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Title

Bleeding patterns and endometrial safety with a 1-year, segesterone acetate/ethinyl estradiol contraceptive vaginal system

Permalink

https://escholarship.org/uc/item/0d49g4nr

Journal

Fertility and Sterility, 112(3)

ISSN

0015-0282

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Publication Date

2019-09-01

DOI

10.1016/j.fertnstert.2019.07.163

Peer reviewed

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DESIGN: We conducted a prospective, candidate gene study to test for associations between genetic variants and both subjective weight gain and objective weight changes in ENG implant users.

MATERIALS AND METHODS: We recruited healthy, reproductive-aged women using ENG implants for 12-36 months. We asked participants about subjective weight gain (yes/no) during contraceptive implant use and performed medical record review to calculate objective weight changes from implant insertion to study enrollment. We genotyped each participant for 120 single nucleotide polymorphisms (SNPs) in 14 genes involved in progestin metabolism, regulation, and function. To identify genetic variants associated with subjective weight gain and objective weight changes, we performed backwards stepwise multivariable logistic regression and generalized linear modeling, respectively, adjusting for age, body-mass index (BMI), and self-reported race/ethnicity.

RESULTS: We enrolled 350 ethnically-diverse participants. Median BMI was 26.0 kg/m^2 (range 18.5-52.0) and 41.4% reported experiencing subjective weight gain during contraceptive implant use. Weight at time of implant insertion was available for 276 participants with a mean weight change of +3.8 kg (±7.2). We found two genetic variants significantly associated with subjective weight gain. Carriers of *CYP3A4*1G* and participants homozygous for the *ESR1* rs9322335 variant were both more likely to report weight gain (aOR 2.32, p=0.001 and aOR 2.41, p=0.001, respectively). Frequencies of these genetic variants were 33.3% and 68.1%, respectively. We found two genetic variants associated with objective weight changes. Participants homozygous for the *ESR1* rs9340799 variant gained 10 kg more weight, on average, compared to all other participants (β= 10.09, p=0.002). Carriers of the *CYP2C19* rs7088784 variant lost 3.9 kg more weight, on average, compared to all other participants (β= -3.88, p=0.001). Frequencies of these genetic variants were 8.3% and 22.5%, respectively. Higher BMI was the only variable significantly associated with both outcomes: aOR 1.10 (p=1.6x10^{-5}) and β= 0.56 (p=6.3x10^{-13}).

CONCLUSIONS: We identified two genetic variants in the *ESR1* (estrogen receptor 1) gene that were associated with subjective and objective weight gain in ENG contraceptive implant users. Neither SNP (rs9322335 or rs9340799) has known associations with obesity or metabolic syndrome, and thus, this may be a progestin-dependent effect. Additional genetic research is needed to facilitate advances in individualized counseling on the risk of weight gain with exogenous steroid hormones.

SUPPORT: This work was primarily supported by the Society of Family Planning Research Fund [grant number SFPRF17-3]. This work was also supported by NIH/NCATS Colorado CTSA Grant Number UL1 TR001082. Dr. Lazorwitz's time is also supported by the NICHD K12 Women's Reproductive Health Research Scholar Program (grant number 5K12HD001271-18). Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

O-23 Monday, October 14, 2019 11:45 AM

EFFICACY AND SAFETY OF A MULTIPURPOSE VAGINAL PH-REGULATOR: RESULTS FROM THE PHASE 3, AMPOWER CONTRACEPTION CLINICAL TRIAL.

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OBJECTIVE: Amphora® (formerly known as Acidform), a multipurpose vaginal pH-regulator (MVP-R), is a novel, non-hormonal, woman-controlled, on-demand, water-based, petroleum-free vaginal gel being investigated for prevention of pregnancy and sexually transmitted infections. Here we present primary results from the confirmatory phase 3 contraception trial, AMPOWER.

DESIGN: This was a single-arm, open-label study conducted at 112 sites within the US (ClinicalTrials.gov number NCT03243305).

MATERIALS AND METHODS: All sites obtained IRB approval and all women provided informed consent. Eligibility criteria included healthy, monogamous, sexually active women aged 18-35 years who had normal cyclic menses of length 21-35 days, reported having intercourse ≥3 times per cycle, and were willing to use the study drug as the only method of contraception over the course of the study. Women were instructed to administer a single prefilled applicator of study drug intravaginally immediately before or up to 1 hour before each episode of vaginal intercourse. Women used eDiaries to record timing of product administration, coital information, and side effects. The primary efficacy analysis was the cumulative pregnancy percentage over 7 cycles with typical-use calculated by the Kaplan-Meier method.

RESULTS: A total of 1384 women were included in the Intent-to-Treat (ITT) population, 1182 were included in the primary efficacy analysis (modified ITT [mITT]), and 1330 used at least 1 application of study product and were included in the Safety population. In the ITT population, select baseline characteristics were as follows: mean age, 27.7 years (standard deviation [SD], 4.5); mean body mass index, 28.7 kg/m^2 (SD, 8.1); Caucasian, 69.0% (955/1384); and non-Hispanic or non-Latino origin, 58.2% (805/1384). The mean number of prior pregnancies was 2.5 (SD, 1.8) and the most common contraceptive methods used immediately prior to enrollment were reported to be male condom (56.9% [787/1384], withdrawal method (14.2% [196/1384]), and rhythm method (5.1%, 70/1384). Fewer than 2% of study participants discontinued due to adverse events (AEs) (1.7% [23/1384]). For the primary efficacy analysis in the mITT population, the 7-cycle cumulative pregnancy percentage with typical-use was 13.9% (95% confidence interval [CI]; 10.0%, 17.8%), which met the prespecified primary endpoint of having the upper bound 95% CI ≤21%. The most common AEs (>2.0%) were vulvovaginal burning sensation (20.0%, 266/1330), vulvovaginal pruritus (11.2%, 149/1330), urinary tract infection (5.7%, 76/1330), vulvovaginal pain (3.8%, 51/1330), vulvovaginal mycotic infection (2.9%, 38/1330), bacterial vaginosis (2.8% [37/1330]), and nasopharyngitis (2.6% [35/1330]). Fourteen women (1.1%) experienced a serious AE with only 1 event (cystitis, 0.1%) considered treatment related.

CONCLUSIONS: In this large phase 3 study, the MVP-R, Amphora, was found to be safe and effective in preventing pregnancy. Amphora provides women with an important new non-hormonal, woman-controlled contraceptive option.

SUPPORT: Evofem Inc.

O-24 Monday, October 14, 2019 12:00 PM

BLEEDING PATTERNS AND ENDOMETRIAL SAFETY WITH A 1-YEAR, SEGESTERONE ACETATE/ ETHINYL ESTRADIOL CONTRACEPTIVE VAGINAL SYSTEM.

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OBJECTIVE: We analyzed bleeding patterns and endometrial safety of a contraceptive vaginal system (CVS) releasing a daily mean of segesterone acetate (SA) 0.15 mg and ethinyl estradiol (EE) 0.013 mg for up to 13 cycles of use.

DESIGN: Two multicenter, single-arm, open-label, pivotal, phase 3 studies of the SA/EE CVS conducted at 20 US and 7 international sites (3 in Europe, 3 in Latin America, 1 in Australia).

MATERIALS AND METHODS: Participants initiated CVS use on day 2-5 of their menstrual cycle, followed a 21/7-day in/out schedule of CVS use for up to 13 cycles, and recorded vaginal bleeding in paper diaries. We summarized scheduled (occurring on cycle days 22-28) and unscheduled bleeding/spotting (occurring on cycle days 1 to 21) by 28-day cycles. We performed multiple logistic regression analyses to identify factors associated with unscheduled bleeding/spotting from the first 4 cycles of CVS use. Women could also participate in an endometrial safety sub-study at 5 sites. Three blinded pathologists examined histology of endometrial biopsies obtained at screening, at cycle 6 (first 25 women reaching 6 cycles), and at end of study (cycle 12/13) or early study termination in the remaining women. We excluded women with endometrial hyperplasia or cancer at baseline and evaluated histologic changes in women with both screening and follow-up biopsies.

RESULTS: We analyzed bleeding data from the 2070 of 2308 participants in the two phase 3 studies who had daily bleeding diary data for cycle control analysis. Most women (97.9%) documented scheduled bleeding/spotting (during ring removal days) with a mean of 4.6–5.2 scheduled bleeding/spotting days per cycle. The proportion of women reporting any unscheduled bleeding/spotting occurred in 13.2%-21.7% of women per cycle with a mean of 3.4–5.1 days per cycle for those who had unscheduled bleeding. Absence of scheduled bleeding/spotting was 5%-8% of women per cycle; absence of any bleeding/spotting (complete amenorrhea) was 2.6%-4.9% of women per cycle. A low percentage of women (1.7%) discontinued early due to unacceptable bleeding.

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Of the 156 women in the endometrial safety sub-study, 83 had follow-up biopsies. Pathologists reported no cases of endometrial hyperplasia or carcinoma at cycle 6 (n=24), cycles 12/13 (n=30) or other end of therapy times (n=29). The most frequent histologic diagnoses were atrophic/inactive or secretory; atrophic/inactive (cycle 6: 29%, cycles 12/13: 27%, and other end times: 28%, respectively), secretory (29%, 37%, and 45%, respectively), proliferative (17%, 7%, and 21%, respectively), mixed (17%, 10% and 3%, respectively), menstrual (4%, 7%, and 0%, respectively), or insufficient/no tissue (0%, 10%, and 3%, respectively).

CONCLUSIONS: Women using the SA/EE CVS (FDA approved in August 2018) for up to 13 cycles experienced good cycle control with few bleeding discontinuations, and did not have any unexpected endometrial histology safety findings.

SUPPORT: The Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (NICHD; Contract Number HHSN27500403372) funded and conducted the US study; the US Agency for International Development (USAID; Grant Number GPO-A-00-04-00019-00) funded the international study, which was conducted by the Population Council; the World Health Organization (WHO) Reproductive Health Research Department funded two international study sites.

CRYOPRESERVATION AND FROZEN EMBRYO TRANSFER

O-25 Monday, October 14, 2019 10:45 AM

UNIVERSAL WARMING PROTOCOL" FOR A TRANSNATIONAL EGG DONATION PROGRAM WITH VITRIFIED OOCYTES: A RETROSPECTIVE MULTICENTRE STUDY. Lodovico Lodovico Parmegiani, PhD, Maria Giulia Minasi, M Sc, Alessandra Arnone, M Sc, Valentina Casciani, PhD, Graciela Estela Cognigni, MD, Rita Viñoles, MD, Maria Teresa Varricchio, MD, Luis Alberto Quintero, MD, Ermanno Greco, MD, Marco Filicori, MD, GynePro Medical Centers- Nexct-Clinics International, Bologna, Italy.

OBJECTIVE: We have previously demonstrated that it is possible to warm vitrified human oocytes using a "universal warming protocol" based on subsequent steps with 1M and 0.5 M of ECCP regardless of the warming kit brand; this study investigated the clinical efficiency of this protocol on shipped oocytes in a transnational donor program.

DESIGN: Retrospective multi-center observational study on a cohort of 238 patients enrolled in egg donation programs from 02 March 2017 to 19 September 2018. Primary endpoint was the survival rate (n° oocytes surviving/ n° oocytes warmed). Secondary endpoints were fertilization rate (n° fertilized oocytes / n° injected oocytes), blastulation rate (n°blastocysts obtained / n° fertilized oocytes), implantation rate (n°implanted embryos / n° of transferred embryos) and live birth rate (n° of pregnancies giving births /n° of embryo transfer).

MATERIALS AND METHODS: Donated oocytes vitrified in Spain, warmed in 2 centers in Italy where ICSI and embryo transfer (ET) were performed. Number of oocytes 1898, ET 238. Vitrification with Vitrification Kit (Kitazato, Japan); warming with two different kits: Kitazato Warming Kit and Vit Kit®-Thaw (Irvine-Fujifilm, US). Warmed oocytes assigned to 2 groups: KK (Kitazato/Kitazato) 939, and KI (Kitazato/Irvine-Fujifilm) 959. Vitrification with Cryotop (Kitazato); embryo culture with Embryoscope (Vitrolife, Sweden). ET at blastocyst stage.

RESULTS: Mean age of donors and recipients was comparable. Survival, fertilization, blastulation and implantation rates were all statistically comparable between the study groups. Survival rate was 84.6% (795/939) in group KK vs 82.1% (787/959) in group KI. Fertilization rate was 75.7% (602/795) vs 80.4% (633/787), and blastulation rate 58.5% (352/602) vs 57.8% (366/633). Implantation rate was 38.3 % (80/209) in group KK vs 45.9% (84/183) in group KI. Live birth rate was 52.5% (62/118) in KK and 45.0% (54/120) in KI.

CONCLUSIONS: The proven clinical efficiency of this "universal warming protocol" with ready-to-use warming kits with 1 and 0.5 M of ECCP simplifies vitrified oocyte exchange between AR centers in different countries, overcoming potential regulatory/commercial/availability differences affecting clinical practice.

References: **Parmegiani L**, Tatone C, Cognigni GE, Bernardi S, Troilo E, Arnone A, Maccarini AM, Di Emidio G, Vitti M, Filicori M. warming increases survival of slow-frozen sibling oocytes: a step towards a single warming procedure irrespective of the freezing protocol?Reprod Biomed Online. 2014 May;28(5).

Parmegiani L, Beilby KH, Arnone A, Bernardi S, Maccarini AM, Nardi E, Cognigni GE, Filicori M.Testing the efficacy and efficiency of a single "universal warming protocol" for vitrified human embryos: prospective randomized controlled trial and retrospective longitudinal cohort study.Â J Assist Reprod Genet. 2018 Oct;35(10):1887-1895.

SUPPORT: None.

O-26 Monday, October 14, 2019 11:00 AM

MORPHOLOGY STILL MATTERS WHEN SELECTING EUPLOID EMBRYOS: INNER CELL MASS (ICM) AND TROPHECTODERM (TE) ARE PREDICTIVE OF PREGNANCY OUTCOMES. Sarah Druckenmiller, MD,[a] Nicole Noyes, MD,[b] Megan E. Sutter, PhD,[a] David H. McCulloh, Ph.D.,[c] James A. Grifo, MD, PhD[c] [a]NYU Langone Health, New York, NY; [b]Northwell Health, New York, NY; [c]NYU Langone Prelude Fertility Center, New York, NY.

OBJECTIVE: Morphologic grading of embryos has been an ART standard for nearly 4 decades. More recently, PGT-A has improved embryo selection. Data conflicts regarding whether morphological evaluation improves outcomes of euploid embryo transfers [1, 2, 3]. Our objective was to determine whether morphology is predictive of pregnancy outcomes among single thawed euploid embryo transfers (STEETs).

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: We reviewed all STEETs at a university-based ART center from 2014-2018. STEETs were excluded if oocytes were cryopreserved, embryos were created at another facility, embryos were frozen or biopsied twice, PGT-M or -SR was used, or an oocyte donor or gestational carrier was used. Only the first STEET during the study period that did not meet any exclusion criterion from each patient was included. Embryo morphology was graded according to Gardner [4]. Outcomes included implantation rate of all transfers and live birth (LB) rate, excluding 154 ongoing pregnancies and 28 pregnancies with unknown birth outcomes. Statistical analysis included chi-square, one-way ANOVA, and 2 multivariable log-binomial regression models to determine the association of predictors (age, expansion, ICM, TE) with implantation and LB.

RESULTS: We reviewed 1323 STEETs (mean age 37y; range 24-46y). Overall, implantation was 69% and LB (n=1141) was 55%. ICM and TE were bivariately associated with both implantation and LB ($p<0.01$), but age and expansion were not. ICM significantly predicted implantation, but TE did not. Both ICM and TE independently predicted LB (see Table for adjusted predicted probabilities of implantation and LB based on ICM and TE grades at mean levels of all covariates in the models).

CONCLUSIONS: Ploidy status is not the sole determinant of embryo competence. ICM and TE are strong predictors of LB and can improve selection among euploid embryos. Poor ICM is the greatest negative morphological predictor of implantation and LB. Our model can serve as a counseling tool for patients banking embryos.

Morphological Parameter	Counts	Probability of Implantation (95% CI)	Probability of LB (95% CI)
ICM-A	181	72%(65 – 79%)	57%(50 – 65%)
ICM-B	1088	70%(67 – 72%)	55%(52 – 59%)
ICM-C	54	37%(24 – 51%)	31%(18 – 44%)
TE-a	37	71%(57 – 85%)	67%(51 – 84%)
TE-b	1149	69%(67 – 72%)	56%(52 – 59%)
TE-c	137	59%(50 – 67%)	43%(34 – 52%)
Combined Effect of ICM+TE:	-	-	-
ICM-A + TE-a	23	75%(61 – 89%)	71%(55 – 87%)
ICM-B + TE-a	14	73%(58 – 87%)	68%(52 – 86%)
ICM-A + TE-b	158	73%(66 – 80%)	59%(51 – 67%)
ICM-B + TE-b	950	71%(68 – 74%)	57%(53 – 60%)
ICM-C + TE-b	41	38%(24 – 52%)	32%(18 – 45%)
ICM-B + TE-c	124	60%(51 – 69%)	44%(35 – 53%)
ICM-C + TE-c	13	32%(20 – 44%)	25%(13 – 36%)

No combinations of ICM-A + TE-c or ICM-C + TE-a were present in the sample so these probabilities are not shown.

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