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ARTICLE

Does elevated progesterone on day of oocyte maturation play a role in the racial disparities in IVF outcomes?

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Abstract The aim of this study was to evaluate if premature progesterone elevation on the last day of assisted reproduction technique stimulation contributes to racial disparities. A total of 3289 assisted reproduction technique cycles were evaluated in Latino, Asian, African American, and white women. Live birth was more likely in white women (42.6%) compared with Asian (34.8%) and African American women (36.3%), but was similar to Latino women (40.7%). In all racial groups, progesterone was negatively associated with live birth and the negative effect of progesterone persisted when adjusting for confounders. Although the effect of elevated progesterone was similar in all racial groups, the prevalence of elevated progesterone differed. $P > 1.5$ ng/ml occurred in only 10.6% of cycles in white women compared with 18.0% in Latino and 20.2% in Asian women. $P > 2$ ng/ml occurred in only 2.3% of cycles in white women compared with 6.3% in Latino, 5.9% in Asian and 4.4% in African American women. The increased prevalence of premature elevated progesterone persisted when controlling for IVF stimulation parameters. In conclusion, premature progesterone elevation had a negative effect on live birth in all racial groups studied. The prevalence of elevated progesterone was higher in racial minorities.

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KEYWORDS: ART outcomes, ethnicity, racial disparity, serum progesterone level

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Introduction

Racial disparities in assisted reproductive techniques demonstrate decreased pregnancy and live birth in African American, Asian, and Latino women compared with white women (Bendikson et al., 2005; Butts and Seifer, 2010; Csokmay et al., 2011; Dayal et al., 2009; Dhillon et al., 2015; Fujimoto et al., 2010; Humphries et al., 2015; James et al., 2012; Kan et al., 2015; Nichols et al., 2001; Sharara and McClamrock, 2000). Potential causes for racial disparities with assisted reproduction techniques include uterine leiomyomas, tubal disease, Fragile X gene mutation, obesity, hormonal milieu, access to care, parental consanguinity, vitamin D deficiency and socioeconomic status (Bosdou et al., 2016; Seher et al., 2015). Interestingly, controlling for these potential confounders in assisted reproduction technique outcomes does not ameliorate racial disparities among the outcomes, suggesting other unrecognized causes.

Recently published studies have shown that premature elevated progesterone on the day of ovulation trigger results in lower pregnancies and live births in fresh assisted reproduction technique cycles (Bosch et al., 2010; Hill et al., 2015; Papanikolaou et al., 2009; Xu et al., 2012). This phenomenon is most likely a result of the advancement of the endometrium, leading to embryo–endometrial asynchrony and resulting in failure of implantation (Bosch et al., 2010; Hill et al., 2015). Gene expression studies demonstrate differential expression of global and implantation genes when premature elevated progesterone levels are present (Lahoud et al., 2012; Li et al., 2011). The implementation of cryopreserved embryo transfer cycles may represent a method of ameliorating the effect of elevated progesterone on live birth (Healy et al., 2016).

Premature progesterone elevations may differentially affect races. To our knowledge, premature elevated progesterone has not been explored as a potential factor for racial disparities in assisted reproduction technqiues. Our objective was to assess if premature progesterone elevations were associated with racial disparities in assisted reproduction technique outcomes.

Materials and methods

Study design

This retrospective cohort study was conducted between 2009 and 2013 at Shady Grove Reproductive Science Center. This time frame was chosen as collected, verified live birth data were available at the time this retrospective study was initiated. The study was designed to determine the effect of progesterone on the last day of assisted reproduction technique stimulation and its effect on assisted reproduction technique outcomes in Latino, Asian, African American, and white women. The study was carried out under an exempt IRB protocol at Shady Grove Fertility Center for outcomes analysis of de-identified data collected under routine clinical care, approved by Schulman IRB on 4 March 2016 (IRB reference no. 200912670).

Study population

Inclusion criteria were women undergoing assisted reproduction techniques with fresh autologous embryo transfer. Cycles with donor oocytes, frozen transfers or no embryo transfers were excluded. Preimplantation genetic screening cycles were excluded as they require frozen embryo transfer in our practice. A total of 3289 cycles met inclusion criteria. Patients self-identified race upon enrolment into the clinic. Self-identified races other than Latino, Asian, African American and white women were excluded owing to inadequate numbers for analysis (**Supplemental Figure S1**). All fresh autologous cycles with a progesterone value on the last day of stimulation were included if they were from any of the four identified racial groups.

Stimulation protocol

For ovarian stimulation, mixed FSH and LH (Gonal-F Merck, Kenilworth, NJ, USA, Menopur Ferring USA, Bravelle Ferring, Parsippany, NJ, USA) protocols under GnRH antagonist or GnRH agonist pituitary suppression were used (Hill et al., 2015). The stimulation protocols used Menopur in all patients for LH activity and either Bravelle or Gonal F for additional FSH activity. In general, oral contraceptive pills were started 21 days before stimulation. For antagonist protocols, the antagonist (Ganirelix) was started when the dominant follicle was 14 mm in size. Ovarian stimulation was achieved with mixed protocols using both recombinant FSH and HMG. When the dominant follicle was 18 mm or wider, final oocyte maturation was triggered with 10,000 IU of HCG or 4 mg of GnRH agonist. The GnRH agonist trigger was used in patients clinically determined to be at risk of ovarian hyperstimulation syndrome in a GnRH antagonist cycle. Serum progesterone levels were obtained on day of trigger. Oocyte retrieval occurred 36 h later. Fertilization was achieved with conventional IVF or intracytoplasmic sperm injection as clinically indicated. Sperm was obtained by masturbation or surgical extraction. If three or more high-quality embryos were available on day 3, embryos were placed into extended culture and transferred on day 5. Otherwise, the embryos were transferred on day 3. Embryos were graded as good, fair, or poor according to the simplified Society for Assisted Reproductive Technology scoring system (Heitmann et al., 2013). Luteal support was given generally with vaginal progesterone in HCG trigger cycles or intramuscular progesterone with exogenous oestrogen in GnRH agonist triggers. Serum HCG levels were assessed at 4 weeks' gestational age followed by ultrasonography confirmation of a gestational sac obtained in all pregnant patients.

Hormone assay

Serum progesterone levels were measured using a solid-phase, competitive chemiluminescent enzyme immunoassay (Immulite 2000 Progesterone assay; SiemensMedical Solutions Diagnostic, Malvern, PA, USA). During the study period, no changes in the progesterone assay occurred. The lower limit of detection for the assay was 0.2 ng/ml, and the analytical sensitivity of the assay was 0.1 ng/ml. The

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