



Congress Review

Review of the European Society of Human Reproduction and Embryology (ESHRE) virtual 36th Annual Meeting 2020

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DISTANCE and disease were no barrier to this year's annual meeting of the European Society of Human Reproduction and Embryology (ESHRE), their first to be held entirely online. The ESHRE virtual 36th Annual Meeting 2020 saw 12,389 clinicians, embryologists, and researchers come together online to share in the latest research, expert insights, and 'coffee room' discussions of reproductive and fertility medicine.

The canals of Copenhagen, Denmark, were a sorely-missed backdrop to the global meeting, and attendees missed the chance to stroll the picturesque harbourfront Nyhavn, take in the beauty of the home city of Hans Christian Andersen, or appreciate the wonder of the world's most environmentally friendly city. But participants of ESHRE 2020 built a new online community, celebrating their time together in virtual chat rooms, across social media, and by taking part in the annual ESHRE Fun Run from their own homes. In

her opening welcome, Prof Christina Magli, Chair of ESHRE, highlighted the importance of these varied congress activities "to feel the sense of community that is so typical of ESHRE events."

Insights shared at the congress were an engaging split between clinical and basic science, but sessions highlighted the overlap of the two aspects of reproductive medicine and the focus on improving patient care. Participants shared in journal clubs, poster presentations, and virtual 'coffee room' discussions, alongside >260 oral presentations by expert speakers across 74 sessions.

Prof Magli opened the congress with a welcome address and outlined the timeline of decisions and actions undertaken by ESHRE to help address the ongoing COVID-19 pandemic. She highlighted the formation of the ESHRE COVID-19 Working Group, collating data on the impact of the disease on pregnancies and provision of care in reproductive medicine, and invited



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all congress participants and ESHRE members to contribute to this global dataset. This cooperative spirit was embodied throughout the congress, where presentations demonstrated collaboration between countries and across disciplines in the name of scientific understanding and improved patient care.

Over 1,800 abstracts were submitted to ESHRE this year, showcasing the wide array of ongoing research in fertility and reproductive medicine. Amongst the hundreds of included studies was research analysing Nordic birth registries to determine whether cerebral palsy risk has changed over the past 20 years as a result of using *in vitro* fertilisation treatment, alongside a large-scale, randomised UK trial assessing the impact of endometrial scratch procedures on embryo implantation rates in *in vitro* fertilisation, as well as a summary of the first long-term study to share the success of fertility preservation techniques for helping women to conceive following fertility-affecting cancer treatments.

The virtual congress format provided many engaging presentations, with chat functions allowing audience interaction and the opportunity for participants to up-vote their preferred questions for presenters to address live. One fascinating, important session addressed the question of whether stress contributes to infertility, with >500 people attending to hear Prof Jacky Boivin, Cardiff University, Cardiff, UK, and Dr Angela Lawson, Northwestern University, Evanston, Illinois, USA, provide scientific evidence bases for the two competing arguments.

The impressive programme was honoured with the annual prizes awarded to standout presentations. The Basic Science Award for oral presentation was awarded to Dr Chih-Jen Lin, University of Edinburgh Centre for Reproductive Health, Edinburgh, UK, for his research on the histone variant H3.3 chaperone complex HIRA, while the Clinical Science Award for oral presentation was presented to Hugh Taylor, Yale School of Medicine, New Haven, Connecticut, USA, for his presentation of a Phase III trial of linzagolix on heavy menstrual bleeding caused by uterine fibroids. The work of Alexandra Claire Benoit, Antoine Bécclère University Hospital, Clamart, France, was celebrated when her presentation, discussing a web-based patient decision aid of fertility preservation for women with breast cancer, received the Nurses Award for best oral presentation by a nurse.

The work of all clinicians, researchers, and scientists was celebrated at ESHRE 2020 through the Humans of ESHRE 2020 campaign. Providing insight into the experiences of 10 ESHRE members in the setting of the COVID-19 pandemic, this humanising initiative upheld the community atmosphere of the ESHRE event itself. In her Humans of ESHRE 2020 profile, Prof Magli commented on this spirit: "A connection through the cyberspace will not undermine our capacity of communication, because this is what ESHRE is, a big community where everybody wants to learn, to exchange experiences and to network in that spirit of sharing that is typical of us, the people of ESHRE."

ESHRE 2020 REVIEWED →

Cerebral Palsy Risk in Assisted Reproductive Technologies Has Fallen

FEWER children born following the use of assisted reproductive technologies (ART) have cerebral palsy, compared with 20 years ago. Reduction in twin birth rates and preterm birth rates are likely to have contributed to this >50% fall in cerebral palsy cases.

A Nordic study, presented at the ESHRE virtual 36th Annual Meeting, of 55,233 children born following ART, alongside 2,327,350 spontaneously conceived children, analysed the rates of cerebral palsy by year to determine the change over time. The registry-based cohort study used data from Denmark, Finland, and Sweden and adjusted for maternal age, parity, child's sex, plurality, country, and birth year.

Of the >55,000 ART-assisted births, 307 children were diagnosed with cerebral palsy (0.6%), compared to 5,911 spontaneously conceived children out of >2.3 million (0.3%) in the period 1990–2010. The data were studied within time periods (birth year 1990–1994, 1995–1999, 2000–2004, and 2005–2010). Comparing 1990–1994 to 2005–2010, rates of cerebral palsy decreased within the ART group (0.9% to 0.4%) and remained constant in the spontaneously conceived group (0.3%).

Further analysis considered the impact of singleton versus plural births on cerebral palsy rates for both groups. Risk of cerebral palsy was overall greater in ART singleton children compared with spontaneously conceived singletons (adjusted odds ratio [aOR] 1.32; 95% confidence interval [CI]: 1.10–1.57), but similar for twins between the two groups. Over the 20 years studied, there was a reduction in risk of cerebral palsy for the ART group versus the spontaneously conceived group (1990–1994 aOR: 2.88; 95% CI: 1.81–4.32; and 2005–2010 aOR: 1.34; 95% CI: 1.12–1.61).

“Limiting the number of twins born after ART treatment lowers the risk of CP in the ART population,” explained Dr Anne Lærke Spangmose, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. She highlighted the importance of these findings in supporting a change in standard of care in ART from multiple to single embryo transfer: “Our findings emphasise that single embryo transfer should be encouraged worldwide.”



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Low Oocyte Yield in Assisted Reproductive Technology Associated with Increased Risk of Age-Related Diseases

OOCYTE harvest yield in assisted reproductive technology (ART), according to a new study presented in a press release at the ESHRE virtual 36th Annual Meeting dated 8th July 2020, can serve as a marker of accelerated ovarian ageing and increased risk of age-related diseases.

Early identification of women at risk of premature menopause has become increasingly important to initiate early preventive health initiatives. Repeated low oocyte harvest in ART is a marker of accelerated general ageing; however, could this also serve as a risk predictor of age-related morbidity and mortality? This was the hypothesis that drove the study of lead investigator and PhD student Mette Wulf Christensen, Aarhus University Hospital, Aarhus, Denmark.

The study recruited the national registries of Denmark, dividing women ≤ 37 years old who had a first cycle of *in vitro* fertilisation or intracytoplasmic sperm injection between 1995 and 2014. The groups were based on their response to stimulation and consisted of: 1) those who produced ≥ 5 oocytes for collection, defined as 'early ovarian ages' (n=1,234); and 2) those who responded normally, producing ≥ 8 oocytes (n=18,614). The number of oocytes harvested in first and subsequent cycles was used as a marker of ovarian reserve and several national registers were applied to assess morbidity and mortality.

The 6-year average follow-up period showed that women in Group 1 had a 26% and 39% increased risk of all-cause mortality and cardiovascular diseases, respectively; increased risk of osteoporosis; and were more likely to be listed on the 'early retirement benefit' register compared to those in Group 2.



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Although the risk of cancer and other age-related diseases was not statistically significant, Christensen noted that the data underlines an increased risk of age-related morbidity in young women with early ovarian ageing and she strongly supported the hypothesis that "low ovarian reserve may be a useful marker of later health problems and may therefore be important for introducing preventive measures such as lifestyle changes or the use of hormone replacement therapy to reduce the adverse health risks which follow an earlier menopause."

Hair Samples Could Be Used for Assessing Fertility

FERTILITY assessments are often conducted by testing blood samples for circulating biomarkers, including anti-Müllerian hormone (AMH). Researchers postulated whether this biomarker could be analysed in human hair, and the results were presented at the ESHRE virtual 36th Annual Meeting and in a press release dated 6th July.

As a result of AMH being a product of granulosa cells of the preantral and small antral follicles in women, it is often used as a biomarker when assessing fertility. Obtaining blood samples invasively through median cubital vein punctures is the typical approach to test circulating AMH; however, hair samples may provide a superior understanding of the accrual of the hormone concentrations over longer periods of time. While steroid hormones have been analysed in hair for psychoneuroendocrinological studies, this is the first study to quantify AMH levels in humans.

In the prospective study, 152 females aged 18–65 years were included over a period of 10 months (recruitment is still ongoing). Blood and hair samples were collected in a clinical setting, but hair follicles were not required. An ultrasound to measure participants' antral follicle count was then performed. Once the biologically active AMH was extracted from the hair using a proprietary method, Western blotting was used to detect AMH presence in the hair extract. ELISA was used to measure AMH in plasma and serum.

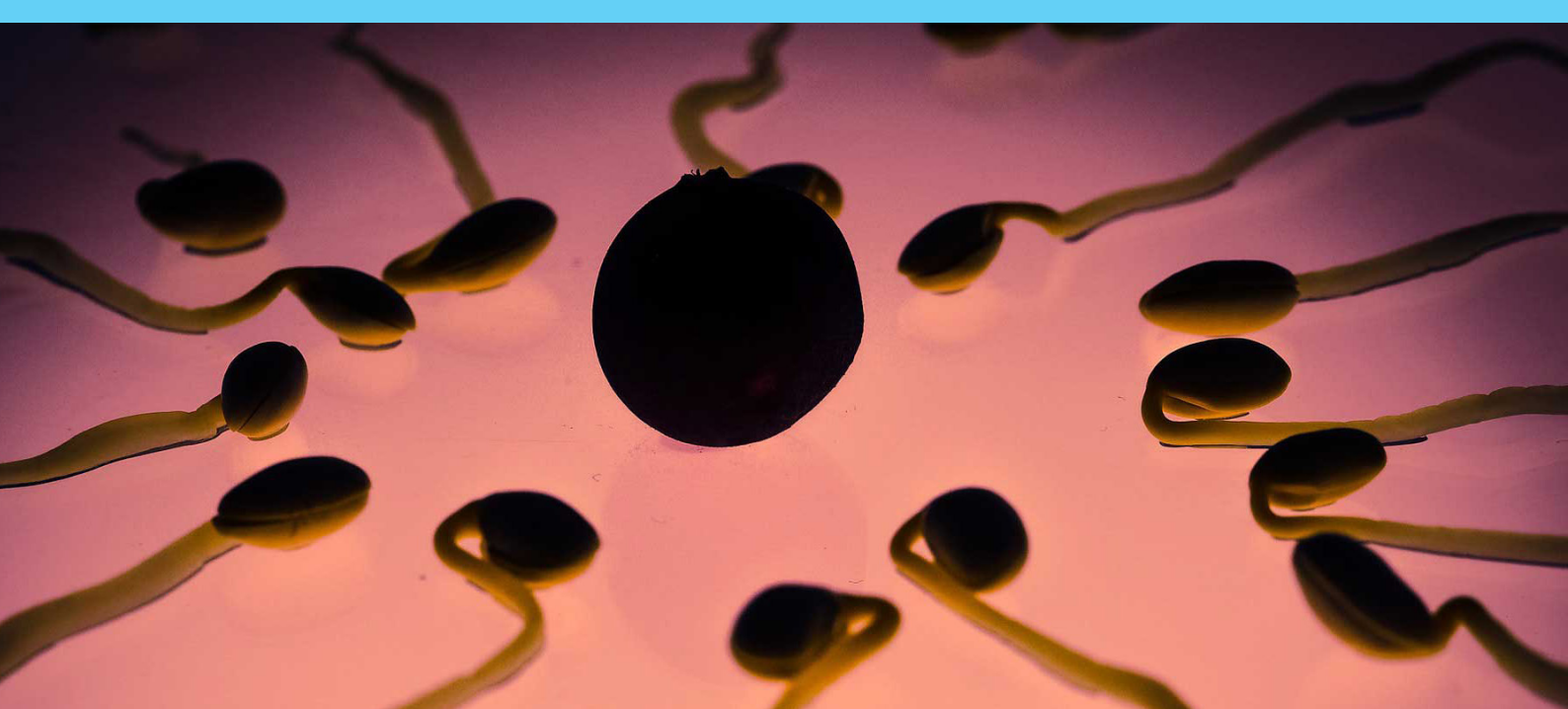
A 70 kDa band representing AMH was successfully detected using Western blots in all samples (N=152). In the <25 years age group, AMH was detected in hair at an average level of 9.37 pg/mL (95% confidence interval [CI]: 6.77–12.00) and at 3.68 ng/mL (95% CI: 2.79–4.56) in serum. Detection results in the age group >39 years were much lower, with a mean of 3.02 pg/mL (95% CI: 2.19–3.85)

in hair and 0.92 ng/mL (95% CI: 0.43–1.141) in serum samples. AMH measurements from hair correlated with age more strongly than plasma ($p=1.26 \times 10^{-5}$ [hair]; $p=0.088$ [serum]), and hair AMH levels also strongly correlated with antral follicle count.

The researchers commented: “We have a novel method of detecting AMH in a longitudinal matrix (hair) that could be a more appropriate representation of hormone levels compared to acute matrices like serum or saliva.”

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Results from the UK Multicentre Endometrial Scratch Randomised Controlled Trial

ENDOMETRIAL scratch, a procedure in which a small biopsy is taken of the uterus lining, is performed in the hope of improving embryo implantation in first-time *in vitro* fertilisation (IVF) users. However, results from the UK Multicentre Endometrial Scratch Randomised Controlled Trial have revealed that this technique is no more effective than routine treatment.

These results were reported in a press release from the ESHRE virtual 36th Annual Meeting on 8th July 2020.

More than 1,000 females from 16 UK centres were enrolled in the study, in what is the largest trial of the procedure to date. The women were aged <37 years, were undergoing their first ever cycle of IVF, and were randomised equally to endometrial scratch or no scratch. The primary outcome was a live birth and the secondary outcomes included clinical pregnancy, implantation, ectopic pregnancy, miscarriage, preterm delivery, and stillbirth rates.

The live birth rate of the intervention group was 38.6%, compared to 37.1% in the control group; there was no statistical significance. Additionally, there were no significant differences in secondary outcomes between the two groups: clinical pregnancy rate was 42.6% in the scratch group compared to 40.6% in the control group. Adverse event occurrence was similar between the two treatment arms and no deaths or neonatal deaths were reported.

Despite previous studies which have come to similar, discouraging conclusions, the endometrial scratch procedure is currently recommended to patients undergoing IVF in 83% of clinics in Australia, New Zealand, and the UK.

Dr Mostafa Metwally, chief investigator of the study, University of Sheffield, Sheffield, UK, stated that: "Our study is the largest and most conclusive study in women having first-time IVF treatment, and the findings conclusively indicate that the practice of performing scratch in this group should stop."

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Positive Live Birth Rates for Fertility Preservation in Female Patients with Cancer: A 19-Year Study

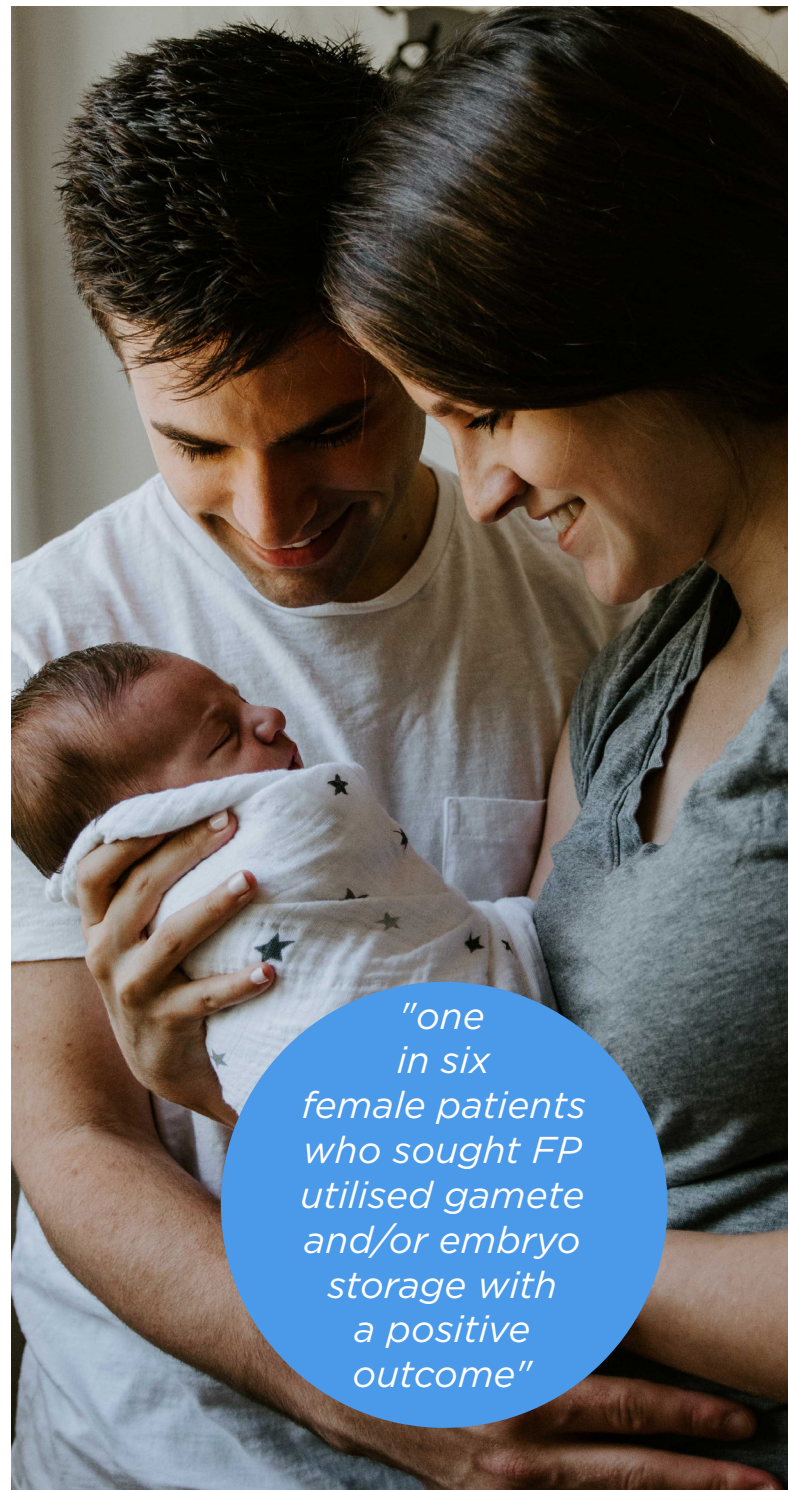
FEMALES opting for fertility preservation (FP) at the time of cancer diagnosis may have good outcomes for utilisation and live birth rates. This is according to the results of a new study presented at the ESHRE virtual 36th Annual Meeting by researchers from the Assisted Conception Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK.

Many countries offer the chance of FP with cancer care but there are limited data on the return of female patients to their stored gametes after cancer treatment, despite FP utilisation being on the rise. This prospective cohort study enrolled 879 females with a cancer diagnosis who requested FP counselling at Guy's and St Thomas' Hospital between January 2000 and December 2019. Data analysis was carried out using the patients' ages, anti-Müllerian hormone levels, and antral follicle count with a primary outcome of live birth rate and secondary outcome of return and utilisation rates (calculated by the number of patients who returned for follow-up and those who had undergone embryo transfer).

Follow-up assessment was attended by 297 patients (33.8%) for review of ovarian function, menopausal symptoms, hormone replacement therapy, and fertility treatment. Mean time taken to follow-up was 21.2±19 months, with 66.0% of patients returning for follow-up within 2 years after their cancer diagnosis. In total, 373 female patients received FP: 40.7% selected embryo cryopreservation, 53.4% selected oocyte cryopreservation, 5.1% had both treatments, and 0.76% underwent ovarian tissue cryopreservation elsewhere. The utilisation rate of females with stored gametes was 16.4% (61/373), the live birth rate was 72.1% (44/61), and the rate of miscarriage was 12.2% (8/61).

Notably, patients with breast cancer were more likely to return for follow-up of gamete utilisation compared to patients with other malignant diseases (44.3%), and they had higher live birth rates compared to patients with lymphoma.

Limitations included uncertainty of outcome for births from natural conception and underestimation of live birth rates because some patients require more time to attempt pregnancy. In the first publication on the utilisation rate after FP, the authors showed that one in six female patients who sought FP utilised gamete and/or embryo storage with a positive outcome.



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