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 primor– dial follicles.It is therefore, of paramount importance to understand the mechanisms by which che– motherapy injures the follicular stockpile to develop ways to improve fertility post anticancer drug exposure.Clinically, patients may suf– fer from complete ovarian failure result– ing 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 stock– piles, menstrual irregularities, and hormo– nal 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 popu– lation is exclusively owing to age and anal– ysis showed that 95% of the fluctuation in follicularreservesisowingtoagealonefor agesupto25years.In mice, chemotherapy causes the destruction of growing folli– cles.9 Chemotherapy also results in dimin– ished primordial follicle stockpiles in mice in a dose–dependent manner10 and has been correlated to a reduction in primor– dial 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.Chemo– therapy 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 there– fore, the number of primordial follicles is a direct indication of fertility reserve.Mice exposed to combination chemo– therapy (Ironotecan HCl) show TUNEL positive granulosa cells in large ovarian follicles (Fig.In animal studies, chemotherapy has been shown to cause a significant loss in both maturing follicles and dormant pri– mordial follicles.Clini– cally, patients exposed to chemotherapy initially stop menses as a result of the destruction of growing follicles and re– sume cycling after a period of recovery.The means by which chemother– apy induces damage to the primordial follicle stockpiles, which represent future fertility potential, remains unclear.Throughout the life cycle, there is an on– going decline in the number of primordial follicles that is the result of apoptotic cell death. 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