



Abstract Highlights

The following selected highlights draw attention to numerous interesting timely abstracts presented at the European Society of Human Reproduction and Embryology (ESHRE) 39th Annual Meeting, covering topics such as obstetric and neonatal outcomes following embryo biopsy, the role of genital tract infection and pelvic surgery in endometriosis, and the impact of fertility and preservation in patients with cancer.

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Cardiovascular Morbidity and Mortality in Females with Polycystic Ovary Syndrome

POLYCYSTIC ovary syndrome (PCOS) is strongly linked to cardiovascular risk factors. However, in females (aged 40–60 years), it does not heighten the risk of cardiovascular morbidity and mortality. PCOS is a common endocrinopathy in individuals of reproductive age, and can be characterised by anovulation, hyperandrogenism, and polycystic ovaries on ultrasound surveillance.

Females diagnosed with PCOS are at an elevated risk of developing adverse cardiometabolic outcomes, inclusive of Type 2 diabetes, metabolic syndrome, hypertension, and dyslipidaemia. These unfavourable risk factors would seemingly increase the risk of cardiovascular morbidity and mortality in these individuals. However, the evidence from epidemiological studies showcases a heterogeneous body of research with conflicting results.

At the European Society of Human Reproduction and Embryology (ESHRE) 39th Annual Meeting, held in Copenhagen, Denmark, Triada Doulgeraki, Obstetrics and Gynaecology, Royal London Hospital, UK, presented data from a cohort study. The study included a total of 75,142 participants from the UK Biobank, of whom 15,747 were diagnosed with PCOS. The participants were followed up for 11.1 years on average. Cox regression analysis was performed and adjusted for confounders as well as risk factors to quantify the risk of cardiovascular morbidity and mortality.

The study's primary outcome was the morbidity and mortality from ischaemic heart disease and stroke. The findings reveal that, in females with PCOS, the rate of cardiovascular events was 1.92 per 1,000 person-years, whereas the rate was 1.90 per 1,000 person-years in females without PCOS. It should be noted that PCOS was correlated with a heightened risk of obesity (odds ratio [OR]: 1.63; 95% confidence interval [CI]: 1.56–1.70), hypertension (OR: 1.18; 95% CI: 1.13–1.23), and Type 2 diabetes (OR: 1.44; 95% CI: 1.31–1.58).

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The UK Biobank recruitment experienced a low response rate of 5.5%. Hence, the authors acknowledged that this may introduce a potential healthy responder bias, which may limit the representation of the population. Nonetheless, the findings highlight the need to strengthen public health strategies for surveillance, lifestyle interventions, and prompt treatment of comorbidities in females with PCOS. ●

Declining Sperm Motility Between 2017–2022 in Denmark

CHANGES in sperm quality have been assessed in several recent studies. However, while some studies report a decline in sperm quality, others dispute it due to potential biases in the populations studied, or differences in the methodological approach to investigating sperm quality. Resolution of these inconsistencies is critical due to the implications for human fertility, as well as for those involved in donor recruitment in medically assisted reproduction.

A research team, led by Robert Montgomerie, Queen's University, Kingston, Ontario, Canada, therefore sought to investigate the sperm quality among candidate sperm donors in Denmark between 2017–2022.

The semen quality of 6,774 candidate sperm donors attending Cryos International, Denmark, for their first semen analysis between 2017–2022 was analysed, regardless of whether the candidate was accepted as a donor. Four centres across Denmark were used to recruit participants aged 18–46 years. Ejaculates were examined within 1 hour of production. Specifically, semen volume was estimated by weight and sperm concentration, and the concentration of Grade A and B spermatozoa were measured across all years at each of the four sites. Data analyses were controlled for age, site, ejaculate volume, and average monthly temperature. Further analysis of longitudinal data was possible for accepted donors, allowing the research team to test for methodological biases.

Between 2017–2022, there was no evidence of changes in either semen volume (median: 3.5 mL) or sperm concentration (median: 58 million/mL) in the included population. However, there was a clear decline in the concentration and total number of Grade A and B motile sperm. The average concentration of Grade A sperm declined from 5.15 million/mL in 2018 to 3.33 million/mL in 2022. The same pattern was evident across the four test centres, but candidates from the city of Aarhus had lower overall sperm quality, measured as Grade A sperm motility. Longitudinal data from accepted repeat donors during the same period allowed the research team to rule out methodological factors that might have influenced these findings.

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Overall, there was no change in sperm concentration for candidate donors between 2017–2022. However, sperm quality declined by approximately 35% after controlling for age and other potential cofounders. Furthermore, this study suggests candidate sperm donors are a useful population in which to monitor changes in semen quality. The research team acknowledge, however, that they cannot rule out the possibility that males with poor sperm quality were more likely to apply to be donors. ●





Endometriosis: Do Genital Tract Infection and Pelvic Surgery Play a Role?

INFLAMMATION is considered to be a key contributor in endometriosis pathology. Both surgery and genital tract infections induce inflammation in the pelvis, and could therefore contribute to the pathogenesis of endometriosis.

Data from a retrospective cohort study evaluating whether endometriosis incidence was higher in females with a recent history of pelvic surgery and/or genital tract infection was presented at the European Society of Human Reproduction and Embryology (ESHRE) 39th Annual Meeting. Using data from the Korean National Health Insurance Service–National Sample Cohort I (KNHIS-SC I) from 2002–2013, researchers identified females aged 20–49 years who had received a diagnosis of genital tract infection, or underwent pelvic surgery between 2002–2008. Once identified, these patients were followed for 5 years.

A total of 34,018 females were identified and categorised into three groups: history of pelvic surgery (n=2,984), recent genital tract infection (n=30,336), and both pelvic surgery and recent genital tract infection (n=788). Comparison groups were matched for sociodemographic factors.

The analysis revealed that the incidence of endometriosis per 1,000 person-years in each

case group was 5.37 for the recent genital tract infection group, 5.17 for the history of pelvic surgery group, and 20.81 for the group with both a history of recent genital tract infection and pelvic surgery. The incidence was significantly higher in case groups compared to comparison groups.

The adjusted hazard ratio for recent genital tract infection and endometriosis development was 2.29 (95% confidence interval: 1.99–2.63). Adjusted hazard ratios were also elevated for history of pelvic surgery at 2.10, and a history of both recent genital tract infection and pelvic surgery at 7.82, indicating that pelvic inflammation secondary to genital tract infection and pelvic surgery may contribute to endometriosis development.

These interesting findings highlight that appropriate treatment for genital tract infections and minimising tissue injury during surgical procedures may contribute to reducing the incidence of endometriosis. However, the authors noted several study limitations, including discrepancies between KNHIS diagnosis and treatment codes, and the clinical diagnosis and/or treatment; absence of information on diagnostic method; disease severity; and indication for pelvic surgery. ●

"The incidence was significantly higher in case groups compared to comparison groups."

Is Pregnancy Following Hormone Receptor-Positive Breast Cancer Safe?

PREGNANCY following treatment for hormone receptor-positive breast cancer is safe, according to research presented at the European Society of Human Reproduction and Embryology (ESHRE) 39th Annual Meeting. A common malignancy in females of childbearing age, patients and healthcare professionals are often concerned about potential detrimental effects of pregnancy following treatment.

However, several studies have demonstrated the safety of pregnancy after treatment, and the researchers searched for these using Medline, Embase, and Cochrane as part of a systematic literature search. There were no language or date restrictions up to 1st January 2023. Retrospective or prospective case studies were included, as well as cohort studies and prospective clinical trials that compared survival outcomes for patients who were pre-menopausal with reported pregnancy, or not after breast cancer treatment.

There were eight eligible studies, including 3,805 patients with hormone receptor-positive breast cancer. Of these, 1,285 had become pregnant after treatment. The median follow-up for all these studies ranged from 3.81–15.80 years.

Six of these studies reported overall survival, where patients who had become pregnant after breast cancer had a better overall survival compared with patients who did not (hazard ratio [HR]: 0.46; 95% confidence interval [CI]: 0.27–0.77; $p < 0.05$). Three studies reported on disease-free survival, and no difference was observed in patients, regardless of subsequent pregnancies (HR: 0.96; 95% CI: 0.75–1.24; $p = 0.781$).

Furthermore, no detrimental effect was seen in terms of disease-free survival in patients achieving a late pregnancy, which was defined as 2 or 5 years after breast cancer diagnosis, compared with patients who did not get pregnant post-treatment (HR: 0.63; 95% CI: 0.80–1.46; $p = 0.611$). Patients who had an early pregnancy saw an increase in disease-free survival (HR: 0.63; 95% CI: 0.47–0.85; $p < 0.05$).

However, there were some limitations. The meta-analysis consisted of abstracted data, with most studies being retrospective cohort studies. Furthermore, adjuvant hormone therapy was not available in many of the included studies. Despite this, these results do strengthen evidence that pregnancy after hormone receptor-positive breast cancer is safe. ●

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Obstetric and Neonatal Outcomes Following Embryo Biopsy

RESEARCH presented at the European Society of Human Reproduction and Embryology (ESHRE) 39th Annual Meeting sought to investigate whether genetic testing of embryos pre-implantation was linked to adverse outcomes, both obstetric and neonatal. This practice has been used since 1990, to prevent transmission of diseases. It has evolved to include testing for couples who both carry the same autosomal recessive disorder, females experiencing recurrent miscarriage, and those at higher risk during pregnancy.

Currently, genetic testing of embryos pre-implantation is carried out at the blastocyst stage (5–7 days following fertilisation), along with the biopsy of a few trophoblast cells from what would become the placenta, the transport of biopsy tissue to another site for genetic analysis, and the cryopreservation of blastocysts. Following this process, a single euploid embryo is transferred to the uterus as a frozen embryo.

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A team from the University of Massachusetts' Chan School of Medicine, East Longmeadow, USA, compared the outcomes of frozen-thawed single embryo transfer with biopsy to frozen-

thawed single embryo transfer without biopsy. The team linked birth certificates and maternal and neonatal hospitalisation discharge with surveillance data held on assisted reproductive technology in the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART-CORS). All data was reported across the state of Massachusetts between 2014–2017. Only singleton births following frozen-thawed single embryo transfer were included. Outcomes of cycles that underwent embryo biopsy (n=585) were compared to those with no biopsy (n=2,191). Comparison was adjusted for the mother's age, race, education, parity, birth year, previous infertility diagnoses, insurance, and BMI.

The study identified no differences between either cohort with regard to many outcomes, including pre-eclampsia, placental disorders, pregnancy-induced hypertension, low birthweight, Caesarean-section delivery, length of stay after birth for mother or baby, or gestational diabetes. Results were compared to four other studies, which focused on contemporary frozen-thawed embryo transfers, and were found to be consistent, with no effects observed on low birth weight, gestational diabetes, placenta previa, placenta accreta, and pregnancy-induced hypertension. The study concluded that the practice of genetic testing of embryos pre-implantation is generally safe, with regard to both maternal and neonatal outcomes. ●





Intra-Ovarian Injection of Platelet-Rich Plasma Does Not Improve Outcomes

INTRA-OVARIAN injection of autologous platelet-rich plasma (PRP) does not increase the oocyte yield number in young patients with poor ovarian response (POR), according to data presented at the the European Society of Human Reproduction and Embryology (ESHRE) 39th Annual Meeting. When it comes to controlled ovarian hyperstimulation (COH) for *in vitro* fertilisation (IVF), POR is a major hurdle. Several methods aiming to attempt follicular reactivation, such as intraovarian injection of autologous PRP, have shown promising results in prospective and retrospective cohort studies. A multicentre, randomised control trial evaluated whether PRP improved IVF outcomes in patients with POR.

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In total, 83 patients were randomised to receive no intervention (control group; n=42), or autologous intra-ovarian PRP injection (PRP group; n=41) prior to COH. Participants were younger than 38 years, had two or more prior cycles with <3 oocytes retrieved, and did not have single gene disorders, endometriomas, prior ovarian surgery, severe male factor

infertility, or BMI >35. After receiving treatment, participants underwent COH, oocyte retrieval, intracytoplasmic sperm injection, pre-implantation genetic testing for aneuploidy, and single frozen euploid embryo transfer. The primary outcome was number of MII oocytes obtained, and secondary outcomes included sustained implantation, blastocyst and euploid blastocysts yield, and ovarian reserve tests.

The team did not note any significant differences in number of MII oocytes retrieved (3.1 ± 3.3 versus 2.8 ± 2.4 in PRP versus control, respectively; $p=0.9$), euploid blastocysts (0.9 ± 1.6 versus 0.8 ± 1.1 ; $p=0.5$), or blastocysts (1.3 ± 2.1 versus 1.0 ± 1.3 ; $p=0.8$) per cycle. Furthermore, there were no differences in the rate of sustained implantation (29% versus 31%; $p=0.9$; relative risk: 1.0; 95% confidence interval: 0.7–1.3) or the likelihood of obtaining at least one euploid blastocyst (37% versus 45%; $p=0.4$; relative risk: 0.9; 95% confidence interval: 0.6–1.2).

Limitations of the study included the lack of evaluation of long-term effects due to oocyte retrieval taking place in the cycle immediately following treatment. The team concluded that intra-ovarian PRP did not improve outcomes, and they therefore do not support the wide utilisation of PRP for IVF in patients with POR. ●

The Impact of Fertility Preservation in Patients with Cancer

TECHNIQUES used to preserve fertility in females with cancer include oocyte vitrification (OV), ovarian cortex cryopreservation (OCC), and embryo vitrification. Whilst these techniques have become a pivotal part of cancer care, data on their impact on ovarian damage, pregnancy outcomes, disease relapse, and survival is limited.

Researchers from the Research Health Institute La Fe, Reproductive Medicine Research Group, and IVI Foundation, Valencia, Spain, performed a prospective cohort study to investigate this further. They enrolled 695 patients referred to fertility preservation (FP) units in two hospitals between 2001–2016. Patients were followed up for at least 5 years from time of enrolment. The primary outcome was median survival after FP. Usage rate of FP, relapse rate, premature ovarian insufficiency (POI), poor ovarian response, clinical pregnancy, and live birth rates were secondary outcomes.

Of the 695 enrolled, 556 received OV, OCC, or embryo vitrification. The remaining 139 patients received no FP treatment. Overall, the study found that treatment resulted in ovarian damage in almost half of patients, and natural live birth was achieved in approximately one-third of those with a pregnancy wish.

There was no significant difference in survival between those who received FP and those who did not (median survival time of 89.67 months and 92.81 months, respectively; $p=0.3$). However, a significant survival difference was seen when comparing patients who had received approval to get pregnant (98.84 months) to those who had

not (84.79 months; $p<0.001$). No difference was seen between patients with hormone-dependent breast cancer undergoing ovarian stimulation for OV versus OCC at 95.62 months and 87.38 months, respectively ($p=0.37$).

Ovarian damage occurred in 334 patients (48.06%), and the incidence of POI was 20.29%. Patients with POI were of significantly increased age ($p<0.001$), and had received high-risk chemotherapy more frequently ($p<0.001$). Cryopreserved material was used by 86 patients.

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Spontaneous live birth occurred in 84/266 patients with a pregnancy wish (31.58%). Those able to conceive naturally were significantly younger at 30.71 years compared to 33.46 years for those unable to conceive naturally ($p<0.001$), and more frequently received low-risk chemotherapy ($p=0.018$). Live births occurred in 37/86 patients after use of FP.

The authors noted that the higher survival seen in patients who used their cryopreserved material was mediated by disease prognosis, which limits pregnancy chance to those with stable disease, and concluded that even when ovarian stimulation is used, fertility preservation does not negatively impact survival. ●



Plasma Rich in Growth Factors Treatment Produces Improved Reproductive Outcomes

ENDOMETRIAL plasma rich in growth factors (PRGF) therapy produced interesting reproductive outcomes in patients with thin endometrium (ThE), recurrent implantation failure (RIF), and recurrent miscarriage (RM). Researchers in Alicante, Spain, observed significantly increased reproductive success rates with PRGF in patients with ThE and RIF, and unaffected results for pregnancy loss in the RM group. The findings from this study were presented at the European Society of Human Reproduction and Embryology (ESHRE) 39th Annual Meeting.

Use of PRGF has been successfully applied in other medical fields, but has become a novel treatment method in reproductive medicine. The current research investigated its usefulness in ovarian follicle activation and enhancing endometrial receptivity. This research was a retrospective analysis from 2016–2022, including 107 patients recruited into ThE (n=64), RIF (n=36), and RM (n=7) groups.

Live birth and ongoing pregnancy rates per embryo transfer were compared with success rates obtained in previous embryo transfers that preceded PRGF intervention. The total of 107 patients underwent 150 endometrial PRGF treatments and 131 embryo transfers. Altogether,

19 embryo transfers were cancelled, higher in the ThE group than RIF (16% versus 7%). In both the ThE and RIF cohorts, positive pregnancy, clinical pregnancy, and ongoing pregnancy/live birth rates per embryo transfer were significantly higher with PRGF treatment compared with previous embryo transfer. Meanwhile the RM group showed no significant difference for these measures, and no ongoing pregnancies were achieved. To date, 20 singletons and one set of twins have been confirmed to be born from the PRGF cycles involved in this study, with 12 more pregnancies still ongoing.

The tangible results from endometrial PRGF that are reported show real promise for application in reproductive medicine; however, the researchers did report several limitations. Patients with RM were too few in number to evaluate pregnancy loss rates, and the self-controlled design of study may have influenced the comparison between pre- and post-intervention pregnancy rates. Heterogeneity of clinical severity between included patients with ThE could also affect observed reproductive outcomes. Regardless, this study has presented that regenerative therapy using PRGF is a safe, affordable, and efficient treatment option for patients with ThE and RIF. ●

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