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COMMENTARY

A 2019 reproductive update from the Midwest Reproductive Symposium International

Jessica R. Zolton[1] · Gretchen G. Collins[2] · Eleni A. Greenwood[3] · Elie Hobeika[4] · Roohi Jeelani[5] · Angeline Beltsos[5] · William G. Kearns[6]

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Abstract

"Mystery, Medicine, and the Magnificent Mile," the theme for the annual Midwest Reproductive Symposium International (MRSi) in Chicago, IL, captured the attention of reproductive professionals all over the world. Each year, the conference agenda encompasses emerging technologies in assisted reproduction, updates in the management of reproductive diseases, and common challenges encountered in clinical practice. The structure of the meeting, offering a mixture of lectures, panel discussions, and interactive workshops, creates a collaborative environment for physicians, geneticists, embryologists, nurses, mental health professionals, basic scientists, business administrative professionals, reproductive endocrinology and infertility fellows, and obstetrics and gynecology residents. The goal of the MRSi meeting is to provide all reproductive professionals the opportunity to exchange ideas, foster relationships, and deliver quality patient care. As the field continues to evolve, MRSi provides an exciting venue to uncover the mysteries of reproductive medicine with enthusiasm and collaboration.

Keywords infertility · genetics · reproductive endocrinology · continuing medical education · medical conference

The Midwest Reproductive Symposium International (MRSi) was established in 2003 with the goal of bringing together professionals with a variety of roles in the fertility world to discuss current reproductive technology and best practices. The theme of this year's meeting in Chicago was "Mystery, Medicine, and the Magnificent Mile," which captured the over-reaching message of the meeting; research has uncovered clues to many processes of reproduction, but we have yet to crack the code. World-renowned experts presented topics that continue to challenge our field, such as endometrial receptivity, mosaic embryos, and ovarian aging. While the conference provides traditional plenary lectures in the morning, panel discussions and interactive workshops create an ideal opportunity for participants to network with other professionals. The opportunity to collaborate with

✉ Jessica R. Zolton
jessica.zolton@nih.gov

Gretchen G. Collins
gg.garbe@gmail.com

Eleni A. Greenwood
Eleni.Greenwood@ucsf.edu

Elie Hobeika
elie.hobeika@integramed.com

Roohi Jeelani
Roohi.Jeelani@viosfertility.com

Angeline Beltsos
Angie.Beltsos@viosfertility.com

William G. Kearns
wgkearns@advagenix.com

[1] Program in Reproductive Endocrinology and Gynecology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 10 Center Drive, Bldg 10; Room 8N248B, MSC 1840 Bethesda MD 20892 USA

[2] Wisconsin Fertility Institute, Middleton WI USA

[3] Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco CA USA

[4] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Illinois College of Medicine, Chicago IL USA

[5] Vios Fertility Institute, Chicago IL USA

[6] Advagenix, Rockville, MD, Department of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Johns Hopkins University School of Medicine, Baltimore MD USA

reproductive professionals that include physicians, embryologists, geneticists, nurses, allied health professionals, mental health professionals, business administration professionals, Reproductive Endocrinology and Infertility (REI) fellows, and Obstetrics and Gynecology (OBGYN) residents is unique to MRSi and is central to its mission to engage all who are dedicated to the advancement of reproductive medicine.

This year's conference began with a fascinating presentation by Prof. Dr. Thomas Hildebrandt, a pioneer in the field of animal in vitro fertilization (IVF). Challenged with rescuing endangered species across the globe, Dr. Hildebrandt discussed the similarities and differences between animal and human IVF. The complexity of sperm and egg extraction in mammals such as elephants and rhinoceros requires ingenuity and teamwork due to the massive size of these animals. Techniques common to human IVF are modified for use in these large animals, such as the adoption of transrectal ultrasound-guided follicle aspiration in order to reach the ovaries. The development of gametes from embryonic stem cells is also of interest to recover endangered species and, in the case of the northern white rhino, is necessary for their survival. Hopefully, future developments in assisted reproductive technologies (ART) will enrich reproduction in both animals and humans. This topic is important for all, as it is unknown what effect the loss of species may have on our environment, ecology, and the human species. This common theme of the environment and identification of proactive initiatives to enhance reproductive health was present throughout the meeting. Dr. Lora Shahine presented data regarding the associations of bisphenol A (BPA) and phthalates and reduced reproductive potential. Both are common chemicals as 93% of Americans have BPA in their urine [1] and 95% of pregnant women have phthalates in their urine [2]. Higher levels of BPA are associated with lower estrogen levels, lower egg yield, lower fertilization rate, lower blastocyst formation rate, and lower implantation rate [3] and higher levels of phthalates are associated with lower egg yield and lower clinical pregnancy and live birth rates [4]. While more studies are needed to identify the impact of environmental toxins, it is important to educate patients about potential risks prior to pregnancy and methods to limit exposures.

Dr. Kazuhiro Kawamura presented his fascinating research on ovarian activation as a treatment for premature ovarian insufficiency (POI). His work focuses on activating residual dormant follicles in patients with POI by disruption of the Hippo signaling pathway, which regulates follicular growth. His research has resulted in two live births thus far [5]. Although more research in this area is required, his results are encouraging for patients with either POI or advanced reproductive age. Dr. Jani Jensen provided insight into current options for patients with diminished ovarian reserve (DOR). The data does not identify a superior protocol for poor responders, as similar pregnancy rates are obtained with conventional and mild ovarian stimulation protocols. Mild stimulation protocols are less costly, which should be considered when treating patients with DOR [6]. The discussion also included the commonly utilized, but controversial, growth hormone (GH) for poor responders. Data is conflicting, as one study utilizing GH during controlled ovarian hyperstimulation (COH) found an increase in the number of oocytes and embryos although there were no differences in implantation, pregnancy rate, or miscarriage [7]. A 2017 meta-analysis concluded that GH significantly improved clinical pregnancy and live birth rates [8]. The controversy of GH will continue, as the medication is not approved by the US Food and Drug Administration (FDA) as an adjuvant therapy for IVF. Next, Dr. Kara Ehlers highlighted fertility management for women with polycystic ovarian syndrome (PCOS). She presented the 2018 international evidence-based guideline for the assessment and management of PCOS [9] and discussed the recent article by Mejia et al. using the combination of letrozole and clomiphene citrate (CC) for the treatment of women with PCOS who are resistant to ovulation induction. While the study was not powered to detect differences in pregnancy rates, it did report a higher rate of ovulation (77% vs 43%) in women treated with combination therapy, which will hopefully encourage a larger randomized controlled trial (RCT) to evaluate live birth outcomes [10]. The sessions on stimulation protocols in special populations clearly highlighted the importance of individualized care. It is important that patients are adequately counseled and have realistic expectations. Hopefully, future research will provide more treatment options for patients at risk of poor response or treatment failure.

Ever-expanding utilization of preimplantation genetic testing for aneuploidy (PGT-A) has led to the controversies surrounding the detection of mosaic embryos. The challenges encountered with the reporting of mosaic embryos were highlighted by Dr. Amber Cooper and Dr. William Kearns. An emphasis that the detection of mosaicism differs depending on the testing platforms used creates a level of uncertainty in the diagnosis. The birth of healthy babies from mosaic embryos presents the question of whether we are erroneously discarding otherwise normal embryos. The complexity of the situation requires the input of genetic counselors or medical geneticists. Dr. Eric Forman discussed how important it is to balance the risks of transferring a mosaic embryo in absence of a euploid embryo and potentially prioritizing different types of mosaic embryos. The challenge exists when only a single mosaic embryo is available for transfer. Patients may not have the chance to undergo another IVF cycle. For some, deciding to transfer a mosaic embryo is their only option for a baby. The discussion of mosaic embryos will continue as technology continues to evolve and larger studies are performed analyzing specific mosaic embryos and outcomes of live birth and neonatal health.

Research is emerging that recurrent implantation failure (RIF) patients may suffer from a viral uterine infection. Dr.

Kevin Doody presented evidence that infection of the endometrium with human herpes virus 6 (HHV-6) may be a hidden contributor to infertility. A study reported a 37% prevalence of HHV-6 in a cohort of women with RIF compared with 0% in the fertile control based on endometrial biopsy [11]. It is proposed that the infection may alter natural killer (NK) cells, impairing implantation. No studies have been performed assessing whether treatment of HHV-6 improves fertility. RIF is a subject that continues to perplex physicians as does the optimal regimen of the endometrium for frozen embryo transfer (FET). Dr. Kate Devine discussed the current literature on luteal support in programmed FET cycles, including the results of her recently published RCT, which was awarded a prize paper at the American Society for Reproductive Medicine (ASRM) 2019 Society Congress and Expo. The study reported a higher ongoing pregnancy rate in patients randomized to a protocol utilizing intramuscular progesterone compared with vaginal progesterone only [12]. This data enriches our knowledge regarding management of FET cycles, but future research is needed to determine the optimal timing and duration of progesterone replacement in FET cycles. Hopefully, as our knowledge of the endometrium continues to expand, pregnancy rates will increase and less patients will be diagnosed with RIF.

Reproductive medicine is complex, and it can be challenging for patients in search for information. Dr. Natalie Crawford shared with the audience how she has harnessed social media to educate and attract infertility patients. It is important for medicine professionals to provide accessible health information on social media platforms. Otherwise, patients are exposed to false information, which may result in delayed care or poorly informed decisions.

The conference also provided a platform for young investigators to share their research, providing a glimpse into the future directions of the field. Dr. Luis Hoyos, REI fellow, presented his prized oral abstract "Euploid rates among age subgroups of young oocyte donors." The prior evening, a poster session during the "Moonlight Mystery Masquerade" featured an array of research topics by REI fellows, OBGYN residents, and industry partners. To close out the conference, a live Fertility and Sterility Journal Club, hosted by Dr. Micah Hill, featured experts from the MRSi conference, where they discussed and debated "The association of assisted reproductive techniques and epigenetics: Is it clinically relevant?" It is a complex topic that relies on large retrospective studies which limits interpretation of the data. In addition, the effects of epigenetic modifications are largely unknown. Future studies are warranted to determine epigenetic changes that result from ART. Currently, experts on both sides of the discussion agreed that there is insufficient evidence to confirm that epigenetic changes during ART pose a risk to children conceived by IVF.

The future of reproductive surgeons is a continuing debate. Dr. Grace Janik presented a broad review of the most commonly performed reproductive procedures, suggesting that reproductive surgery is best performed by REIs as they are motivated to adopt approaches that reduce adhesion formation and minimize loss of ovarian tissue. Techniques to improve surgical efficiency and decrease morbidity were discussed and the implementation of minimally invasive approaches, when possible, was recommended. She concluded by noting the deficit in surgical training of graduating specialists in REI, highlighting the need to implement robust surgical training curriculums in order to optimize care for infertile couples. A recently created 1-year fellowship offered by the Society of Reproductive Surgeons (SRS) provides an additional opportunity for REI physicians to achieve the surgical expertise necessary for complex gynecologic pathologies. With continued interest and investment in surgical education, REI physicians will continue to serve as leaders in the field of reproductive surgery.

MRSi provides participants the opportunity to select small break-out sessions of interest. While plenary lectures bring everyone together at the start of each day, separate sessions were created to identify the unique goals and challenges of specific reproductive care specialists. Topics that were geared towards nursing specialists included optimizing treatments for over-responders and advanced ovarian aging, management of sperm and egg donors, and key facts of fertility preservation. The business professionals' sessions focused on why patients leave a practice and how to retain them, reducing patient anxiety, best hiring practices, sharing clinical responsibilities, and balancing treatments with different religious views. Lectures on mental health for the fertility patient included how to manage guilt and loss when terminating a pregnancy, how to deliver news of an unsuccessful cycle, and challenges unique to same-sex couples becoming parents. The REI fellows had excellent discussions on applying for jobs and negotiating contracts, managing difficult patient populations, creating work-life harmony, and transitioning from the role of fellow to attending. The break-out sessions encouraged discussion, as an exchange of ideas and experience is central to the goal of MRSi.

Knowledge of reproductive biology is constantly evolving, corresponding to the adoption of new guidelines for the treatment of infertility and reproductive diseases. Reproductive medicine is a unique field of medicine, where technological advances are quickly applied into daily practice. It is very important that practitioners stay current and practice evidence-based medicine. MRSi provides an excellent opportunity for continuing medical education, networking, and collaboration with similar-minded individuals in other parts of the world.

Compliance with ethical standards

Disclaimer The views expressed in this manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.

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