follicles, but partial ovarian reserve remains intact, allowing for the eventual resumption of menses. Chemotherapy targets actively dividing cells, and therefore, destroys mature ovarian follicles during treatment, specifically by inducing apoptosis in granulosa cells. By 5 months of gestational age, the female ovary establishes a fixed number of primordial follicles and therefore, the number of primordial follicles is a direct indication of fertility reserve. Mice exposed to combination chemotherapy (Ironotecan HCl) show TUNEL positive granulosa cells in large ovarian follicles (Fig. 1A).^{9,12} However, the effects that chemotherapy has on primordial, dormant follicles are variable and the question remains as to whether the same effect is observed in these follicles. When ovarian functioning is disrupted by anticancer drugs, the effects can be devastating. Eventually, this loss of primordial follicles results in menopause at an average age of 50 to 51 years.