**O-14** Monday, October 14, 2019 11:00 AM

**SEX DIFFERENCES IN BIRTH OUTCOMES FOR MASSACHUSETTS INFANTS FOLLOWING ART.** Sunah S. Hwang, MD MPH,[a] Dmitry Dukhovny, MD MPH,[b] Daksha Gopal, MPH,[b] Howard Cabral, PhD, MPH,[c] Hafsatou Diop, MD, MPH,[d] Judy E. Stern, PhD[e] [a]University of Colorado School of Medicine, Aurora, CO; [b]Affiliation not provided; [c]Boston University, Boston, MA; [d]MDPH, Boston, MA; [e]Dartmouth-Hitchcock, Lebanon, OR.

OBJECTIVE: Sex differences in child and adult health outcomes have been demonstrated. While prior studies have shown adverse birth outcomes for infants conceived by assisted reproductive technology (ART), data on whether outcomes differ by infant sex are lacking. Our objective in this study was to determine the presence and magnitude of sex differences in neonatal health outcomes among infants conceived by ART.

DESIGN: Retrospective observational cohort analysis of singletons born in Massachusetts between July 1, 2004 and December 31, 2013 who were conceived by ART.

MATERIALS AND METHODS: We linked the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS), a clinical database of treatment information on all ART cycles and the Pregnancy to Early Life Longitudinal (PELL) data system, which links birth certificates to hospital discharge records for mothers and infants in Massachusetts. The analysis was limited to singleton, live births to women $\geq$18 years, conceived by ART. Birth outcomes for ART deliveries were compared between male and female infants using chi-square tests. Health outcomes were obtained from PELL. Multivariable logistic regression was used to model the potential association between infant sex and adverse health outcomes, controlling for maternal age, race/ethnicity, education, insurance, chronic and gestational diabetes, hypertension, parity, and gestational age (results displayed as adjusted odds ratio; 95% confidence interval).

RESULTS: A total of 16,034 singleton live births conceived by ART were included: 7,737 female and 8,297 male. In the adjusted analysis, compared to female infants, male infants had greater odds of being preterm (1.19; 1.07-1.32), having birth defects (1.31; 1.05-1.63), experiencing respiratory (1.37; 1.24-1.51) and neurologic (1.29; 1.09-1.53) conditions, and prolonged hospital stay (1.25; 1.09-1.43). Despite the higher odds of preterm birth, male infants had lower odds of being low birthweight (0.8; 0.7-0.92) compared to their female counterparts.

CONCLUSIONS: Sex differences in birth outcomes of infants conceived by ART exist. Further studies are needed to elucidate the biologic mechanisms underlying the relationship between infant sex and these adverse health outcomes among infants conceived by ART.

**SUPPORT:** NIH R01HD067270.

**O-15** Monday, October 14, 2019 11:15 AM

**CONCEPTION BY INFERTILITY TREATMENT AND NEWBORN DNA METHYLATION.** Edwina Yeung, PhD,[a] Pauline Mendola, PhD,[a] Rajeshwari Sundaram, PhD,[a] Xuehuo Zeng, PhD,[b] Weihua Guan, PhD,[c] Michael Y. Tsai, PhD,[c] Sonia L. Robinson, PhD,[a] Judy E. Stern, PhD,[d] Erin M. Bell, PhD[e] [a]National Institutes of Child Health and Human Development, Bethesda, MD; [b]Glotech Inc, Rockville, MD; [c]University of Minnesota, Minneapolis, MN; [d]Dartmouth-Hitchcock, Lebanon, OR; [e]University at Albany, Albany, NY.

OBJECTIVE: To determine whether newborns conceived by infertility treatment have different DNA methylation patterns from newborns not conceived by treatment.

DESIGN: The Upstate KIDS Study recruited women and their newborns (2008-2010), oversampling on infertility treatment exposure.

MATERIALS AND METHODS: Mothers reported on use of infertility treatment and the specific type (assisted reproductive technologies (ART) or ovulation induction (OI) / intrauterine insemination (IUI)) at 4 months postpartum. Maternal report of ART use was previously verified by linkage to SART-CORS. Mothers provided permission to use archived newborn dried blood spots collected by Newborn Screening. DNA methylation was measured using the Infinium EPIC microarray. Samples from 855 newborns were used in analysis. Singletons (n=688) and unrelated twins (n=167) were included to maintain independent samples. Quantile normalization was applied for probe type normalization and robust linear regression used to model the associations between 837,933 CpGs and any infertility treatment as well as by type (i.e., ART, OI/IUI, none). Bonferroni significance of $p<6x10^{-8}$ was used to account for multiple testing. Analyses were adjusted for maternal age, race, education, pregnancy smoking, private insurance, estimated cell type and batch effects.

RESULTS: Newborns conceived with infertility treatment (n=335, 39%) had higher methylation at one CpG in *C14orf166B* (cg21616682, $p=4.74x10^{-8}$) compared to newborns not conceived with treatment (n=514). When the specific techniques were examined, no genome-wide associations were found for conception by OI/IUI (n=177, 20%). However, ART conceived newborns (n=158, 19%) had hypomethylation (ranging from 1.5 to 5.3%) at four CpGs in several gene regions (*Table 1*). Additional adjustment for plurality, infant sex, gestational age and birthweight did not meaningfully alter the findings.

CONCLUSIONS: In one of the largest studies examining differences in newborn DNA methylation by conception with infertility treatment, several genes were identified, with biological evidence linking them to infertility. For instance, *SYCE1* encodes for a synaptonemal complex protein, which is necessary for meiosis, and whose mutations were previously found in association with male and female infertility. Ongoing child follow-up will validate whether methylation differences persist.

TABLE 1. Newborn DNA methylation differences between conception by ART versus no treatment

| CpG | Beta | SE | p-value | Chromosome | Position | Gene |
|---|---|---|---|---|---|---|
| cg17676129 | -0.01747 | 0.002484 | 2.02E-12 | 10 | 135382545 | *SYCE1* |
| cg24413339 | -0.01587 | 0.002703 | 4.35E-09 | 10 | 135237754 | *SPRN* |
| cg01050010 | -0.04998 | 0.008442 | 3.21E-09 | 17 | 31149877 | *MYO1D* |
| cg27119318 | -0.05358 | 0.009847 | 5.28E-08 | 21 | 40759574 | *WRB* |

**O-16** Monday, October 14, 2019 11:30 AM

**BABIES BORN FOLLOWING ADMINISTRATION OF NOLASIBAN BEFORE EMBRYO TRANSFER (ET) AFTER IVF: NEONATAL AND INFANT DEVELOPMENT OUTCOMES FROM A DOUBLE-BLIND, PLACEBO-CONTROLLED, CLINICAL TRIAL.** Andrew Humberstone, PhD,[a] Paul Terrill, PhD,[b] Lynne Macgregor, MSc,[a] Ernest Loumaye, MD, PhD[a] [a]ObsEva SA, Plan-les-Ouates, Switzerland; [b]Cytel Inc, London, United Kingdom.

OBJECTIVE: Nolasiban, an oral oxytocin antagonist, has been shown to increase live birth rate when administered prior to ET (Visnova 2018). The objective of this study was to assess neonatal and infant development outcomes after administration of nolasiban or placebo at the time of ET.

DESIGN: Multinational, double-blind, randomized, parallel group, placebo-controlled, Phase 3 trial assessing a single oral 900 mg dose of nolasiban or placebo (1:1), administered about 4 hours before ET following IVF. Neonatal outcomes were assessed up to 28 days after birth and infant development assessed using the Ages and Stages Questionnaire-3® (ASQ-3) completed at 6 months after birth.

MATERIALS AND METHODS: 778 subjects were recruited from 41 fertility clinics in Europe from Mar–Oct 2017. Eligibility criteria included age $\leq$ 36 years, $\leq$ 1 failed ART cycle, use of a GnRH antagonist, $<$ 1.5 ng/mL serum progesterone on the day of hCG, and luteal support with vaginal micronized progesterone. One good quality embryo was transferred on either D3 (n=388) or D5 (n=390). Neonatal and infant development outcomes were summarized for each treatment group using descriptive statistics for the pooled D3/D5 population. No hypothesis testing was planned.

RESULTS: There were 108 deliveries (1 set of twins) resulting in 109 infants in the placebo group and 131 deliveries (5 sets of twins) resulting in 136 infants in the nolasiban group. At birth, mean $\pm$ SD 5 min Apgar-scores (placebo 9.65 $\pm$ 0.76; nolasiban 9.61 $\pm$ 0.84), weight (placebo 3174 $\pm$ 517 g; nolasiban 3137 $\pm$ 690 g), height (placebo 51 $\pm$ 4 cm; nolasiban 50 $\pm$ 5 cm) and head circumference (placebo 34 $\pm$ 2 cm; nolasiban 34 $\pm$ 2 cm) were very similar between the treatment groups. There were 4 (3.7%) congenital abnormalities in the placebo group and 5 (3.7%) in the nolasiban group.

At 28 days after birth, weight, height and head circumference continued to be similar between groups. 9 (8.3%) infants had been admitted to intensive care in the placebo group and 9 (6.6%) in the nolasiban group. Neonatal morbidities were reported in 29 (26.6%) infants in the placebo group and 26 (19.1%) in the nolasiban group. The most common neonatal morbidities were jaundice (20 (18.3%)) placebo and 18 (13.2%) nolasiban) and respiratory distress syndrome (10 (9.2%) placebo and 11 (8.1%) nolasiban).

At 6-months after birth for those subjects with follow-up data, mean $\pm$ SD total ASQ-3 scores were 208.7 $\pm$ 38.8 in the placebo group and 208.5 $\pm$ 44.7 in the nolasiban group. The No. (%) of infants with an ASQ-3 score below the normal range in $\geq$ 1 domain was 33 (37.5%) in the placebo group and 43 (41.7%) in the nolasiban group.

CONCLUSIONS: The neonatal and infant developmental outcomes were similar between the nolasiban and placebo groups.

References: Visnova H, Tournaye H, Humberstone A, Terrill P, Macgregor L, Loumaye E. A placebo-controlled, randomized, double-blind, phase 3 study assessing ongoing pregnancy rates after single oral administration of a novel oxytocin receptor antagonist, nolasiban, prior to single embryo transfer. Fertil. Steril. 2018 110 (4 Suppl.) e45.

SUPPORT: The trial was funded by ObsEva SA.

**O-17** Monday, October 14, 2019 11:45 AM

**SIMILAR SUCCESS RATES WITH FROZEN OOCYTES BUT INCREASED RATE OF LARGE FOR GESTATIONAL AGE (LGA) INFANTS COMPARED TO FRESH OOCYTES.**

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OBJECTIVE: Evaluate pregnancy and perinatal outcomes of embryos derived from fresh and frozen oocytes in autologous cycles.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: The SART database was used to identify autologous oocyte cycles that resulted in an embryo transfer during 2014 and 2015. Generalized linear regression models were used to compare pregnancy and perinatal outcomes of fresh versus frozen oocytes. Models were adjusted for the following factors: maternal age, BMI, current smoking status, parity, infertility diagnosis, prior IVF attempt, ICSI, assisted hatching, number of embryos transferred, multiple gestation and fetal heart reduction. Live birth rate was the primary outcome. Secondary outcomes include miscarriage rate and birth weight.

RESULTS: The mean maternal age in autologous oocyte cycles (N=139,734) was 35 years (SD ±3.6). There was no significant difference in live birth rates when comparing embryos derived from fresh and frozen oocytes in autologous cycles (25.7% versus 23.9%, aRR 0.94, 95% CI 0.8-1.1). No significant differences were noted in biochemical pregnancy losses (5.8% versus 6.9%, aRR 1.3, 95% CI 0.94-1.79) or clinical miscarriages (10.9% versus 11.2%, aRR 1.04, 95%CI 0.82-1.33) in embryos derived from fresh and frozen autologous oocytes. Increased risk for large for gestational age infants (4.5% versus 12.5%, aRR 2.69, 95% CI 1.66-4.33) was seen in embryos derived from frozen oocytes. No significant difference was noted in low birth weight infants between the two groups.

CONCLUSIONS: Frozen oocytes have similar success rates as fresh oocytes in autologous cycles that resulted in embryo transfer. However, an increased rate of large for gestational age infants was seen in embryos derived from frozen oocyte. This finding warrants further study.

**O-18** Monday, October 14, 2019 12:00 PM

**PREVALENCE OF CLINICALLY SIGNIFICANT CONGENITAL HEART DEFECTS IN LOW-RISK IVF PREGNANCIES.**

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OBJECTIVE: Current research has shown increased prevalence of congenital heart defects (CHD) among *in vitro* fertilization (IVF) pregnancies compared to spontaneous pregnancies. We describe the prevalence and characteristics of CHD in IVF pregnancies at a high-volume fetal echocardiography center and outline a low-risk subset of patients for whom echo may not be clinically indicated.

DESIGN: Historical Prospective Observational Study.

MATERIALS AND METHODS: All fetal echocardiograms for singleton and dichorionic twin pregnancies performed January 1, 2004 to December 31, 2018 at a large tertiary care center utilizing gray scale, color Doppler, and spectral Doppler were reviewed and categorized by gestational age (GA), indications for fetal echo, and presence of structural CHD. All initial diagnoses were made by experienced sonographers and a maternal-fetal medicine specialist, recorded on videotape, and confirmed by a pediatric cardiologist. Neonatal echocardiographic examinations were performed to confirm diagnoses in cases with prenatal diagnoses of CHD. Prevalence and 95% confidence intervals (CI) calculated utilizing standard statistical methods. Clinical outcomes were available for cases of CHD after 2011.

RESULTS: 18,879 fetal echocardiograms were completed during the study period. Of those, 3,893 echocardiograms were performed with only indication being IVF gestation. Patients with previous child with CHD, family history of CHD, mediation exposure, diabetes, non-cardiac anomaly, anomaly in previous pregnancy, other abnormality noted on ultrasound, or monochorionic twins were excluded. Mean GA at time of echo for IVF only group was 22.2 ± 1.4 weeks. Prevalence of CHD summarized in Table 1. 25 cases were diagnosed with CHD after 2011. 22 were isolated ventricular septal defects (VSD), 10 CHD were not resolved at time of pediatric cardiology follow-up by 16 months, and 3 were clinically significant requiring intervention or cardiology follow-up after 2 years of age. Prevalence of clinically significant CHD in IVF only pregnancies was 0.15% (95%CI [0 – 0.40%]).

CONCLUSIONS: (1) In this low risk IVF cohort, the prevalence of clinically significant CHD is similar to population risk previously reported. (2) A large proportion of CHD in this population are VSD and most spontaneously resolve.

SUPPORT: None.

TABLE 1. Prevalence of CHD in IVF Pregnancies

| Group | # | # CHD | % with CHD | 95% CI |
|---|---|---|---|---|
| All IVF Pregnancies | 4242 | 76 | 1.79 | 1.39 - 2.19 |
| IVF Only Ind. | 3893 | 33 | 0.85 | 0.56 - 1.14 |
| IVF Only (2012-18) | 2040 | 25 | 1.23 | 0.75 - 1.70 |
| IVF Only (2012-18) CHD Not Resolved | 2040 | 10 | 0.49 | 0 - 1.10 |
| IVF Only (2012-18) with Clinically Significant CHD | 2040 | 3* | 0.15 | 0 - 0.40 |

* Cases were Coarct/VSD, Pulmonary Stenosis, and asymptomatic vascular ring.

## CONTRACEPTION AND COMPLEX FAMILY PLANNING

**O-19** Monday, October 14, 2019 10:45 AM

**TOPICAL LIDOCAINE-PRILOCAINE CREAM VERSUS LIDOCAINE 1% SUBCUTANEOUS INFILTRATION DURING NEXPLANON INSERTION: A RANDOMIZED CONTROLLED STUDY.**

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OBJECTIVE: Adequate anesthesia is an important procedural step when inserting contraceptive implants. Subcutaneous injection of lidocaine 1% is a widely used anesthetic method in implant insertion. However, lidocaine injection may be painful due to the penetration of the skin by the needle, and there is a theoretical risk of needle stick injury. This may also cause bleeding or edema which may mislead the intact subdermal insertion of the implant. Lidocaine-prilocaine (LP) cream is an oil/water emulsion in which the oil phase is a eutectic mixture of two anesthetics: lidocaine 2.5% and prilocaine 2.5% in a ratio of 1:1 by weight. Our objective is to compare the anesthetic effect of LP cream versus lidocaine subcutaneous infiltration during insertion of Nexplanon.

DESIGN: Randomized, open-label controlled study (Clinicaltrials.gov: NCT03187392).

MATERIALS AND METHODS: Reproductive-aged parous women requesting Nexplanon insertion for contraception were counseled to participate. Eligible women based on WHO guidelines were recruited and randomized (1:1) to LP cream vs. lidocaine 1% subcutaneous infiltration. In the cream group, 5 mg was applied on the insertion site, and Nexplanon rod was inserted after 5 minutes later. In the injection group, 2 ml of 1% lidocaine was slowly injected through a 24 G needle at the Nexplanon insertion