

ESHRE 2023



Review of the European Society of Human Reproduction and Embryology (ESHRE) Annual Meeting 2023

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The 39th European Society of Human Reproduction and Embryology (ESHRE) Annual Meeting, which took place in Copenhagen, Denmark, welcomed 10,831 participants from 129 countries around the globe, with 90% attending in person. With a record number of 2,109 abstracts submitted, the main topics covered embryology, reproductive endocrinology, andrology, and more, which were certain to leave participants cleverer and more inspired.

With the decline in fertility rates worldwide and the needs for fertility treatments continuously increasing, the role of the ESHRE and its congress in emphasising high quality treatments, with a focus on efficient and safe treatments, as well as prevention, has become more important in recent years. At the opening ceremony, Anja Pinborg, Copenhagen University Hospital, Denmark, emphasised the proactive approach taken by Denmark, where this year's congress was hosted, by introducing fertility counselling into regions, and incorporating the importance of fertility awareness into the school curriculum. With these steps, they hope to spread the

message of optimal timing of parenthood and its significance for both males and females.

ESHRE Chair, Carlos Calhaz-Jorge, shared the many activities of the Society, which aim to share knowledge and provide education, set standards, support research, and collect data. One example of this is the European Monitoring of Medical Assisted Reproduction (EuMAR) project, co-founded by the European Union (EU), which aims to develop a pan-European registry of data on the use of medical assisted reproduction treatments. This ambitious project has three objectives: to establish a data-flow that is flexible and adjusted to the context of all member states; to define, standardise, and harmonise parameters that will be collected, as well as the definitions; and to create new solutions establishing web-based data registry. Other activities of ESHRE that contribute to their goals include a portfolio that collects guidelines and good practice recommendations; the four journals published by the Society; the strong certification and standard setting programme; their support in research; and the strong policy-

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making awareness and advocacy programme, mainly with EU organisations, with new regulations coming out, and the need to be fully involved as stakeholders in the field.

This year, ESHRE granted six awards for content, which were presented at the meeting. The Basic Science Award for oral presentation was presented to Inmaculada Pérez-Prieto, University of Granada, Spain, for their work entitled 'Gut microbiome in endometriosis: a cohort study on 1000 individuals'. Second, the Clinical Science Award for oral presentation was awarded to Andrew Horne, Medical Research Council (MRC) Centre for Reproductive Health, Queen's Medical Research Institute, Edinburgh, UK, for their presentation entitled 'Combination of gefitinib and methotrexate to treat tubal ectopic pregnancy (GEM3): a multicentre, randomised, double-blind, placebo-controlled trial'. The winner of the Basic Science Award for poster presentation was Ying-Chun Guo, Reproductive Medicine Research Center, Yat-sen University, Guangzhou, China, for their presentation on 'Neurotrophin-4 supplementation during human secondary follicle in-vitro-culture supports morphologically normal blastocyst formation'. The Clinical Science Award for poster presentation was presented to Katja Drechsel, Cancer Center Amsterdam, the Netherlands, whose work was entitled 'Gonadal function and fertility preservation in girls with Hodgkin lymphoma treated according to the EURONET-PHL-C2 Protocol: the fertility add-

on study'. ESHRE also presented the Fertility Society of Australia and New Zealand educational grant, allowing one of the participants to present their data at the Annual Meeting of the Fertility Society of Australia and New Zealand. This was awarded to Nada Kubikova, Nuffield Department of Women's and Reproductive Health, and Jesus College, University of Oxford, UK, for their work entitled: 'Deficiency of DNA double-strand break repair in human preimplantation embryos revealed by CRISPR-Cas9'. Finally, the Nurses Award was presented to Sarah Bailey, University Hospitals Southampton NHS Foundation Trust, UK, for their presentation entitled 'The Positive Reappraisal Coping Intervention: how it works in recurrent pregnancy loss'.

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Read on for scientific highlights of the congress, covering topics such as the optimal embryo transfer time, and whether COVID-19 infection affects male fertility. EMJ was delighted to attend this congress, and is looking forward to the ESHRE's 40th Annual Meeting, which will be held next year from 7th–10th July in Amsterdam, the Netherlands. ●

Vaginal Progesterone Could Reduce Unexplained Fertility

UNEXPLAINED infertility affects approximately one-third of couples attending fertility services. These couples could benefit from a hormone treatment, suggests breaking research presented at the 39th ESHRE Annual Meeting.

The study, conducted at Queen Mary University of London, UK, included 143 couples with unexplained infertility. Pregnancy outcomes were compared between couples trying to conceive naturally and couples where females used a vaginal progesterone treatment during the second half of their menstrual cycle. All participants used ovulation test kits to plan intercourse for three menstrual cycles, with half of the females receiving 400 mg of progesterone twice daily via a vaginal suppository for 14 days.

Among the females treated with progesterone, 11 babies were conceived (15.3%), while five were conceived in the non-treated group (7%). The rate of miscarriage was 20% in the progesterone treatment group compared with 40% in the untreated group. Furthermore, there were no miscarriages among females who took progesterone according to the treatment protocol (throughout the second half of their

menstrual cycle and early pregnancy with no breaks). However, the included population size is too small for researchers to claim that these results are statistically significant.

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Claudia Raperport, Queen Mary University of London, commented that "we need to do further research to prove these results in a larger group of people, but this trial suggests a potential treatment for couples with unexplained fertility. Given its safety and low price, there is no harm in offering this treatment in the meantime." Vaginal progesterone has been safely used for over 30 years and the cost of this progesterone treatment would be less than 200 EUR. Raperport therefore concluded: "The cost of progesterone is minimal compared to the cost of *in vitro* fertilisation and other fertility treatments. It also carries far less clinical risk, and physical and emotional burden for the couples involved." ●





What Is the Optimal Embryo Transfer Time?

NO DIFFERENCE in cumulative live birth rates is seen when cultured embryos are transferred after 3 or 5 days, but the results may be impacted by age, according to research presented at the ESHRE Annual Meeting, on 26th June 2023.

Transfer typically occurs after 5 days, once the embryos reach blastocyst-stage, as opposed to cleavage-stage (3 days); however, there are risks associated with increased culture time outside of the womb prior to transfer.

To evaluate if embryo culture time impacts live birth rate, researchers performed a large randomised controlled trial, which recruited 1,202 patients with ≥ 4 embryos available to be transferred after 2 days of culture, across 21 Dutch fertility centres, who were randomised to receive embryo transfer after either 3 days ($n=599$) or 5 days ($n=603$) of culture. Birth rate was derived from the transfer of either fresh or frozen embryos after one round of egg retrieval. The team also assessed cumulative live birth rate in those <36 years of age and those ≥ 36 years of age.

Overall cumulative live birth rates were 58.9% for blastocyst-stage and 58.4% for cleavage-stage embryo transfer, and there was no difference in time to achieve a pregnancy that resulted in live birth between the two groups.

When evaluating the impact of age, for those <36 years, the cumulative live birth rate for cleavage-stage embryos was 67% compared with 63% for blastocyst-stage embryos. However, this was not a statistically significant difference. In those

≥ 36 years of age, cumulative live birth rates for cleavage- and blastocyst-stage embryos was 43% and 52%, respectively. This difference was not found to be statistically significant. Whilst no statistical significance was reached, the authors commented that the results are still clinically significant and highlight a potential benefit of cleavage-stage transfer in females aged up to 36 years, as well as a potential benefit of blastocyst-stage transfer in females ≥ 36 years.

"Cumulative live birth rates were 58.9% for blastocyst-stage and 58.4% for cleavage-stage embryo transfer."

Live birth rates following fresh embryo transfer alone were significantly higher in the blastocyst-stage than the cleavage-stage at 37.0% and 29.5%, respectively. This difference was more apparent when stratifying by age. Live birth rate in patients ≥ 36 years was 35.0% for blastocyst-stage and 18.5% for cleavage stage. However, in patients <36 years of age the difference was not significant, at 38.0% and 36.0% for blastocyst- and cleavage-stage embryo transfer, respectively.

The team emphasised the importance of evaluating new techniques in clinical trials before introducing into clinical practice and looking towards the future. They are conducting a cost-benefit analysis and plan to assess the risks and burden of treatment to patients. ●

Cancer Risk Greater in Females with Polycystic Ovary Syndrome After Menopause

FEMALES with polycystic ovary syndrome (PCOS) who have been through menopause are more than twice as likely to be diagnosed with ovarian cancer compared with those without this condition, according to data presented at the 39th ESHRE Annual Meeting.

Data presented was based on close to 2 million females, the first large-scale study of its kind, aiming to increase awareness for the management of health in females with PCOS, which affects one in 10 females. This study was led by Clarissa Frandsen, Danish Cancer Research Center, Copenhagen, Denmark, who advocated for clinical guidelines including recommendations on the potential ovarian cancer risk when managing the long-term health consequences of patients with PCOS. They stated: "Our results and those from previous studies should be taken into account when revising guidelines on how to manage the health of women with PCOS," going on to stress that, "unfortunately, there is no effective screening for early detection of ovarian cancer. Both patients and clinicians will benefit from improved knowledge of the potential long-term health risks associated with PCOS."

Age-adjusted incidence rates of ovarian cancer were 11.7 per 100,000 person-years and 13.2 per 100,000 person-years for females with and without PCOS, respectively. The cohort under surveillance included 1.7 million females born in Denmark between 1st January 1940–31st December 1993. Excluded from this population were females who emigrated, died, were diagnosed with cancer, or underwent surgery to remove their ovaries/fallopian tubes. Details about diagnosis of PCOS and cancer, as well as migration, were obtained from national registers.

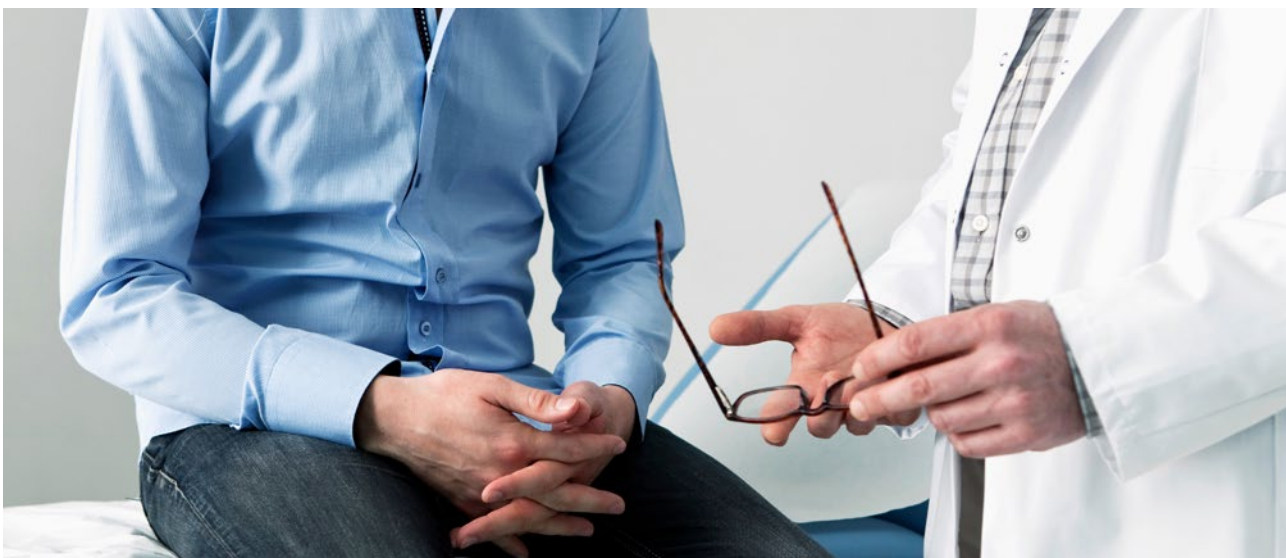
Further analysis was performed on females reaching 51 years, which is the average age in Denmark for menopause.

"The risk of developing ovarian cancer was significantly greater among post-menopausal females."

In total, 6,490 females were diagnosed with epithelial ovarian cancer, and 2,990 with borderline ovarian tumours, over a median follow-up time of 26 years. The investigators discovered that increased risk was not statistically significant for ovarian cancer and borderline ovarian tumours among females with PCOS compared with those without the condition. Other factors, such as obesity and education level, were considered as potentially affecting the risk of ovarian cancer. Notably, the risk of developing ovarian cancer was significantly greater among post-menopausal females compared with those without PCOS. Plus, risk of a serious borderline ovarian tumour was more than doubled among patients with PCOS.

The authors of this work did acknowledge the low number of ovarian cancer cases, despite a large study population. This research did not examine why post-menopausal females are more likely to develop ovarian cancer, and future study is warranted to delve deeper into this area. Frandsen described PCOS as a complex condition and suggested that long-term exposure to potential cancer-causing factors could be behind findings, such as excess production of male sex hormones. ●





Does COVID-19 Infection Impact Male Fertility?

SEMEN quality is reduced long-term following COVID-19 infection, according to new research presented at the 39th ESHRE Annual Meeting on 26th June 2023.

The study, led by Rocio Núñez-Calonge, UR International Group, Scientific Reproduction Unit, Madrid, Spain, enrolled 45 males with a confirmed diagnosis of mild COVID-19 who had available data on semen analysis pre-COVID-19 infection, from six reproductive clinics in Spain between February 2020–October 2022. A second semen sample was taken between 17–516 days post-infection. Median patient age was 31 years and median duration between pre- and post-COVID-19 infection semen samples was 238 days.

Semen samples taken within 100 days post-infection were analysed separately to those taken >100 days. The results revealed that following COVID-19 infection there was a statistically significant reduction in semen volume, total motility, sperm concentration, sperm count, and number of live sperm, with sperm count and total motility being most affected, according to Núñez-Calonge.

Analysis of patients who had a semen sample within 100 days of infection found that on average, sperm count reduced by 37.5%, sperm concentration by 26.5%, semen volume by 20%, total motility by 9.1%, and live sperm numbers by 5.0%. However, the shape of sperm was not

found to be significantly affected. Half of those in the study experienced a 57% reduction in total sperm count in their post-infection sample compared to their pre-infection sample.

"Half of those in the study experienced a 57% reduction in total sperm count in their post-infection sample."

Separate analysis of patients who had a post-infection semen sample taken >100 days after infection showed that sperm concentration and motility had still not improved at this time. Núñez-Calonge highlighted that this prolonged impact on semen quality could be secondary to permanent damage caused by COVID-19 infection. However, Núñez-Calonge noted that impairment of semen quality may not be a direct effect of severe acute respiratory syndrome coronavirus 2, and studies have previously shown that COVID-19 infection can impact testosterone levels, which were not measured during the study.

This study highlights how long-term follow-up following COVID-19 is important in understanding the impact of infection on male fertility. The researchers plan to continue their research by evaluating semen quality and hormone levels temporally. ●

Risks of Gene Editing in Early Human Embryos

CAUTION should be adopted when considering gene editing techniques to remove inherited diseases from human embryos, according to new research presented at the 39th ESHRE Annual Meeting.

To determine if the gene editing method, CRISPR-Cas9, is safe to use for human embryo genetic error correction, Nada Kubikova, University of Oxford, UK, and fellow researchers created 84 embryos using intracytoplasmic sperm injection to fertilise donor eggs with donor sperm. CRISPR-Cas9 was used to create double-strand DNA breaks in areas containing no genes in 33 of the embryos. The remaining 51 were kept as controls.

The desired method of DNA repair to limit errors and mutations is homologous directed repair. Non-homologous end-joining has a greater risk of introducing mutations than homologous directed repair. However, complete failure to repair DNA damage can be lethal. In their study, the researchers found that alterations at the targeted DNA sites occurred in 24/25 embryos, highlighting the efficacy of CRISPR. Repair at the targeted DNA sites occurred via non-homologous end-joining in 51% and by homologous directed repair in 9%. The remaining 40% displayed no repair, which resulted in large chromosomal areas being deleted or duplicated. This can impact embryo viability and lead to serious congenital abnormalities.

These findings highlight that repair of DNA damage by homologous directed repair is limited in early human embryos and that DNA repair during these early stages is not optimal. The majority of repair that did occur in the study, took place by non-homologous end-joining, resulting in introduction of additional mutations. This suggests that in the majority of human embryos with inherited disorders, CRISPR-Cas9 is unlikely to be a successful gene editing technique.

"Repair of DNA damage by homologous directed repair is limited in early human embryos."

Kubikova stated: "Our new findings provide a warning that commonly-used gene editing technologies may have unwanted and potentially dangerous consequences if they are applied to human embryos." The study findings may aid understanding of *in vitro* fertilisation embryo failure and subsequently lead to improved *in vitro* fertilisation treatments.

Looking towards the future, the researchers plan to identify methods of protecting early human embryos against DNA damage and explore other gene editing techniques that avoid DNA strand breakage. ●





Why Are So Many Frozen Eggs Not Used?

RESEARCH presented at the 39th ESHRE Annual Meeting has demonstrated that whilst over 40% of females who chose to freeze their eggs during their 30s were able to have children later in life, many females did not return to the fertility clinic, and others chose fertility treatments that did not involve using their own frozen eggs.

The study, which focused on females who underwent elective oocyte cryopreservation, was carried out by Ezgi Darici and colleagues from the Centre for Reproductive Medicine, Universitair Ziekenhuis (UZ) Brussels, Belgium. In total, 843 females who had elective oocyte cryopreservation for reasons that were not medical at the Centre for Reproductive Medicine between 2009–2019 were included. Mean age was 36 years and the majority of females were single.

As of May 2022, 231 females (27%) in the cohort had returned to the same centre for treatment. Mean age upon their return to the clinic was 40 years, and the majority had partners. Of these, 110 (48%) used their own frozen eggs in their fertility treatment, 50 (22%) underwent intrauterine insemination, and 71 (31%) had fertility treatments like *in vitro* fertilisation, using fresh eggs. In this subgroup, 106 females (46%) had a live birth (a cumulative live birth rate included every live birth following any fertility treatment), and the rate of miscarriage was 31%.

Of those using frozen eggs in their treatment, 41% had live births, and with fresh eggs, this rose to 48%.

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Darici commented: "To our knowledge, this is one of the first and largest reports of reproductive outcomes in women who had elective oocyte cryopreservation at a European fertility centre." Darici went on: "The choice of whether to use fresh or frozen eggs is made based on what treatment is best for each individual woman, and factors such as the woman's age are important. We cannot really compare the two groups, as there will be many differences that could underlie any disparity in pregnancy and birth rates."

The study found positive rates of pregnancy and birth in fertility treatment using both fresh and frozen eggs. Limitations of the study are the small sample size and the use of retrospective data. Carlos Calhaz-Jorge, Northern Lisbon Hospital Centre and Hospital de Santa Maria, Lisbon, Portugal, and Chair of ESHRE, stressed that more research was needed to prove that freezing eggs successfully aided fertility in older females. ●

Childhood Hodgkin Lymphoma Treatment May Cause Early Fertility Decline

FERTILITY of patients who were treated for Hodgkin lymphoma in childhood may decline at a younger age, according to a study presented by Katja Drechsel, Princess Máxima Center for Paediatric Oncology, Utrecht, the Netherlands, at the ESHRE Annual Meeting 2023. However, data also showed that the majority of those who tried to get pregnant were ultimately successful. Most people with Hodgkin lymphoma survive thanks to improvements in treatment; however, treatments such as radio- and chemotherapy can reduce fertility.

In total, 84 females who were treated for Hodgkin lymphoma as children, and 798 who were not treated for this condition were included in the study. Participants were asked whether they had children and at what age they first became pregnant. They were also tested for markers of fertility, such as anti-Müllerian hormone, follicle-stimulating hormone, and inhibin, and the number of egg cells in the ovaries were gauged by ultrasound. Data showed that those who were treated for the condition were more likely to have abnormal fertility markers and a lower number of egg cells compared with those who were

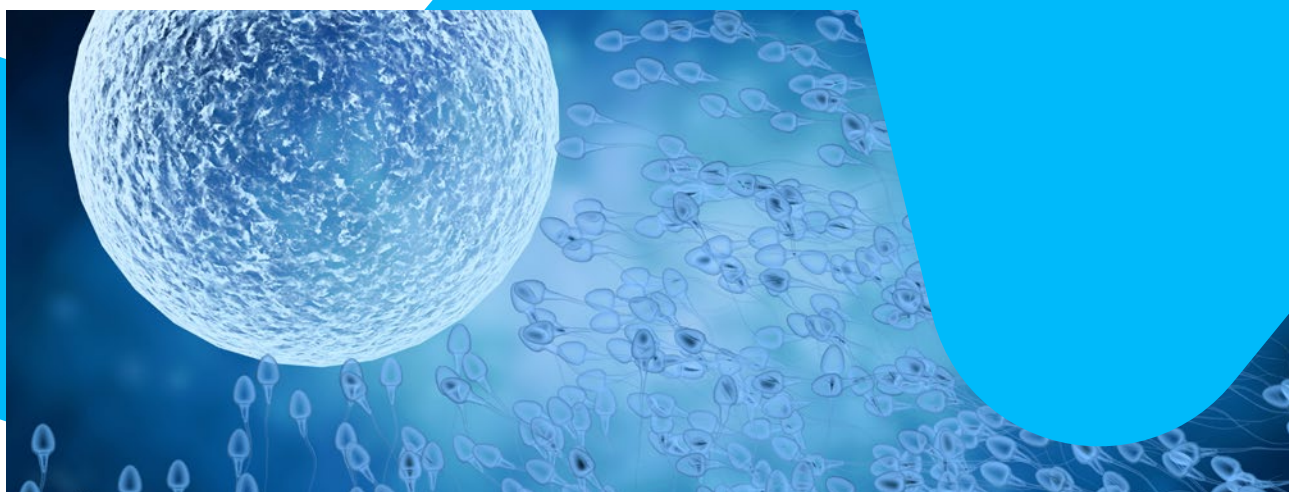
not. Furthermore, those who survived Hodgkin lymphoma were almost 2.5-times more likely to try for 1 year before becoming pregnant for the first time.

Researchers noted similar pregnancy and live birth rates in both groups, but females who were treated for Hodgkin lymphoma were on average 2 years younger when they had their first child compared with the control group. Researchers hypothesise that this may be due to doctors advising them about the effects of cancer treatments on fertility.

The team concluded that treatment for childhood Hodgkin lymphoma may lead to an earlier decline of fertility. Drechsel noted: "These women were treated for cancer in the 1970s, 80s, and 90s. It is important to note that treatment for childhood Hodgkin lymphoma has changed in recent years and the effects of current treatment schedules on fertility are likely to be less toxic." More research is needed to follow patients' fertility long-term and determine if they have more difficulties becoming pregnant at an older age. ●

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Artificial Intelligence Accurately Detects Sperm in Males with Infertility

NEW research presented at the 39th ESHRE Annual Meeting heralds a new artificial intelligence (AI) tool which has the ability to identify sperm in males with the most severe form of infertility, non-obstructive azoospermia, where no sperm is detectable in semen.

In current practice, patients have to undergo a procedure to remove a portion of their testes. Tissue is partially shredded, and sperm is extracted manually by an embryologist, which is then used to fertilise their partner's eggs through intracytoplasmic sperm injection. Currently, it can take as long as 6 hours to detect and isolate sperm in human tissue; this makes it more difficult to identify, due to mental and physical fatigue on the part of the embryologist. Contamination from other tissue particles can also make this process difficult. The longer this process takes, the higher the chance that the sperm will not be viable for treatment.

"The algorithm improves antiquated approaches that have not been updated in decades."

Research was carried out at an *in vitro* fertilisation clinic in Sydney, Australia, over 5 months, using a two-stage process. Researchers initially trained the AI algorithm using thousands of still microscope photographs, featuring sperm and high levels of other cells; only the sperm was

highlighted in this process. The AI tool was able to learn, through image analysis, what sperm looked like using an evaluation system able to check and adjust its performance. Healthy sperm, along with testicular tissue from seven patients aged 36–55 years, all of whom had been diagnosed with non-obstructive azoospermia, were used.

In several seconds, the SpermSearch (University of Technology Sydney, Australia) AI tool can instantly identify sperm. An embryologist can then decide whether intracytoplasmic sperm injection treatment is viable. AI detected more sperm overall, but some were found only by the embryologist (560), and some by AI alone (611). AI found 60 more sperm overall, and was 5% more accurate than the embryologist when based on viewable droplet area.

Lead author Dale Goss, University of Technology Sydney, commented: "The algorithm improves antiquated approaches that have not been updated in decades. It will ensure the rapid identification of sperm in samples, which will not only increase the chance of a couple conceiving their own biological children, but also reduce stress on sperm, and increase efficiency in the laboratory."

It is hoped that this algorithm will bring hope to males with severe infertility who wish to have a biological child, but have no sperm detectable in their semen. ●

Data Suggests More Patients Are Using Single Embryo Transfer

PRELIMINARY data shared at the 39th ESHRE Annual Meeting shows that more females are having just one embryo transferred per cycle of fertility treatment in order to get pregnant. In 2020, nearly three out of five (57.6%) of all *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection procedures in Europe involved the transfer of just a single embryo. This number represents an increase over the half (55.4%) who used single embryos in 2019.

Corresponding to the reduction in multiple embryos, there was a resultant increase in singleton babies, which accounted for 88.8% of all assisted reproductive technique deliveries compared with 87.7% the previous year. There was a decreased number of twins (11.0%) and triplets (0.2%) from the previous year, 11.9% and 0.3%, respectively.

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This ESHRE European IVF-monitoring Consortium (EIM) report represents the largest data collection on medical assisted reproductive techniques in Europe, with lead author Jesper Smeenk, Elisabeth-TweeSteden Ziekenhuis (ETZ), Tilburg, the Netherlands, stating: "The continued rise in single embryo transfer means women are less likely to face complications

in pregnancy and during birth. The result has been that fertility treatments have become safer for mothers and babies without compromising success rates."

Additionally, according to research from 1,326 clinics in 38 European countries, the number of treatment cycles throughout 2022 dropped compared to the year before. A total of 843,776 cycles occurred in 2020 compared with over 1 million in 2019. However, the presenters stressed that the number of cycles is likely to increase once the full data is reported.

The report also provided data on the frequency of fertility preservation methods. In total, 15 countries carried out a total of 18,270 fertility preservation procedures, including egg, sperm, and ovarian tissue freezing. These techniques, often used to allow for pregnancy in patients with cancer, were carried out both pre- and post-puberty.

The authors highlighted that their findings were not yet complete due to incomplete data returns from several countries, including the UK. They therefore encouraged interpretation of the results with a degree of caution.

"The hope is that this upwards trend in single pregnancies, as highlighted by the EIM data, continues," stated Carlos Calhaz-Jorge, Northern Lisbon Hospital Centre, Portugal. "Clinics must always prioritise the safety of patients who undergo fertility treatment, and that of their offspring." ●





Adenomyosis Linked to Increased Risk During Pregnancy

FEMALES with adenomyosis have an increased risk of problems during pregnancy and birth, according to research presented at the 39th ESHRE Annual Meeting. Lead author, Mohammed Bazarah, University of Western Ontario, London, Canada, stated that females with adenomyosis are more likely to “experience infertility, pre-term delivery, and other gynaecological conditions, such as endometriosis.”

A chronic condition similar to endometriosis, adenomyosis causes heavy menstrual bleeding and pelvic pain. Occurring when endometrial tissue and glands that line the womb grow into or are found in the uterus’ muscle wall, one in 10 females of reproductive age have adenomyosis. However, some females have no physical signs, making the condition difficult to diagnose.

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Using records from the Nationwide Inpatient Sample (NIS) database from 2004–2014, the researchers analysed 2,467 pregnant females with adenomyosis and 9,094,321 females without the condition. The outcomes of both

cohorts were then compared. Using this data, the researchers wanted to provide insights into maternal, pregnancy, and neonatal outcomes in females with the condition.

The results indicate that females with adenomyosis were 1.69-times and 1.5-times more likely to develop pre-eclampsia and hypertension, respectively. Females with adenomyosis have a 5.86-times higher risk of placenta previa, with a relative risk of obstetric complications for Caesarean section being 21.63-times higher than females without adenomyosis.

Furthermore, the results showed that females with adenomyosis were more likely to have had a previous Caesarean section and *in vitro* fertilisation treatment, as well as have pre-gestational diabetes, chronic hypertension, and thyroid disease. Relative risk was also higher for hysterectomy, wound complications, blood transfusions, placenta detachment, excessive bleeding after the birth, and maternal infection in females with adenomyosis.

While the database used did not provide disease severity or how adenomyosis was diagnosed, the researchers believe that more females with adenomyosis need to be monitored worldwide to help reduce the risk of serious complications, such as death of the mother and their baby. ●