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FERTILITY & STERILITY

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COMPLETE PURGING OF EWING SARCOMA FROM HUMAN OVARIAN CORTEX TISSUE FRAGMENTS BY INHIBITING THE mTOR PATHWAY WITH EVEROLIMUS.

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OBJECTIVE: To assess the use of Everolimus for the ex vivo purging of Ewing sarcoma metastases from human ovarian cortex before autotransplantation by inhibiting the mTOR pathway, without compromising ovarian tissue integrity.

MATERIALS AND METHODS: Patient-derived cell lines representing different types of Ewing sarcoma were introduced in human ovarian tissue fragments to form tumour foci. Next, these tissue fragments were exposed to Everolimus for 24 hours to purge the ovarian tissue from Ewing sarcoma cells. After treatment with Everolimus the tissue was cultured for an additional 6 days to allow any remaining tumour cells to establish new metastatic foci. Next, the presence of any residual cancer cells in the tissue was analysed by (immuno)histochemical staining for Ewing sarcoma specific CD99 and by a highly sensitive RT-PCR analysis for the Ewing sarcoma specific EWS-FLI1 fusion transcripts. Possible detrimental effects on the viability of ovarian cortex and follicles after purging were determined by (immuno)histology, a follicular viability assay and an assay to determine the in vitro growth capacity of small follicles.

RESULTS: Foci of experimentally induced Ewing sarcoma cells were completely eliminated from ovarian cortex after purging with Everolimus, as indicated by the absence of viable tumour cells and lack of staining for CD99. The histological results after purging with Everolimus were confirmed by RT-PCR, as the EWS-FLI1 mRNA could no longer be detected in the treated tissue. In the control treated tissue CD99 positive Ewing sarcoma metastases were abundantly present and RT-PCR demonstrated the presence of high levels of EWS-FLI1 fusion gene transcripts. Treatment with Everolimus had no detrimental effects on ovarian tissue morphology, follicle viability or the in vitro growth of small follicles.

CONCLUSIONS: Purging Ewing sarcoma metastases from ovarian cortex tissue fragments ex vivo by inhibiting the mTOR pathway with Everolimus leads to complete elimination of malignant cells but has no apparent effect on ovarian tissue integrity.

IMPACT STATEMENT: Purgng Ewing sarcoma metastases from ovarian cortex tissue fragments without impairing ovarian tissue integrity is possible by targeting the mTOR pathway with Everolimus. This provides a feasible therapeutic strategy for former Ewing's sarcoma patients to restore their fertility and to prevent reintroduction of the cancer by autotransplantation of the ovarian graft.

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FERTILITY PRESERVATION COUNSELING AND FAMILY PLANNING PRIOR TO AND DURING THE COVID-19 PANDEMIC.

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OBJECTIVE: The delivery of women’s healthcare has changed drastically with the onset of the COVID-19 pandemic. This has undoubtedly created significant uncertainties for those interested in conception counseling. In particular, fertility preservation (FP) is time-sensitive and often emergent or urgent for patients undergoing gonadotoxic therapy. ASRM provided close monitoring and guidelines during this time of crisis. Our objective was to examine the effect of the pandemic on fertility preservation counseling and family planning.

MATERIALS AND METHODS: Claims data from Symphony Health, one of the largest databases of patient-level data on more than 280 million patients in the US, was examined from May 1, 2019 to February 28, 2021. Reproductive-aged women were included in the analysis. March - April 2020 was used as a threshold for when healthcare restrictions became widespread. We compared 10 months prior to the pandemic (May 2019 - Feb 2020) and the same time period after the start of the pandemic (May 2020 - Feb 2021). Fertility preservation counseling (Z31.62), FP procedures (Z31.84), and general family planning counseling (Z31.61 and Z31.69) were identified using ICD-10 codes. Data analysis was conducted in Stata, version 16.1, using 2-sided t-tests with significance set at P < 0.05.

RESULTS: In our search, 14,491 FP consultations, 15,049 FP procedures, and 359,218 family planning encounters were identified. The mean age of women undergoing FP and family planning counseling decreased significantly when comparing prior to and during the pandemic (31.9±7.6 vs 31.4±7.1 years, and 32±6.1 vs 31.6±6 years, respectively). The average age for patients who underwent a FP procedure (33.5±6.5 vs 33±6.4 years) was also statistically different. Time series plot shows a substantial drop in focal variables in March - April 2020. Interestingly, all three variables quickly recovered to pre-pandemic baseline by June 2020, FP consultations increased from 542 encounters per month pre-pandemic vs 737 per month during the pandemic, P < 0.001. Similarly, FP procedures increased from 640 to 781, P=0.02. In contrast, family planning did not change significantly (16,376 vs 17,552, P=0.21).

CONCLUSIONS: FP counseling and procedures increased during the pandemic, despite healthcare restrictions and lockdown measures. On the other hand, family planning encounters did not change. Despite barriers to care related to the pandemic, time-sensitive fertility preservation counseling and procedures continued to be utilized. Our findings also reflect ASRM recommendations regarding suspension of non-emergent fertility management at the onset of the pandemic, and continuity of urgent services afterwards.

IMPACT STATEMENT: FP counseling and treatment are emergent services that were not negatively impacted by pandemic-related healthcare restrictions. Under ASRM guidelines, FP continued at an increased pace. This experience shows that, under close guidance, emergent or urgent services may be continued during a public health crisis.

SUPPORT: None.

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NEONATAL OVARIAN RESERVE FOLLOWING CHEMOTHERAPY EXPOSURE, EX VIVO MURINE MODEL.

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OBJECTIVE: To determine the impact of exposure to maternal serum chemotherapy on formation of the ovarian reserve.

Breast cancer complicates 1:3000 pregnancies, and current safety data is limited to congenital anomalies and early childhood outcomes. Chemotherapy is known to have significant germ cell toxicity, and yet little has been done to understand the transgenerational effect of in utero exposure. Murine ovarian reserve establishment mimics the human fetus but with a significant time shift to postnatal development.

MATERIALS AND METHODS: A randomized ex-vivo animal study with 100 postnatal day 0 C57BL/6 mouse ovaries was performed under IACUC approval. After sacrifice, sister ovaries were randomized to control and 100 postnatal day 0 C57BL/6 mouse ovaries was performed under IA-CUC approval. After sacrifice, sister ovaries were randomized to control (drug carrier alone) or drug exposure. Planned exposures were derived from widely used chemotherapy treatment regimens for maternal malignancy: doxorubicin, cyclophosphamide, paclitaxel, docetaxel, and cisplatin.

Ovaries were cultured in hanging well organ culture media with addition of exposure on culture day 2. Drug dosing replicated known Cmax, concentration. A mid dose of half the Cmax was also used to gain greater understanding of dynamics. A single drug exposure was utilized, and planned analysis occurred at 48 hours and 5 days. Immunofluorescence with TRA98 and VASA was used to quantify oocyte number and density. Data was then transferred to Graphpad Prism to generate descriptive statistics and apply a two-way ANOVA for each condition.

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