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While many delegates outside the US had to contribute and attend via the virtual platform rather than in person, the volume and quality of data indicate we've all been keeping ourselves busy throughout lockdowns, with many high-quality presentations of retrospective clinic and registry data.

Developments in Female Fertility Preservation and Extension

The boldly titled ESHRE symposium "Reproduction has defeated cancer" (SYT-02) included detailed overviews of:

- Multidisciplinary approaches to cancer in pregnancy
- Fertility preservation in adolescent and young adults with cancer
- Fertility sparing strategies in women with endometrial cancer

Fertility preservation in both oncologic and non-oncologic female patients was examined in terms of existing, new, and future interventions for patients.

Ovarian tissue cryopreservation is an approach to fertility preservation in pre-pubescent females. Wasserzug Pash (O-218) addressed the issue that this patient group subsequently suffers from low rates of oocyte maturation and high rates of abnormal *in vitro* maturation. They showed this to be associated with reduced levels of heterochromatin, with maturation rates and normal *in vitro* maturation increased by incorporating the heterochromatin enhancer Curcumin.

Oktay and Marin (O-159) compared orthotopic and heterotopic autologous cryopreserved ovarian tissue transplantation outcomes. Both approaches show a similar resumption of endocrine function, but orthotopic transplantation resulted in higher fertilization rates, higher numbers of viable embryos, and higher live birth rates. They conclude, therefore, that orthotopic transplantation should be favored in patients wishing to conceive and opposed to solely resuming ovarian endocrine function.

Kirillova (O-6) examined the efficacy of ovarian tissue oocyte *in vitro* maturation for fertility preservation in patients with gynecological cancers, making them unsuitable candidates for ovarian stimulation or ovarian tissue cryopreservation procedures. AMH predicted the oocyte number, but not the maturation rate. Fertilization rates, blastulation rates and euploid PGT-A results suggest this approach enables safe fertility preservation in this patient group.

Petrikovsy (O-20) presented long-term follow-up from a study examining whether harvesting ovarian tissue impacts the age of menopause, concluding that removal of 20% of one ovary neither causes primary ovarian insufficiency or early menopause.

Platelet-rich plasma (PRP) is being utilized in a number of ways in attempts to retard or reverse reproductive aging and preserve female fertility. Cozzolino (O-49) did not find intra-ovarian PRP to be effective in treating primary ovarian insufficiency in knockout mice models with mitochondrial dysfunction. However, the same group concluded it may be useful for ovarian activation in primary ovarian insufficiency in mice models created via injections of chemotherapeutic agents. Cakiroglu (O-245) targeted the endometrium and concluded PRP could improve endometrial thickness and sustained implantation rates.

A future potential approach to fertility preservation under current study is *in vitro* gametogenesis. Clark (PLE-03) gave a thorough overview of important considerations in this area. While it has proven successful in laboratory animals, it is not ready for human reproductive purposes. However, research in this area is contributing to a better understanding of the molecular basis of gametogenesis and reproductive pathologies. Greely (PLE-04) estimates 5-15 years of safety data is required before clinical application and believes it may profoundly change access to and application of ART.

Male factor fertility in the IVF lab

The impact of the SARS-CoV-2 virus on sperm quality and male fertility remains a subject of many studies to improve clarity of the risks. Unfortunately, there is still no consensus. Antonelli (O-215) indicated no clear impact on sperm quality excluding temporary decline in symptomatic males with febrile illness inevitably leads to transient reduction. Khalafalla (P-450) demonstrated symptomatic men also show reduced testosterone levels. Penrose (O-154) suggested effects on semen parameters and IUI outcomes might be linked to at-home production rather than infection. Parikh (P-451) demonstrated a molecular effect of COVID-19 infection, by means of downregulation of fertility-related proteins with the potential for impact on sperm-egg recognition and male reproductive processes. Reassuringly, Gonzalez (P-453) reported no impact on semen profiles following COVID-19 mRNA vaccination.

Iwamoto (O-37) provided a thorough retrospective analysis of SART data, comparing the use of IVF versus ICSI in non-male factor infertility, reporting a reduction in the cumulative live birth rate when ICSI is used unnecessarily in non-male factor cases. Several studies followed which focused on optimizing ICSI via improved sperm selection. Hasanen (P-409) suggested that using a second ejaculate (so minimizing abstinence) may have the same impact (by reducing %DNA-damaged sperm) as selecting the single sperm with PICSI but the study used only younger women which may have masked the full benefit of reduced miscarriage (as reported by the large HABSelect study[1]); the same group (P-415) did show however that use of PICSI normalized results across all samples regardless of initial level of DNA damaged sperm. Ito (P-423) applied SpermSlow and IMSI in combination, reporting an improvement in the number of useable blastocysts, higher pregnancy rates, and higher live birth rates.

An alternative strategy was presented by Elmagd (O-11), where immature oocytes were inseminated via IVF and zona-bound sperm were removed and used in ICSI. While this physiological test did not improve fertilization or blastocyst formation rates, improved blastocyst quality was reported.

A new approach to sperm cryopreservation was presented by Morris (O-152), describing a novel mail-in cryopreservation system. Declines in motility and motile counts were observed compared with in-site production and freeze, indicating refinements required in the system, but the service has the potential to improve access to patients. Cryopreservation of sperm has remained largely unchanged despite the adoption of vitrification for oocytes, zygotes and embryos. Tanaka (O-274), however, described a vitrification method for low numbers of sperm collected in micro-TESE cases. Good clinical results were reported and repeat surgery was avoided for patients.

PGT in the IVF lab and clinical decision making

While the efficacy of PGT-A is very often a topic for heated discussion, less attention is often paid to how much data variations may be due to embryology and clinical practice and decision making. This year's program certainly redressed this, with extensive content examining laboratory practice and clinical factors.

Touzour (O-81) retrospectively examined SART data for non-male factor PGT-A cycles, questioning guidance for ICSI in these cycles. They found no significant differences in the number of embryos biopsied, embryos suitable for transfer, or pregnancy outcomes between IVF and ICSI cycles. Sub-group analyses for advanced maternal age and low egg numbers gave the same results. Very similar data was presented by Wang (P-73). Yoder (P-128) examined the same question but instead looked at the potential for sperm DNA contamination of trophectoderm samples for analysis. Presenting a 0% rate of paternal cell contamination, they concluded ICSI was not necessary for PGT-A cycles in the absence of male factor infertility.

With respect to cycles where male factor was present, Ghatnekar (O-239) demonstrated statistically significant higher aneuploidy rates in PGT-A cycles where the male partner had teratozoospermia. However, encouragingly, Alkon (O-151) presented data indicating elevated sperm DNA fragmentation does not result in increased pregnancy loss rates when PGT-A has been employed to identify and transfer a euploid embryo. Keating (P-53) suggested the use of microfluidic sperm selection, as opposed to density gradient centrifugation, could increase fertilization rates, euploidy rates, and implantation rates, via the reduction of double-stranded DNA breaks present in the prepared sample.

Wozniak (O-7) built on existing data examining the genetic viability of blastocysts derived from 0PN and 1PN embryos. The first step is to confirm developmental competence by the formation of good quality blastocysts. Blastocysts can then undergo trophectoderm biopsy and genetic testing for aneuploidy status and confirmation of diploidy/bi-parental inheritance. The work adds to a growing body of evidence that viable embryos are missed via standard visual PN checking, but in this case, still required two separate genetic assays to be run. Shaw (P-54) similarly demonstrated 1PN zygotes can progress to usable blastocysts with normal ploidy, but also noted they may take longer to develop and with overall lower blastocyst formation. Henry (P-129) demonstrated the clinical utility of 0PN blastocysts but found the majority of 1PNs and 3PNs to be haploid and triploid respectively. Yoder (P-146) concentrated solely on 3PN derived blastocysts, and found a small percentage to be diploid, but did not identify any which were euploid in this specific study.

Purusothaman (O-240) examined the growing demand for PGT-A of vitrified blastocysts from previous standard cycles. It was demonstrated that euploidy rates and pregnancy rates were equivalent to when biopsy and analysis were performed on fresh blastocysts, indicating no detrimental impact of the additional vitrification event.

Katz-Jaffe (P-172) demonstrated an adverse impact on implantation rates and livebirth rates following transfer of a euploid blastocyst, with increasing cell numbers taken at biopsy. Reassuringly though, Kim (P-429) demonstrated that neonatal outcomes are not impacted by a second biopsy, even if there is evidence that implantation potential has been reduced. Anderson (P-203) compared laser and mechanical biopsy techniques, with both proving effective and neither showing any detriment to the parameters monitored in comparison to the other. Data from biopsy following extended culture to both day 7 (Walter, P-695) and day 8 (Stanhise, P-408) was also presented.

Aharon (O-19) presented an in-house designed algorithm to aid patient planning in repeat PGT cycles. Using baseline, embryo, and transfer cycle characteristics, they could calculate a value for the patient as to how likely they were to have a livebirth, two livebirths, or more, thus helping patients decide whether to proceed with repeat cycles with the aim of increasing their number of banked euploid embryos to achieve their family planning goals. It was acknowledged that the probabilities calculated may vary by clinic.

Conclusion

As we all begin venturing out in the world again, hopefully, we can keep up the high quality of data and research that has been undertaken in the last 12-24 months. ASRM has a lot to live up to in terms of clinical data and retrospective analyses that we can all use to examine our own practice and improve patient care. Fingers crossed we'll all meet in Anaheim in 2022.

References

1. D Miller Lancet 2019;393(10170):416-422