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“Going hybrid - a return to normal with a virtual twist” - the 38th annual ESHRE meeting was held at the beginning of July in Milan. Being the first in-person meeting since Vienna in 2019, the prospect of socializing with a gelato was almost as exciting as the science in the program. Virtual attendance was also available, and content can still be accessed by attendees via a user-friendly and easy to navigate platform on the ESHRE website.

This year saw a strong emphasis on the identification of potential targets for improved diagnostics, therapies, and interventions. From sperm preparation to embryo selection and embryo transfer, we learned about promising new strategies with potential to improve clinical outcomes.

Andrology

Sperm preparation methods have remained unchanged for years, but the meeting presented a lot of data on improving embryology and clinical outcomes by improving the quality of the sperm isolated. Many of these presentations were based on microfluidics (Meseguer F *et al* P-028, Berton CZ *et al* P-120, Brahmhatt N *et al* P-059, Vasilescu S *et al* P-084, Pardinias ML *et al* P-082, Wheldon K *et al* O-295, Tsuji H *et al* P-048). Leung T *et al* (P-117) successfully used electrophoretic sperm sorting while Polese R *et al* (P-009) employed chemotaxis via a horizontal progesterone gradient.

Many employed these newer methodologies with an aim to improving outcomes in cases with high sperm DNA fragmentation, comparing microfluidics, magnetic activated sperm sorting (MACS) and PICSI, against traditional methods and the use of testicular sperm (Mantravadi KC *et al* P-006, Rayapati RS *et al* O-298, Korshunov M *et al* P-096). Promising data was presented in terms of higher clinical pregnancy rates (CPR) and lower miscarriage rates (MR).

Kirkman-Brown J (pcc22-004) presented data illustrating the relationship between sperm DNA fragmentation and miscarriage risk, including a note of caution on the differences between diagnostic tests and potential issues when used interchangeably. Presenting data from the HABselect study (Miller D *et al* 2019, West R *et al* 2022), he concluded that physiological ICSI works as well, or better, than routine ICSI. He highlighted a clear reduction in miscarriage and that this selection of sperm is likely to be even more important in older women. More data can be expected as the study is expanded to include cumulative data. Nakano S *et al* (P-215) also selected sperm by exploiting the hyaluronan binding capabilities of mature sperm, using a hyaluronan containing alternative to PVP, resulting in lower degeneration rates, higher blastulation rates, more good quality blastocysts, and lower MR in the hyaluronan group. Another alternative approach was presented by Ribeiro M *et al* (P-010), who presented encouraging retrospective data using birefringence as a marker of sperm quality at selection for injection in ICSI.

Microbiomes were targeted as a diagnostic and therapeutic marker in many different settings, and Panacheva E *et al* (P-097)

demonstrated a difference between samples displaying normal and abnormal semen analysis parameters. A prospective case-control study from Farahani L *et al* (O-252) suggested interactions between microbiota composition, reactive oxygen species (ROS) and sperm DNA damage which may be implicated in the pathogenesis of recurrent pregnancy loss (RPL). Their next steps are to determine if seminal microbiota play causal roles in RPL, and whether interventions modifying the seminal microbiome may modify pregnancy outcomes in affected couples.

Embryology

Many oral and poster presentations examined embryo morphokinetics, connecting specific developmental time points with success or failure following embryo transfer. However, disparities remain between centers and algorithms. Kieslinger DC *et al* (O-003) were awarded The Fertility Society of Australia Exchange Award for their RCT, the SelectTIMO study. Their study concluded that uninterrupted embryo culture with or without a time-lapse selection algorithm and interrupted culture with morphological embryo selection all resulted in comparable cumulative ongoing pregnancy rates. An interesting addition to timelapse and morphokinetics came from He P *et al* (O-177) who were able to standardize focal stack data and generate 3-D embryo images of cleavage stage embryos. Could 3-D timelapse images be the future? Another exciting potential application is the ability to use patient's embryos in studies on embryo structure, including cell tracking, without the need for invasive interventions.

A novel approach to embryo selection was suggested by Albanese C *et al* (O-074) who used the presence or absence of amplifiable DNA in the blastocoele fluid to prioritize embryos for transfer. Statistically significant higher ongoing pregnancy rates were seen where there was failed DNA amplification.

Mol BW *et al* (O-008) contributed to data on use of low-grade blastocysts, confirming they result in lower live birth rates than high grade blastocysts, but still have a good chance of a healthy live birth. Importantly, these pregnancies and obstetric outcomes were the same as those resulting from good quality blastocysts. Gomez Pena M *et al* (O-077) added to the body of data on the utility of genetically confirming fertilization status, with ongoing pregnancies and livebirths resulting from the transfer of OPN confirmed euploid/diploid following testing.

Vitrification

A number of studies examined the efficacy and effectiveness of universal warming procedures for oocytes and embryos (Troncoso-Perez P *et al* O-205, Salimov D *et al* P-140, Lafontaine M *et al* P-150) with all showing equivalency in CPR across the warming media used.

Okabe-Kinoshita M (P-395) utilized GM-CSF containing media for poor grade blastocysts post warming, and demonstrated an increased CPR and LBR, while K. Ezoë (O-064) demonstrated the addition of prolactin to media at this stage improved trophoblast migration.

Oraiopoulou C *et al* (O-065) investigated the impact of double vitrification and concluded it to have a negative impact on implantation, which could be reduced by culturing embryos for 24hrs prior to the second vitrification procedure. However, a similar study from Makieva S *et al* (P-255) demonstrated equivalent CPR across single and double vitrified embryos, although unfortunately timings of the procedures were not given for insight into this difference.

The endometrium and sustained implantation

The microbiome was investigated in relation to both recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL). Sola-Leyva A (P-431) showed that women with RIF have different functionally active microbiota in the receptive-phase endometria that are involved in distinct metabolic pathways when compared to their control group. Liu F (O-304) identified an altered microbial biodiversity in the vagina, cervix, and uterine lavage fluid in the women with RPL, while Peuranpää P *et al* (O-303) demonstrated reduced relative abundance of *Lactobacillus crispatus* in endometrium and increased relative abundance of *Gardnerella vaginalis* in endometrium and vagina were associated with RPL. Nabeta M *et al* (O-256) detected a higher abundance of *Lactobacillus* in the endometrial fluid of patients with successful pregnancy after frozen embryo transfer. Applying diagnostic microbiome information, while Iwami N *et al* (P-384) demonstrated improved clinical outcomes in patients diagnosed with endometrial dysbiosis after recommended treatment with antimicrobial and probiotic therapy, Bamford T *et al* (P-350) did not. In alternative applications, Hill C *et al* (O-258) discussed the contribution of the vaginal microbiome to the metabolome and showed that the vaginal metabolome can be predictive of live normally sited pregnancies.

Exploring other targets and technologies, Ibañez Perez J *et al* (O-259) used free and extracellular vesicle-associated microRNAs, isolated from endometrial fluid, as non-invasive tools for the detection of endometrial receptivity. Loid M *et al* (P-322) were awarded the Basic Science Award (for poster presentation) for their work demonstrating that the endometrial transcriptome of women of advanced maternal age is significantly different from younger women. Understanding these alterations has the potential to help to improve infertility management in women of advanced reproductive age. Li TC (O-224) presented work indicating cytokines are promising immune markers of implantation, with IFN gamma and IL-17 levels significantly lower from three days after ET in those that conceive, and TGF beta 1 and IL-10 significantly increased.

Scracia M *et al* (O-022) employed subcutaneous GM-CSF in RIF patients resulting in a non-significant increase in the ongoing pregnancy rate. Dzhincharadze L *et al* (P-362) compared intrauterine G-CSF with intrauterine platelet-rich plasma (PRP) with the aim to improve endometrial thickness and clinical outcomes in the same patient group and saw both groups perform significantly better than controls. Jindal PC *et al* (O-026) also investigated administration of intrauterine G-CSF and achieved significantly better IR and CPR than the control group. Importantly, they observed that optimal endometrial thickening was reached approximately 48 -72 hours after G-CSF administration. Gedela DR (O-023) examined the impact of flushing the uterus with hCG but did not achieve increases in IR or CPR. Saravanan M (P-418) demonstrated subendometrial injection of PRP resulted in a statistically significant increase in mean endometrial thickness and vascularity.

Preimplantation genetic testing and mosaicism

There were multiple presentations reporting data on the transfer of mosaic embryos and their positive utility in patient treatment (Fernandez Sanguino A *et al* P-194, Teng ZX *et al* P-518, Pozzoni M *et al* P-786). The largest and most comprehensive data set was presented by Viotti M (O-278). He shared data from an international multicenter consortium, consisting of 1700+ mosaic

embryo transfers, neonate information on 500+ babies born, and 380+ associated prenatal test results. The data demonstrated that mosaic embryos have a lower chance to establish a pregnancy and a higher miscarriage rate (MR) compared to euploid embryos. The percentage of aneuploid cells/level of mosaicism and the type of aneuploidy was shown to impact the clinical outcome, allowing prioritization or ranking by clinics. Reassuringly, apart from a small number of case studies, the data reveals that late-term pregnancies and babies from mosaic and euploid embryos have largely equivalent health.

De Ryke M (O-042) reported on the progress the ESHRE working group established to develop good practice recommendations on managing chromosomal mosaicism in clinical practice. The recommendations have been formulated using the expert opinion of the working group, published data, and outcomes of a survey on current practices in 239 PGT laboratories and ART clinics, mostly within Europe, Asia, and America. The recommendations will cover genetic counselling, technical validation, reporting thresholds and terminology, and embryo transfer policies. They hope to finish and publish the recommendations in 2022.

We still need to talk about Covid

There were a number of high-quality studies and reviews of the risk and impact of COVID-19 in assisted reproduction and pregnancy (Veiga A O-053, Viotti M O-050, Gacci M O-001, Arck P *et al* O-054, Nelson S O-049). Impairment of sperm quality is recognized during the acute and recovery phase of infection (Veiga A O-053, Gacci M O-001, Nelson S O-049), as well as persistence of a genital tract inflammatory condition for at least 3 months after COVID-19 recovery (Gacci M O-001). Neither the ovarian response nor the sperm quality is affected by the administration of COVID-19 vaccines, which are highly recommended in couples planning a pregnancy, either spontaneous or through ART (Veiga A O-053). Vaccines also do not affect fertility rates or birth outcomes (Avraham S *et al* P-710, Bhaduri M *et al* P-288, Anis Heusler A *et al* O-142) – there is no negative impact of vaccination on pregnancy, and it decreases stillbirth by 15%. (Nelson S O-049). It was also demonstrated that the proportion of euploid embryos was unaffected by vaccination (Garrido Puchalt N *et al* O-138).

COVID-19 can be transmitted horizontally and vertically, with approximately a 2-3% risk of transplacental transmission during the third trimester of pregnancy, increasing the risk of pre-term birth and morbidity in the neonate (Viotti M O-050, Arck P *et al* O-054, van Baar *et al* O-139). However, disagreement remains on the risk of miscarriage.

Copenhagen 2023

Next year sees us in Copenhagen, Denmark, where we had planned to meet in 2020. The home of hygge, Hans Christian Andersen, and the very tasty Danish pastry. We look forward to seeing you all there!

