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OVARIAN TRANSPLANTATION WITH SCAFFOLDS FOR DRUG DELIVERY: AN IN VIVO TRANSGENIC MOUSE MODEL. C. Chen,[a,b] S. Tan,[a,c] C. Tzeng.[a,b] [a]Center for Reproductive Medicine and Sciences, Department of Obstetrics and Gynecology, Taipei Medical University Hospital, Taipei, Taiwan; [b]Department of Obstetrics and Gynecology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [c]Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.

OBJECTIVE: Ovarian tissue cryopreservation and autotransplantation is a promising option for fertility preservation of female cancer patients. However, ischemia limits the life span of the ovarian grafts after grafting. Vascular endothelial growth factor (VEGF) can promote angiogenesis, and sphingosine-1-phosphate (S1P) can protect ovarian grafts from ischemic reperfusion injury. This study aimed to investigate the efficacy of scaffolds for delivering different drugs in promoting survival of ovarian grafts.

DESIGN: In vivo study with a transgenic mouse model.

MATERIALS AND METHODS: We use scaffolds served as vehicles for drug delivery to promote the graft survival.Ovaries from 8-week-old FVB/N-Tg(PolII-Luc)Ltc transgenic mice with or without scaffolds loaded with S1P (2 mM, 5 μL) or VEGF (0.2 mg/ml, 5 μL) were transplanted into the peritoneum of wild-type mice. The graft survival was tracked in vivo by bioluminescence imaging (BLI) for 4 weeks, and histological examination was performed at the end of the experiment.

RESULTS: Stronger signals of in vivo BLI were observed in the ovaries with S1P- and VEGF-loaded scaffolds than those in the scaffolds without drugs and those without scaffolds. Histological examination also showed more follicles and surrounding vessels in the S1P group compared with other groups. The above indicated better survival of the grafts.

CONCLUSIONS: We demonstrated that scaffolds loaded with drug can promote ovarian graft survival.Scaffolds mimicking the structure and biological function of native extracellular matrix are beneficial for tissue growth, and applying tissue engineering technology may overcome some limitations in regenerative medicine.

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OBJECTIVE ASSESSMENT OF THE ONCOFERTILITY EDUCATIONAL INFORMATION, AVAILABLE TO WOMEN, ON THE WEBSITES OF NCI-DESIGNATED CANCER CENTERS IN THE US: DO SOCIOECONOMIC DEMOGRAPHIC PROFILES BY STATE MAKE A DIFFERENCE? C. de Haydu,[a] S. V. Eleswarapu,[b] A. A. Dabaja,[b] C. M. Duke.[a] [a]Yale University School of Medicine, New Haven, CT; [b]Henry Ford Health System, Detroit, MI.

OBJECTIVE: Current guidelines recommend that reproductive age women, newly diagnosed with cancer, should be counseled on fertility preservation (FP). Hospital websites increasingly serve as portals for reliable web-based resources to supplement the knowledge of patients and families regarding their diagnoses & treatments. This study aims to assess the quality of hospital web-based resources which are available to women undergoing cancer treatment at major cancer centers.

DESIGN: Prospective observational study.

MATERIALS AND METHODS: A validation rubric for FP/oncofertility content quality standards using a scoring system for commonly accepted definitions & terminology was developed. The publicly available websites of the National Cancer Institute Designated Cancer Centers (NCICC) & the Cleveland Clinic Foundation (CCF) were accessed by independent teams from two different institutions between Nov. 1, 2014 & April 30, 2105 & queried in a systematic fashion. Specific queries included: 1) Does the website discuss the effects of cancer & cancer treatment on female fertility? 2) Are options for FP for all patients discussed? 3) Is there a standalone page dedicated to educating patients on FP? 4) Is parenting-related cancer survivorship addressed? 5) Is there a link to outside FP information?. State & Region based demographic information on racial makeup, household income & poverty status were obtained from the 2010 US Census Bureau's "Geographic Level of Poverty & Health Estimates". Chi-square tests were performed to assess for differences between FP website scores (individually & within Regional groups); analysis was also performed to assess for any correlation between socioeconomic/racial differences within States/Regions where NCICC are located. Multivariate logistic regression analyses are ongoing.

RESULTS: 62 clinical NCICC were identified, including CFF. 92% of queried sites were academic institutions. 84% of all websites mention the risk of cancer treatment on a woman's fertility potential but 44% do not discuss FP options for women. 56% of websites have pages dedicated to discussion of non gender specific FP options & 65% of the websites contain links to further resources. In population based adjusted analyses, NCCIC in States where 50% of the population identified as Non-Hispanic White (even after controlling for socioeconomic status), p-value < 0.04. There were no differences observed when similar adjustments & analyses were performed by for US census bureau geographic Regions.

CONCLUSIONS: Preliminary data suggest that NCICC websites are inconsistent in the quality of oncofertility educational information for female patients. Racial makeup of a State is associated differences in the quality of patient centered oncofertility web-based resources for women. These findings are concerning and suggest that more uniformed efforts aimed at attenuating these racial gaps in patient education are needed.

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THE EFFECT OF VITRIFICATION AND PROGRAMMED FREEZING ON FROZEN-THAWED HUMAN OVARIAN CORTEX TISSUE. X. Wang,[a] C. Fang,[a] C. Di,[a] H. Liu,[b] X. Liang.[a] [a]Reproductive Medicine Research Center, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [b]Obstetrics and Gynecology Department, Guangzhou Development District Hospital, Guangzhou, China.

OBJECTIVE: It has been long remained controversial whether vitrification, compared with programmed freezing, is better for ovarian fertility preservation. Therefore, this study aimed at comparison of the effects of these two techniques on the frozen-thawed human ovarian tissues, to provide some experimental evidences to select a better method to preserve women fertility.

DESIGN: Ovarian tissues came from cases of partial ovariectomy, with necessity of diagnosis or treatment. And all the pathological reports told neither tumor cell metastasis in the ovarian tissue nor existence of other nidi. In each case, the cortex was cut into small pieces, followed by randomly divided into Fresh (F) group, Vitrification (V) group and Programmed Freezing (PF) group. Morphology changes, apoptosis in situ, follicle viability and secretion function were compared with self-control method and in-vitro cultivation.

MATERIALS AND METHODS: Ovarian tissues came from 6 cases, which met the above criteria. The morphology of tissues were examined by HE staining. The cell apoptosis in situ was analyzed by TUNEL assay. Neutral red staining and CaAM/EthD-1 staining were conducted respectively after collagenase-1 digestion of frozen-thawed tissues, and the survival rate of small follicles was analyzed. During in vitro culture of frozen-thawed ovarian tissues, the secretion level of estrogen (E2) and progesterone (P4) in media were examined and analyzed at Day 2, Day 4, Day 6 and Day 8.

RESULTS: The morphology of follicles and stroma cells in both V Group and PF Group were similar as F Group. The apoptosis in situ showed no significance between V Group and F Group, while apoptosis in PF Group is significantly higher than other two groups. After frozen-thawed, no significant differences were showed in assessment of viability of small follicles between PF Group and V Group. Analysis of E2 and P4 level showed that secretion of E2 had a tendency to change over time, and time effect varies with grouping. It increased significantly higher in PF Group at Day 4 and Day 8, but similar at Day 6, when compared with V Group. The secretion of P4 also had a tendency to change over time, but no significant differences were found in the effect of interaction of time and grouping, neither in the grouping effect.

CONCLUSIONS: Both of vitrification and programmed freezing can well preserve the morphological characteristics of ovarian cortex tissue, but vitrification may be better for protection of DNA integrity in cells. Both of vitrification and programmed freezing can well preserve the viability of small follicles in frozen-thawed tissues. Both of the frozen-thawed tissues after vitrification and programmed freezing can recover secretion function. And functional reconstruction of frozen-thawed ovarian tissues with these two techniques still needs further researches.

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MENSTRUATION IS AN UNRELIABLE SURROGATE IN THE ASSESSMENT OF OVARIAN DAMAGE BY CHEMOTHERAPY: A PROSPECTIVE LONGITUDINAL STUDY WITH AMH LEVELS AS THE GOLD STANDARD. G. Bedoschi,[a,b] S. Goldfarb,[c] J. Quistorff,[c] S. Goswami,[d] F. Moy,[a] M. Dickler,[c] K. Oktay.[a,b] [a]Obstetrics and Gynecology, NYMC, Valhalla, NY; [b]Innovation Institute for Fertility Preservation and IVF, Rye, NY; [c]Memorial Sloan Kettering Cancer Center, New York, NY; [d]Yeshiva University, New York, NY.

OBJECTIVE: The majority of studies assessing the impact of chemotherapy (CT) on ovarian reserve continue to use menstruation as a surrogate. We aimed to determine the reliability of menstrual status and pattern in assessing CT-induced ovarian damage, using the serum AMH level as the gold standard.

DESIGN: Prospective longitudinal study.

MATERIALS AND METHODS: 81 women with breast cancer stage 1-3 were prospectively enrolled and followed up for 18 months (18mo). Sera were frozen at baseline (BL) and 18mo post-CT, and were assayed for AMH (ng/ml) at once. Women kept monthly menstrual calendars. Amenorrhea was defined as no menses for >6 months, and regular periods as those with 21-35 day intervals. Results were analyzed with t-test or ANOVA for continuous variables and chi square or Fisher's exact test for discrete variables.

RESULTS: The median age at CT was 38 (range 27-44); 72.1% received anthracycline-based, 13.2% received CMF, 13.2% received taxane-based and 1.5% received other CT regimen. Ten women did not complete menstrual calendars and were excluded from the analysis. Seventeen (23.9%) patients developed amenorrhea and 54 (76.1%) were menstruating at the end of 18mo follow up. The groups were similar in age, BL AMH , CT protocol, and adjuvant tamoxifen use. Of those who were menstruating post-CT, 48.5% had RP and 51.5% had irregular periods (IP). Surprisingly, women who developed amenorrhea post-CT had higher AMH levels than those who retained menstruation post CT (0.77±0.34 vs. 0.23±0.1 ng/ml, p=0.049). However, women with RP showed a trend for higher AMH post-CT than those with IP (0.31±0.15 vs. 0.05±0.02, p=0.076). Of the women who had detectable AMH levels at 18mo, a similar percentage had amenorrhea vs. continued menstruation (41.18% vs. 58.82%, p=0.393). Moreover, their mean AMH levels were not significantly different.

CONCLUSIONS: Our data indicate that menstrual status has very little value in assessing CT-induced ovarian damage. Studies that investigate the impact of CT or interventions to preserve ovarian function should utilize more reliable markers such as the serum AMH.

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DEVELOPMENT OF A NEW LOCAL DRUG DELIVERY SYSTEM FOR THE UTERUS USING BIO-NANOCAPSULE. K. Koizumi,[a] H. Nakamura,[a] T. Matsuzaki,[b] S. Kuroda,[c] Y. Yasui,[a] K. Furuya,[a] T. Miyake,[a] T. Takiuchi,[a] K. Kumasawa,[a] T. Kimura.[a] [a]Obstetrics and Gynecology, Osaka University Graduate School of Medicine, Suita Osaka, Japan; [b]Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita Osaka, Japan; [c]The Institute of Scientific and Industrial Research, Osaka University, Suita Osaka, Japan.

OBJECTIVE: Uterus is the applicable organ for local gene therapy because it is not part of the peritoneum organ and it can be reached directly. However, we still do not have any drug delivery system for uterus.Bio-nanocapsule (BNC) containing hepatitis B virus surface antigen consists of approximately 50-nm hollow particles displaying a human hepatocyte-recognizing molecule (pre-S1 peptide). BNC has been used as an HB vaccine for the last three decades. In this study, we optimized the BNC as a new local drug delivery system for uterus.

DESIGN: Animal experiment.

MATERIALS AND METHODS: The N terminal of Pre-S1 peptide was replaced with the TAT (trans-activating transcription factor) peptide.The Cy7 labeled BNC was transferred into the murine uterine cavity. The distribution of BNC was observed by in-vivo imaging system and also by immunohistochemistry. The luciferase expression plasmid DNA was incorporated into BNC using liposome. The luciferase expression plasmid DNA was transferred into uterine cavity using TAT-BNC-liposome complex. The efficiency of gene transfection was analysed by luciferase assay.

RESULTS: BNCs were observed in the luminal and glandular epithelial cells, but not in stroma and myometrium. The transfection efficiency of the TAT-BNC-liposome complex was significantly higher than lipofection.

CONCLUSIONS: These results suggest that BNC could be an applicable DDS for uterus. In this study, we replaced the N terminal of Pre-S1 peptide with TAT peptide. However, it is replaceable with sugar chains and antibodies. Recently there are some reports that some of special sugar chains are expressed in the uterine endometrium during pregnancy and uterine cancer. If we can find specific sugar chains or cell surface antibodies on uterine endometrium for reproductive dysfunction and uterine cancer, this DDS system can be more targetable.

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SMALL ANTRAL FOLLICLE RESPONSIVENESS TO FSH, ASSESSED BY THE FOLLICULAR OUTPUT RATE (FORT), IS NOT ALTERED IN CANCER PATIENTS, CANDIDATES FOR FERTILITY PRESERVATION. S. Duros,[a] C. Sonigo,[b] J. Benard,[a] C. Sifer,[c] M. Grynberg.[d] [a]Department of Reproductive Medicine, Hopital Jean Verdier, APHP, BONDY, France; [b]Department of Reproductive Medicine, Hôpital Jean Verdier, APHP, BONDY, France; [c]Department of Cytogenetic and Reproductive Biology, Hopital Jean Verdier, APHP, BONDY, France; [d]Department of Reproductive Medicine, BONDY, France.

OBJECTIVE: To evaluate the small antral follicle responsiveness to exogenous FSH, assessed by the Follicular Output RaTe (FORT), in cancer patients, candidates for fertility preservation (FP) using oocyte vitrification after controlled ovarian hyperstimulation (COH).

DESIGN: Prospective study.

MATERIALS AND METHODS: From July 2013 to December 2014, 71 cancer patients, aged 20-40 years, candidates for oocyte vitrification following COH (FP group) were studied. Ovarian stimulation characteristics and outcomes were compared with that of 91 infertile women (Control group), included in an *in vitro* fertilization program in our centre during the same time frame, matched for age, antral follicle count (AFC) and serum Anti-Mullerian hormone (AMH) levels measured just before initiation of the stimulation (d0), as well as FSH starting dose. All patients had 2 ovaries, no previous history of chemotherapy and underwent COH using GnRH antagonist protocols. Antral follicles were counted before FSH administration, and on the day of ovulation triggering (dOT). FORT was determined by the ratio between the pre-ovulatory follicle count (16-20 mm) on dOT × 100/AFC on d0.

RESULTS: By design, mean age, AFC, AMH and FSH starting dose were similar in FP and Control groups (31.5 ± 3.6 *vs.* 32.2 ± 4.9 years; 17.4 ± 9.8 *vs.* 16.6 ± 8.3 follicles, 2.9 ± 2.4 *vs.* 3.0 ± 1.7 ng/mL; 269 ± 81 *vs.* 248 ± 56 IU, respectively, *NS*). Characteristics and outcomes of the stimulation in both groups are reported in the Table.

CONCLUSIONS: The present investigation shows that the cancer status may not impact the responsiveness of small antral follicles to exogenous FSH, assessed by the FORT, in candidates for oocytes vitrification. However, alterations in the granulosa cell function in relation with the malignant disease may account for the significantly lower levels of serum E_2 reached in the end of the ovarian stimulation in these patients when compared to infertile women.

Characteristic and outcome of the stimulation in FP and Control groups.

	FP group (n=71)	Control group (n=91)	*p*
Mean total dose of gonadotropin (IU)	2931±1095	2610±1188	NS
Mean duration of stimulation (days)	10.3±1.7	10.1±2.2	NS
E_2 on dOT (pg/mL)	1261± 806	1904±997	<0.001
E_2 / Foll >12 mm (pg/mL)	132.5±93.2	187.6±94.8	<0.001
No of oocytes recovered	11.6±8.4	10.9±5.4	NS
No of metaphase II oocytes obtained	8.9±7.1	8.4±4.3	NS
FORT (No of Foll > 16 mm on dOT x 100 / AFC on d0) (%)	36±22	37±20	NS

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ANTI-MÜLLERIAN HORMONE PREVENTS CHEMOTHERAPY-INDUCED FOLLICULAR BURNOUT. S. Tan,[a,b] C. Chen,[a,c] C. Tzeng.[a,c] [a]Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Taipei Medical University Hospital, Taipei, Taiwan; [b]Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [c]Department of Obstetrics and Gynecology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.

OBJECTIVE: Chemotherapeutic drugs may damage the reproductive system and lead to infertility and premature ovarian failure. How to prevent follicular loss is the key to preserve ovarian reserve. Anti-Müllerian hormone (AMH), which is produced by the granulosa cells of growing follicles, can inhibit primordial follicle activation and follicle growth stimulated by follicle-stimulating hormone. This study aimed to investigate the inhibitory effect of recombinant AMH on chemotherapy-induced follicular burnout.