Title: Cryopreservation and Transplantation of Ovary Tissue and Ovarian Longevity

Purpose: To report the results from a series of cryopreserved ovary tissue transplantations using slow freeze or vitrification, for leukemia and other cancers, in a single U.S. center, to elucidate the mechanisms of primordial follicle recruitment, and ovarian longevity.

Materials and Methods: First we will discuss fresh ovary transplants. Nine women have undergone fresh donor ovary cortex transplantation from identical twin sisters for premature ovarian failure. Recovery of ovarian function occurred in all recipients of fresh transplants with FSH returning to normal at 4 to 5 months, and eleven healthy babies were born to seven of the nine recipients. Then we will discuss frozen ovary transplants.

Results: 108 females between age 6 and 35 were referred for possible ovary tissue cryopreservation over a 20 year period, with either slow freeze or vitrification. Thus far 13 patients whose tissue was frozen prior to age 35 returned up to 18 years later to have their tissue transplanted back. All 13 cases had return of ovarian function 5 months post transplant with regular menstrual cycling. AMH rose to very high levels as the FSH declined to normal. AMH then declined back to very low levels 4 to 10 months later. Nonetheless the grafts remained functional for up to 8 years or even longer. Ten of the 13 (79%) became spontaneously pregnant at least once, resulting in 13 healthy babies. Thus we have a total of 24 healthy babies from spontaneous pregnancy in ovary transplant recipients.

Discussion and Conclusions: Increasing the atmospheric pressure in the incubation with IPS cell derived oocytes will arrest their development and form primordial follicles. In contrast, dissolving the fibrous tissue, which decreases tissue pressure, causes Fox3 to go extracellular, and thus release the "locked" primordial follicles. Thus cortical tissue pressure is found to be a key regulator of fetal primordial follicle arrest, adult primordial follicle recruitment, and ovarian longevity. In addition, the long duration of function of such small pieces of ovarian tissue with very low AMH levels supports the postulate that when there is low ovarian reserve, the rate of primordial follicle recruitment is reduced, promoting ovarian longevity even as the follicle count is going down. This explains why in POF (premature ovarian failure) there are always still functional follicles that can be recruited with fragmentation and in vitro activation. The over recruitment of primordial follicles after transplant is consistent with tissue pressure being a regulator of primordial follicle recruitment and ovarian longevity.