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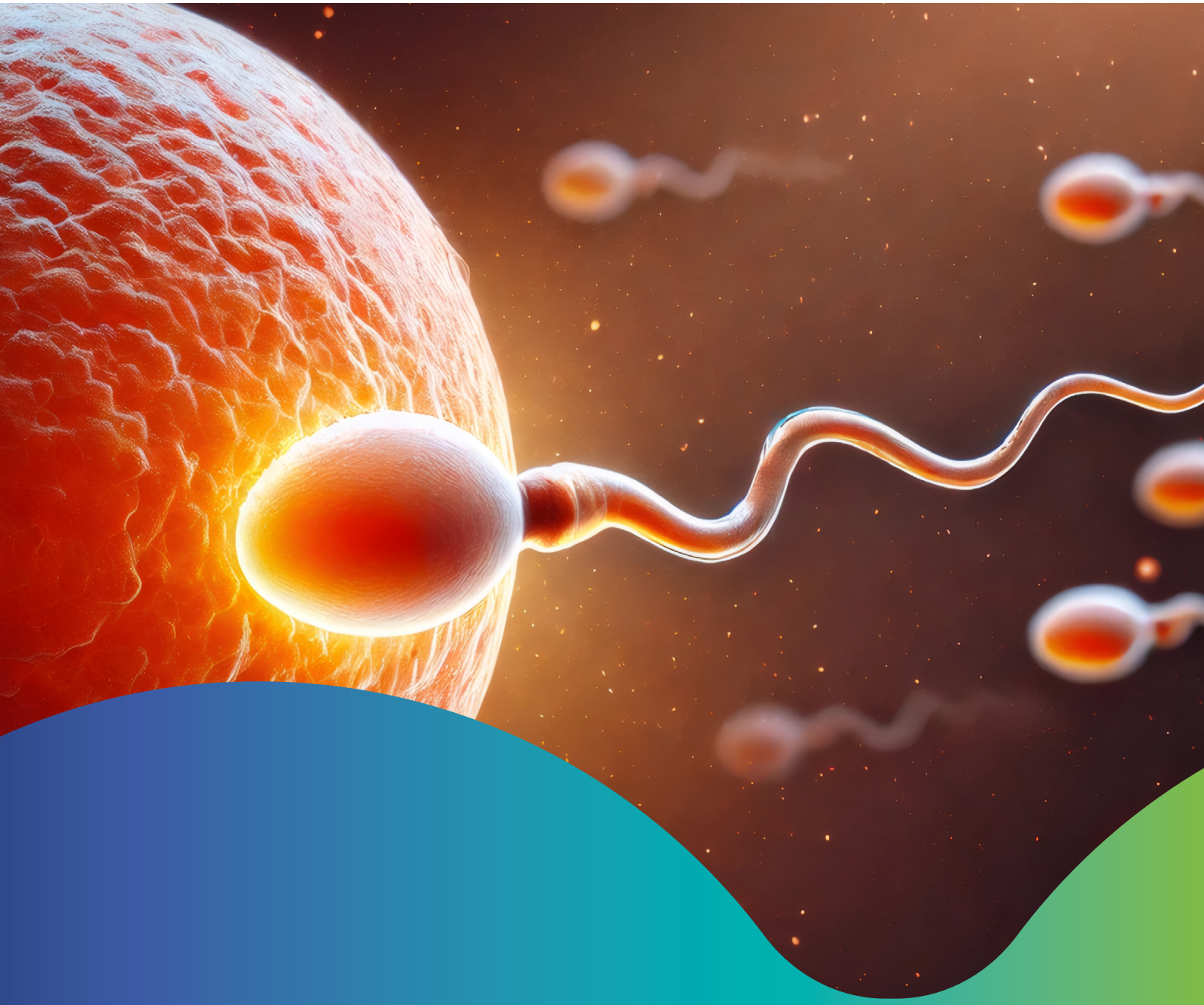

Impacting infertility: a research agenda

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About ESHRE

ESHRE is a European non-profit organisation with international membership, whose main mission is to promote the study and research of reproductive science and medicine as well as the treatment of infertility. Established in 1984, the Society now comprises more than 9.000 members and has become the leading Society in reproductive science and medicine worldwide. Our members are medical professionals, scientists and researchers working in reproductive science, reproductive medicine and embryology. We work in close partnership with the patient organisation Fertility Europe.

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Introduction

Infertility is characterized by the absence of a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner (adapted from (Zegers-Hochschild et al., 2017)).

Infertility is a growing global health concern

Globally, it is estimated that infertility at any moment along reproductive life affects 17.5% of couples (Cox et al., 2022). For many couples, parenthood is considered one of the most important life goals and difficulties in achieving it may have long-term negative implications for their well-being (Gameiro & Finnigan, 2017; Nik Hazlina, Norhayati, Shaiful Bahari, & Nik Muhammad Arif, 2022). The psychological distress that comes with infertility oftentimes creates spillover effects in the person's relationships with their partner, family members and friends. This can be reflected in higher rates of anxiety or depression, as well as troubles with social participation (Katz, Millstein, & Pasch, 2002). Furthermore, evidence suggests that diminished reproductive fitness may be a marker for the general health status of the individual, such as cardiovascular and metabolic health (Cedars et al., 2017). Infertility-related distress and time spent in fertility care may contribute to lower work productivity, resulting in economic losses at both individual and societal level (Collins, 2019). Also, other diseases such as endometriosis that have high quality of life and productivity costs are associated with infertility. Thus, providing fertility care to help people fulfil their reproductive plans not only offers perspectives at the personal level, it also eventually benefits the economy and therefore the individual taxpayer (Keller, Botha, & Chambers, 2023), as does providing health care in any other field.

Certain groups are disproportionately affected by infertility

While the underlying cause of infertility in a heterosexual couple is equally often due to male or female factors, the physical burden of the treatment mostly lies on the woman. Women, particularly those with lower income, have also reported a greater impact of infertility on their relationships and well-being than men (Katz et al., 2002). Other groups that are disproportionately impacted by infertility include cancer patients and members of the LGBTQIA+ community, since they may lack capacity to reproduce with their partners or reproductive capacity may be impaired by medical treatments like chemotherapy or for gender transition (Cheng, Pastuszak, Myers, Goodwin, & Hotaling, 2019). Fertility treatment outcomes also differ between groups. For instance, lower live birth rates after in vitro fertilisation (IVF) are reported for minoritised ethnic groups than for white patients (Humphries, Chang, Humm, Sakkas, & Hacker, 2016).

Research funding programmes should reflect the urgent need to address infertility

Despite the high prevalence of infertility and the known effects it can have on both the individual person and society, infertility is insufficiently covered in recent European Union (EU) programmes for funding health research, such as the latest Horizon Europe work programme (European Commission, 2024). The EU is committed to achieving the United Nations (UN) Sustainable Development Goals (SDGs), which include good health and well-being (SDG 3) and gender equality (SDG 5) (United Nations, 2015). Investing into infertility research can contribute to achieving these goals both directly and indirectly, through building the foundation for more effective infertility prevention and better care and support for those who are affected.

This document was developed by key experts from the European Society of Human Reproduction and Embryology (ESHRE) in collaboration with the patient organisation Fertility Europe. It outlines twelve key topics related to infertility where further research could have a particularly high and beneficial impact in three areas: firstly for basic and clinical science in the field of reproductive medicine, secondly for individuals seeking to fulfil their child wish, and thirdly for the society as a whole.

Maximising the integrity and public value of research

The impact of any type of research is increased by actively being mindful of equity, diversity and inclusion in the research design and by ensuring that the results are made available in accordance with the principles of Open Science. Taking into account the specific sensitivities encountered by people facing infertility, it is of utmost importance that these principles are included in any research funding programmes in the field.

Inclusiveness

In this document, we recognise the impact of language and aim to be inclusive of all people. We understand that binary language may not be appropriate for all and we acknowledge a lack of consensus on optimal language. Therefore, we have used gender-neutral terms wherever possible, but we have retained the terms “women” and “men” in some instances to acknowledge the gendered dimension of human reproduction. Whenever used, the terms “women” and “men” intend to encompass all those that can be affected by the respective condition associated with an individual’s bodily characteristics, regardless of their gender identity.

Research on these 12 key topics will have an important impact to reduce the burden of infertility

Preventing infertility and preserving fertility	1. Better preconception and reproductive care and education for preventing infertility 2. Optimised fertility preservation and restoration techniques to give people a better chance of having a genetically related child
Gynaecological diseases	3. Increased symptom awareness and early and less invasive methods for diagnosis 4. Tailored treatments and psychosocial care to improve quality of life of patients
Male infertility	5. Increased appreciation and understanding of male infertility and contributing risk factors to support prevention and treatment 6. An improved male fertility work-up through advancing current sperm tests and developing new assays
Optimising fertility treatments	7. Personalised fertility treatment based on better patient characterisation 8. Artificial intelligence, prediction and digital tools to advance infertility care
Optimising psychosocial support	9. Adequate psychosocial support for patients, offspring, donors and surrogates in view of the long-term implications of fertility treatment
Deepening knowledge on preimplantation development and early pregnancy	10. Greater insight into oocyte and embryo development by identifying the genetic variants involved 11. A better understanding of embryo implantation through in vitro models and genetic studies 12. Improved knowledge of the causes and risk factors of (recurrent) pregnancy loss for effective prevention

How topics were selected

A broad list of 24 potential research topics was compiled from ESHRE guidelines, prior topic suggestions for the ESHRE research grants and suggestions of experts in the project working group. The potential impact of research on each topic was assessed independently by the working group members using the indicator chart presented below. Each indicator was scored with 0 (low), 1 (medium) or 2 (high), and total scores were calculated giving equal weights to the three dimensions. The twelve topics with the highest impact score were selected for presentation in this document.

Dimensions	Indicators
Individual/ patient impact	**Preventing infertility:** Extent to which research on the topic will contribute to preventing infertility
	QoL and mental health: Extent to which research on the topic will contribute to improving patients' quality of life and mental health
	Satisfaction with care: Extent to which research on the topic will contribute to improving patients' satisfaction with care
	Time to pregnancy/live birth: Extent to which research on the topic will contribute to shortening patients' time to pregnancy and live birth
	Chance of live birth: Extent to which research on the topic will contribute to increasing patients' chances of a live birth
	Reducing risks: Extent to which research on the topic will contribute to reducing the risks of complications during fertility treatment
Societal impact	**Incidence:** Size of the group who will benefit directly from the outcomes of research on the topic
	SDG 3: Extent to which research on the topic will contribute to attaining Sustainable Development Goal 3 "Good health and well-being"
	SDG 5: Extent to which research on the topic will contribute to attaining Sustainable Development Goal 5 "Gender equality"
Scientific impact	**New knowledge:** Level of prior knowledge on the topic (less prior knowledge corresponding to a higher score)
	Positive externalities: Extent to which research on the topic will produce positive spillover effects into other scientific fields

Preventing infertility and preserving fertility

Even before an individual decides to try to have a child, it is essential to consider the impact of certain factors on their fertility. These factors include general preconception health, but also specific pathologies, treatments and environmental exposures that may impair a person's capacity to reproduce.

Improving preconception health may have a positive effect on fertility as well as on offspring health, thereby having an enormous potential to improve public health and reduce healthcare costs. Furthermore, for individuals at risk of losing their fertility prematurely due to a specific pathology or exposure, making use of fertility preservation methods is often the only option to have a genetically related child. There is still a lack of knowledge on how preconception care and fertility preservation can be offered in the most optimal way.

1. Better preconception and reproductive care and education for preventing infertility

Preconception health is considered to have a significant impact on pregnancy outcomes (WHO, 2013). Based on the evidence from life course epidemiology and developmental programming around the time of conception, it is clear that parental lifestyle conditions and environmental exposures can have enduring consequences, leading to increased disease risk for the next generation (Children's Alliance, 2023; ESHRE, 2024). These parental influences on lifetime health can perturb or modify the status of early embryos, potentially changing how they develop. Understanding the causative mechanisms and the exposures that drive them will be essential for the development of specific recommendations for preconception health.

There is an urgent, unmet need to enhance preconception health for individuals aiming to optimize fertility, as well as for those undergoing fertility care, since current antenatal guidance does not adequately address the critical stages of early development – before a woman is aware of her pregnancy. Infertility care providers are uniquely positioned to deliver this essential preconception care. Creating an engaging and sustainable preconception care programme for the improvement of reproductive health would require genuine partnership and communication, both within and between countries.

A case in point is the renewed increase in the number of sexually transmitted infections (STIs) in Europe, some of which have a detrimental impact on fertility (ECDC, 2024). Furthermore, all studies on fertility awareness consistently indicate that the general population lacks knowledge about the factors influencing fertility (Pedro, Brandão, Schmidt, Costa, & Martins, 2018). Unfortunately, the time allocated to education on reproductive health in schools is inexistent or at best under pressure. In addition to the traditional focus on preventing sexually transmitted infections, there is a growing need for greater attention to this topic in schools. Moreover, young people should graduate equipped with knowledge about the impact of a healthy lifestyle on fertility.

Specific recommendations include:

- Investigating engagement and sustainable strategies for improving preconception health.
- Investigating the health economics aspects of preconception care and interventions (through Health Economics Projects).
- Optimising the methods for delivering preconception care to all, including awareness initiatives, delivery modes, timing, settings, and techniques. This should also address inequalities in the context of infertility and include efforts to address social determinants of health.
- Exploring how reproductive health education can be integrated into school curricula and evaluating its impact on knowledge and attitudes.
- Evaluating the implementation and the impact of preconception interventions on fertility outcomes of fertility patients and the underlying biological and/or mechanistic processes.

2. Optimised fertility preservation and restoration techniques to give patients a better chance of having a genetically related child

Fertility declines with age, especially female fertility, but it may also be prematurely lost in infancy, adolescence or adult life, due to specific pathologies (e.g. genetic, chromosomal or immunological conditions), medical treatment (e.g. radiotherapy or chemotherapy for cancer, treatments for gender transition) or acute exposure to environmental factors (e.g. physical and chemical agents in war scenarios) (Anderson et al., 2020). Fertility preservation increases the chances of individuals being able to have genetically related children in the future, which can be a significant contributor to their quality of life and psychological well-being.

For adolescents and adults, the cryopreservation of reproductive cells or embryos offers a unique opportunity to preserve fertility potential. These methods are already fully developed and highly efficient. However, for young, pre-pubertal children, it is not possible to obtain mature sperm or egg cells for cryopreservation, so alternative methods based on immature cells, ovarian and testicular tissue are necessary. These methods are not yet ready for clinical application or need further optimisation (Rodriguez-Wallberg et al., 2021). Future research should be focused on the clinical application of these techniques, which may, in addition to children, also make fertility preservation available and efficient for adults that, for several reasons, may not be eligible to benefit from the established fertility preservation options. Moreover, expanding fertility preservation options would have immense implications for human reproduction, regenerative medicine and treatment options for loss of ovarian reserve due to genetic conditions.

Specific recommendations include:

- Optimising ovarian and testicular tissue cryopreservation, including the management of stored materials.
- Optimising technology for obtaining mature oocytes and sperm from immature cells (i.e. in vitro maturation protocols).
- Promote the development of genetic and non-genetic biomarkers for early-stage presymptomatic prediction of infertility.

Gynaecological diseases

Gynaecological diseases, such as endometriosis, polycystic ovary syndrome (PCOS) and uterine fibroids, affect millions of women globally. These conditions can have a profound impact on health and well-being, including their ability to conceive and carry a pregnancy to term (Leone Roberti Maggiore et al., 2024)

Endometriosis affects approximately 176 million women globally, or about 10% of women of reproductive age (Vizheh, Muhidin, Behboodi Moghadam, & Zareiyan, 2021). It is a chronic and often painful condition in which the endometrium, the tissue that normally lines the inside of the uterus, grows outside the uterus on other organs, such as the ovaries, fallopian tubes, and even the bladder or intestines (Becker et al., 2022). Endometriosis can cause severe pain, heavy bleeding, and infertility (Becker et al., 2022; Leone Roberti Maggiore et al., 2024).

Polycystic ovary syndrome (PCOS) is estimated to affect 8-13% of women of reproductive age (WHO, 2023). It is characterized by hormonal imbalances, irregular menstrual cycles and the presence of small cysts on the ovaries. PCOS can lead to infertility, as well as an increased risk of metabolic disorders such as type 2 diabetes and cardiovascular disease (Mercuri & Cox, 2022; Teede et al., 2023).

Uterine fibroids are present in up to 68% of women (E. Stewart, Cookson, Gandolfo, & Schulze-Rath, 2017). In approximately 30% of those affected, these benign tumours cause severe symptoms like heavy bleeding, pain and infertility (E. A. Stewart et al., 2016).

Research on gynaecological diseases has historically been underfunded and undervalued, while patient's complaints have often been overlooked, such as menstrual pain in patients with endometriosis (Hudson, 2022; Rice et al., 2020). However, in recent years, there has been a growing recognition of the importance of advancing research in female reproductive health. Despite these efforts, there are still significant knowledge gaps that need to be addressed, particularly related to the diagnosis, as well as appropriate treatment and counselling for those affected.

3. Increased symptom awareness and early and less invasive methods for diagnosis

A big challenge in relation to gynaecological diseases lies in the late diagnosis, often due to non-specific symptoms, a lack of symptom awareness by clinicians and patients, and the invasive nature of traditional diagnostic methods.

For PCOS and endometriosis, there is a lack of consensus on the diagnostic criteria, which can lead to misdiagnosis and delayed treatment (Becker et al., 2022; Kiconco et al., 2022; Mercuri & Cox, 2022; Teede et al., 2023). Current diagnostic practices for gynaecological diseases frequently involve invasive procedures like laparoscopy, which, while accurate, carry risks and discomfort (Becker et al., 2022). Recent research has focused on developing less invasive, more accessible diagnostic methods. For example, advancements in imaging techniques such as transvaginal ultrasound and MRI have improved non-invasive diagnostic accuracy (Noventa et al., 2019). Additionally, molecular diagnostics, including blood-based biomarkers and genetic testing, are showing promise (Encalada Soto et al., 2022). Artificial intelligence (AI) is increasingly being integrated into these diagnostic methods, with the aim to enhance the accuracy and efficiency of disease detection. AI algorithms can analyse vast amounts of imaging data quickly, identifying patterns that can facilitate diagnosis and predict the prognosis (Avery et al., 2024).

Continued research into non-invasive diagnostic methods holds significant potential to transform the management of gynaecological diseases. Earlier and more specific diagnosis could support the development of more personalized treatment plans, improve disease outcomes, reduce the need for more invasive procedures, and enhance patients' reproductive outcomes and quality of life.

Specific recommendations include:

- Developing population-level awareness and educational initiatives about symptoms associated with PCOS and endometriosis and other associated gynaecological diseases (e.g., Severe Period Pain), including within medical training, and developing tools for symptom tracking and reporting, to ensure timely healthcare seeking, recognition of symptoms, and referral processes for diagnosis and care.
- Developing minimally invasive methods for early and accurate diagnosis through refined imaging technologies, advanced biomarker identification, genetic profiling, and AI integration to enable earlier intervention.
- Creating deeper understanding of disease characteristics through radiomics, the extraction of large amounts of features from radiographic medical images using data-characterization algorithms.

4. Tailored treatments and supportive care to improve the quality of life of patients

Even if detected early, gynaecological diseases can have a significant impact on well-being, due to barriers in access to care and a current lack of appropriate treatment methods. Also, there is a need to improve obstetric and perinatal care in people with these conditions, since their pregnancies can be high-risk pregnancies. By prioritizing research in these areas, the overall management of gynaecological diseases can be improved, and the chances of having a child can be enhanced for those affected. This will not only improve the health and well-being of

individuals, but also have broader societal benefits, such as reducing the economic burden of these conditions and promoting gender equality (Kiconco et al., 2022; Mercuri & Cox, 2022; Vizheh et al., 2021; WHO, 2023).

Specific recommendations include:

- Developing strategies to improve access to healthcare for all those affected by gynaecological diseases, particularly in low-resource settings, and reducing stigma and discrimination, including by identifying and addressing factors associated with disparities in access to reproductive healthcare.
- Developing new treatments: Investigating new pharmacological and non-pharmacological interventions to manage the symptoms of PCOS and endometriosis, and to maximise fertility potential.
- Making use of augmented reality (AR) to assist surgeons in planning and performing minimally invasive surgeries with higher precision.
- Studying how the size, number, and location of fibroids affect IVF outcomes, and developing tools to integrate these factors in treatment decisions.
- Determining the optimal timing and type of surgical intervention for fibroids in the context of IVF, as well as the long-term outcomes of these surgeries.
- Investigating non-surgical treatment options of fibroids (e.g., medical management, lifestyle changes) and their impact on IVF treatment outcomes.
- Conducting research on the genetic, immunological, hormonal, and environmental factors that contribute to the development of PCOS and endometriosis, in order to develop more targeted and effective interventions.
- Developing resources for self-management of chronic gynaecological conditions, to promote symptom management and quality of life, and prevent infertility.
- Improving preconception, obstetric and perinatal care for people affected by gynaecological diseases. Preconception conditions should be diagnosed and treated. Pregnant individuals with gynaecological diseases should be informed about the risks and the obstetric care should be intensified.

Male infertility

Male infertility affects at least 7% of men globally and contributes to infertility in at least half of all couples struggling to conceive. A systematic review and meta-analysis from 2023 found that overall sperm count declined by half between 1973 and 2018, giving rise to the concern that cases of male infertility may become even more frequent in the future (Levine et al., 2023).

Male infertility is often linked to genetic factors or to medical conditions such as urogenital anomalies, endocrine disorders, impaired spermatogenesis, infections, and sexual dysfunction. Additionally, lifestyle choices, environmental exposures -particularly to chemicals- and underlying health conditions and their treatments play significant roles (ESHRE, 2024). However, there is limited knowledge regarding the specific impact of lifestyle (e.g., diet, smoking, alcohol consumption), environmental (e.g. pollutants and endocrine-disrupting chemicals) and pharmaceutical factors (e.g. chemotherapy, immunotherapy, others pharmaceutical genotoxic drugs) on male fertility, and whether these factors have cumulative effects.

Historically, male fertility has been conflated with sperm count, but experts consider this is only one component of conception. Evidence now demonstrates that events such as miscarriage (West et al., 2022), child health after delivery, and conditions such as autism can be linked to paternal factors and sperm quality more than previously expected (Feinberg et al., 2015). This creates a new scenario where societally the question is not just one of whether a male person can contribute to conception itself, but also the steps that can be taken to improve the sperm quality or selection for the benefit of offspring health. Beyond fertility, sperm quality may be a marker for general health; recent research suggests associations between (in)fertility and risk of cancer, cardiometabolic disease, and even premature mortality (Kasman, Del Giudice, & Eisenberg, 2020).

Significant knowledge gaps related to male infertility persist. In particular, further research on modifiable risk factors and on the value of sperm testing for predicting fertility treatment outcomes is expected to have a substantial impact.

5. Increased appreciation and understanding of male infertility and contributing risk factors to support prevention and treatment

Treatment strategies for male infertility often address modifiable risk factors. Lifestyle modifications, such as smoking cessation, weight management, and reduced alcohol and drug intake may improve sperm parameters and increase the chance of conception. Such lifestyle modifications may have additional benefits, one example being a possible link between healthy diet and offspring intelligence, reported in recent studies (Lv et al., 2024).

While assisted reproductive technologies, such as IVF and intracytoplasmic sperm injection (ICSI), offer couples with fertility issues a chance to have a child, they circumvent rather than resolve the issues. It is essential to recognize that increased paternal age can still have a significant impact on the foetus. De novo mutations that accumulate in the testis with ageing can be passed on to the child. As such, increased paternal age has been linked with increased risk of genetic disorders in the offspring, birth defects, and even death in childhood (Aitken, 2024; Fang et al., 2020).

Research to understand all aspects and implications of male fertility is essential. To improve reproductive health outcomes, men must be supported to modify their risk factors, as well as provided with new targeted treatments.

Specific recommendations include:

- Studying the impact of lifestyle, environmental and pharmaceutical factors on sperm quality and consequently male fertility, child development and morbidity.
- Studying the association between sperm characteristics and general male health.
- Continuing research on molecular mechanisms and large-scale epidemiological studies, which should help towards the development of targeted interventions and novel treatments.
- Improving the methods to process and select sperm for fertility treatments (IVF/ICSI).

6. An improved male fertility work-up through advancing current sperm tests and developing new assays

Sperm cells (or spermatozoa) are highly differentiated cells that possess different structures responsible for several properties: the head, containing the acrosome and nucleus, allows for the interaction with the oocyte and the transmission of paternal genetic and epigenetic material after fertilisation; the flagellum (i.e. the tail) is responsible for sperm motility and ensures the sperm cell can move through the female genital tract. Sperm motility, and sperm morphology, but also sperm count have a significant impact on the chances of achieving a pregnancy, both through spontaneous conception and through fertility treatments (Colpi et al., 2018).

Various sperm parameters and sperm function tests have been developed and serve as potential indicators in determining the chances for achieving a pregnancy or a live birth. In addition to these traditional sperm parameters, sperm function tests provide deeper insights into the functional capacity of spermatozoa. These tests evaluate various aspects of sperm function, such as capacitation, acrosome reaction, sperm-oocyte interaction, and sperm nucleus integrity (WHO, 2021), all of which are critical for successful fertilisation and embryo development.

While significant advances have been made in the field of sperm testing, several areas remain under-researched and warrant further investigation to enhance our understanding and improve clinical practices. By addressing these research gaps, the field of sperm testing and ART can advance, leading to improved diagnostic accuracy, better-targeted treatments, and ultimately, higher chances of a healthy live birth in fertility treatments.

Specific recommendations include:

- Standardising testing protocols through thresholds for tests and universal guidelines to allow firm conclusions of the value of sperm tests.
- Evaluating the effects of sperm nucleus damage (chromosomes, DNA and chromatin) on embryo development, offspring health and development to determine the relevance of sperm nucleus integrity testing.
- Determining the effectiveness of advanced sperm selection techniques and other interventions to improve IVF outcomes through robust clinical trials.
- Investigating the (molecular and cellular) mechanisms underlying sperm function deficits and genetic and epigenetic factors underlying male infertility.

Optimising fertility treatments

Fertility treatments often lack a precise and personalised approach, leaving patients and healthcare providers to navigate complex decisions without guidance that is specific to the patient's case.

7. Personalised fertility treatment based on better patient characterisation

A first aspect of personalised treatment is the diagnostic work up of couples struggling to conceive, which ideally would identify the underlying causes of the infertility and allow targeted treatment. However, infertility cannot always be attributed to a single underlying cause, with recent data reflecting that female and male factors can have a synergistic effect on each other, such that for instance reduced egg quality can lead to a stronger negative effect of poor sperm on prognosis (Kekäläinen, 2021; Makieva et al., 2023). Approximately 30% of couples affected by infertility are considered to experience "unexplained" or "idiopathic" infertility (The Guideline Group on Unexplained Infertility et al., 2023). This diagnosis, made by exclusion when no abnormalities of the female and male reproductive systems are identified, inevitably leads to unspecific treatment. Even in the case where a male or female underlying factor is identified, treatment decisions rely on standardised protocols rather than robust prognostic tools. Such tools could be built on the tests included in the current diagnostic work up protocols, but would likely be much more precise and useful if genetic and molecular profiles could be included.

Building personalised treatment plans requires high quality data on the outcomes of previous treatments in a large number of different patients. However, data collection on medically assisted reproduction is challenging, since treatments are often segmented over several cycles and it is not uncommon for patients to change clinics or even seek treatment in a different country throughout the process. Therefore, a European registry of medically assisted reproduction that follows patients' entire treatment trajectories would significantly improve the accuracy of treatment data and thereby have strong potential for advancing patient care.

Addressing these research gaps in infertility could significantly enhance the effectiveness of personalized fertility treatments and improve live birth rates after IVF for various specific diagnoses and conditions.

Specific recommendations include:

- Identifying biomarkers and developing reliable biomarkers tests and diagnostic tools to help better understand the underlying causes of infertility, and reduce the number of couples diagnosed with unexplained infertility. Novel in vivo/in vitro diagnostics can further support this.
- Identifying genetic and molecular markers and profiles in individuals and couples affected by infertility to support the development of tailored treatment protocols. This includes further exploration of the integration of genomic medicine into IVF protocols to tailor treatments based on patients' genetic profiles.
- Identifying immunological dysfunctions linked to fertility, their role and the relevance of immune-modulating treatments or personalized immunotherapy options to optimise fertility in patients with immune-related infertility issues.

- Developing and adapting treatment protocols (e.g., specific medications, dosing strategies) specifically for different subgroups of patients/couples affected by infertility.
- Exploring the potential of less invasive treatment methods such as intra-uterine insemination (IUI) for different patient groups.
- Exploring new treatment strategies for low ovarian response, endometrial disease, adenomyosis, and recurrent implantation failure and recurrent miscarriage.
- Exploring in vitro maturation (IVM) for individuals with PCOS and people with excessive ovarian response.
- Evaluating add-ons to treatment protocols and their relevance for different subgroups of patients/couples affected by infertility.
- Improving data collection on medically assisted reproduction through inter-institutional and cross-border follow-up.

8. Artificial intelligence, prediction and digital tools to advance infertility care

In addition to more specific diagnostic tests and profiling of patients affected by infertility, development of digital tools - possibly including artificial intelligence (AI) - have the potential to substantially improve the efficacy and safety of fertility treatments and psychosocial care. With the current diagnostic tools and tests, treatment decisions rely on time-consuming manual interpretations of limited data points; they also struggle to account for the interplay of relevant genetic, behavioural, psychosocial, lifestyle, and environmental factors. By analysing vast datasets, encompassing a potentially unlimited number of data points, and considering moderated and cumulative impacts of multiple factors, AI and digital prediction tools can dramatically enhance decision-making processes during fertility care. Therefore, they are being investigated to provide personalized psychosocial care, optimize laboratory procedures and offer evidence-based and objective clinical guidance (Riegler et al., 2021).

Clinically, AI tools can suggest more effective treatments tailored to each patient and forecast potential complications, allowing for proactive intervention and risk mitigation strategies (Hariton, Pavlovic, Fanton, & Jiang, 2023). AI algorithms constructed to analyse images of sperm, oocytes and embryos developing in vitro show promise in recognizing/assessing and selecting those with the best ability to lead to a healthy child. Preliminary research suggests AI-driven tools have the potential to outperform manual assessments and minimize operator-related subjectivity (Fjeldstad et al., 2024; Theilgaard Lassen, Fly Kragh, Rimestad, Nygård Johansen, & Berntsen, 2023; Tran, Cooke, Illingworth, & Gardner, 2019; VerMilyea et al., 2020). AI tools may also help in the psychosocial care of patients undergoing fertility treatments, by tailoring information provision, providing coping strategies and connecting patients with comprehensive support (Jenkins et al., 2020; Senapati et al.).

So far, the effectiveness of most AI-driven tools is yet to be rigorously validated. Further investigation is required to better understand the real-world impact of these tools, while also exploring the ethical implications and addressing potential biases. A commitment to further research from all stakeholders across the healthcare landscape will pave the way for more effective, patient-centred fertility care and reduce the financial burden to patients and to health care systems.

Specific recommendations include:

- Continuing and expanding work on the construction of AI algorithms that analyse images of gametes and embryos developing in vitro, to select those with the best ability to lead to a healthy child.
- Developing automated decision-making AI-driven tools and evaluate against manual or subjective assessors.
- Exploring the potential of AI-tools to improve identification of patients at risk for poor mental health and quality of life, and personalisation of psychosocial care to patients undergoing fertility treatment.
- Developing methodological approaches to better evaluate the effectiveness of AI-driven tools in fertility care that address potential/current biases.
- Developing understanding about the ethical implications and the real-world impact of AI-tools.

Optimising psychosocial support

Providing psychosocial support to infertility patients is of utmost importance, due to the potential long-term implications of infertility and fertility treatment for mental health (Gameiro et al., 2015). In this field, there is a particular need for further research on how to support patients ending fertility care without the children they desire and on how to support all different parties involved in third-party reproduction.

9. Adequate psychosocial support for patients, offspring, donors and surrogates in view of the long-term implications of fertility treatment

Approximately 188,000 of the 400,000 people who undergo fertility treatment in Europe every year end treatment without achieving their parenthood goals, despite its high physical and mental burden (McLernon, Maheshwari, Lee, & Bhattacharya, 2016; The European I. V. F. Monitoring Consortium for the European Society of Human Reproduction and Embryology et al., 2023). Inequalities in fertility outcomes arise due to a variation in factors such as national funding and access to care policies, patients' ability to afford care in private clinics, the geographic location of clinics and levels of fertility awareness (Ekechi, 2021; The European I. V. F. Monitoring Consortium for the European Society of Human Reproduction and Embryology et al., 2024).

Evidence from meta-synthesis shows that ending treatment without children is associated with poorer mental health and well-being, and that patients describe this as a devastating experience associated with intense grief, sadness, and profound existential crisis, taking, on average, two years to overcome (Gameiro & Finnigan, 2017). Despite this profound impact, there is a striking lack of investment in supporting patients' healthy adjustment after their treatment ends without the children they desire. To date, only three psychosocial interventions have been developed and evaluated that focus on supporting this patient group (Kraaij, Garnefski, Fles, Brands, & van Tricht, 2016; Rowbottom, Galhardo, Donovan, & Gameiro, 2022; Sousa-Leite, 2024) and current guidance from fertility guidelines and regulation is insufficient.

Even when fertility treatment does result in patients having the children they desire , evidence suggests that the experience of infertility and fertility treatment can have long-term psychological implications for parents and offspring. These can be particularly pronounced in the case of third-party reproduction (gamete donation and surrogacy), due to multiple factors. First, the lack of genetic link between donor-conceived people and their parents can impact relationships and creates challenges for disclosing donor conception (Golombok et al., 2018; Zadeh, Ilioi, Jadva, & Golombok, 2018). Second, the removal of donor anonymity across many countries in Europe and the growth in use of direct-to-consumer DNA testing has enabled the easy establishment of links between donor-conceived people and their donors, as well as between same-donor offspring, often referred to as "half-siblings" (Crawshaw, 2018; Widbom, Sydsjö, & Lampic, 2022). Third, the association of third-party reproduction with the establishment of complex non-traditional families and novel treatments that allow for shared biological parenting has always and will continue to make it challenging for all family members to navigate these novel family compositions. It also raises concerns about the welfare of offspring that need addressing (Gartrell, Bos, & Koh, 2018; Golombok, Zadeh, Imrie, Smith, & Freeman, 2016). In sum, the complex biopsychosocial context in which third-party

reproduction tends to occur requires in-depth understanding of the short and long-term psychological impacts for parents, donors, surrogates, offspring, and their families. Therefore, professional organisations have called for expanding psychosocial support over the life-course (International Infertility Counselling Organisation, 2024). However, research on how these groups can be adequately supported in their psychological adjustment is lacking.

Further research on this topic will enable European fertility clinics to fully address the unmet and urgent duty of care to fertility patients, gamete donors, surrogates and offspring born from medically assisted reproduction as well as their families.

Specific recommendations include:

- Mapping the heterogeneity of treatment trajectories from the moment patients seek fertility care to when they decide to stop treatment, regardless of outcome.
- Mapping the heterogeneity of those not seeking treatment but exploring other options (adoption, fostering, life without children) and understanding their experiences and needs.
- Mapping the full range of individual and social impacts experienced as a result of different outcomes of fertility treatment on patients, gamete donors, surrogates, offspring, and their families.
- Identifying individual, social, treatment, and care factors associated with (short and long-term) poor mental health, wellbeing, and quality of life in fertility patients, gamete donors, surrogates, and offspring born from fertility treatments and their families.
- Developing and evaluating tools and psychosocial interventions that use cutting-edge knowledge and technology (e.g., AI, telemedicine, big data, wearables) to promote healthy adjustment for fertility patients, gamete donors, surrogates, and offspring and their families.
- Developing care models to support planning and value-based decisions for all possible fertility treatment options and outcomes, including discussion of alternative paths to, and beyond, parenthood.
- Implementing and testing the integration of quality-of-life measures as outcomes that matter in fertility care and monitor these in European Medically Assisted Reproduction registries.

Deepening knowledge on pre-implantation development and early pregnancy

As infertility caused by external factors like infections decreases, the proportion of patients suffering from genetic, immunological, endocrine, and anatomical causes of infertility come to the forefront (Dougherty et al., 2023; Inhorn & Patrizio, 2015; Randeva et al., 2012; Raperport, Chronopoulou, Homburg, Khan, & Bhide, 2023). However, there is still much to be learned about these causes of infertility and further research in this field could have a substantial impact.

Recently, a number of new infertility types of presumed genetic aetiology were identified (Capalbo et al., 2021; Picchetta et al., 2022). IVF procedures allow close observation of gametes and embryos performance during in vitro maturation and development, revealing specific phenotypes causing oocyte maturation arrest, fertilisation failures, and embryo development arrest—issues that would remain undetected in spontaneous pregnancies and be classified as idiopathic or unexplained infertility. Some patients experience recurring patterns of embryonic developmental issues across multiple cycles (Capalbo, Buonaiuto, et al., 2022), suggesting genetic causes rather than random factors like laboratory conditions or hormonal influences (Cimadomo et al., 2023).

We have identified three areas of heretofore poorly researched fundamental causes of infertility: oocyte/zygote/embryo maturation arrest, (recurrent) implantation failure and (recurrent) pregnancy loss.

10. Greater insight into oocyte and embryo development by identifying the genetic variants involved

Genetics of infertility has made considerable progress in recent years, since genetic causes are now the last ones to still be resistant to fertility treatment. While the focus was initially on the male part, this has now shifted to the genetics of female infertility (Van Der Kelen et al., 2023).

Improvements in genomic research, especially through whole exome sequencing (WES), have made significant progress in identifying causative genes for infertility such as PADI6, TUBB8, and WEE2 (Chi et al., 2024; A. Wang et al., 2021; X. Wang et al., 2022; Yao et al., 2022). Genes responsible for premature ovarian failure (POI) have been known for several years, and more recently three additional phenotypes - Oocyte Maturation Defect (OMD), fertilisation failure, PReimplantation EMBryonic Lethality (PREMBL) - have been the subject of genetic studies. Initially considered to be different entities, Online Mendelian Inheritance in Man (OMIM), have taken the view that they are the same pathology but with varying degrees of expression, and have reclassified these phenotypes under the single label of oocyte/zygote/embryo maturation arrest (OZEMA).

To date, only twenty genes have been identified as responsible for an OZEMA phenotype. These genes are involved in several complex processes, including meiosis, with its specific features in female gametes; oocyte maturation, indispensable for correctly executed meiosis; fertilisation and the early stages of embryonic development. It is estimated that several hundred genes have yet to be identified. Although it is currently not possible to put a figure on the number of women affected, the identification of genes remains a priority for the management of infertility patients

as it stands as the last aetiology of infertility for which very little treatment can be offered. Identifying genes involved in an OZEMA phenotype opens up the possibility of developing diagnostic tools and, consequently, appropriate/personalised treatments. A genetic diagnosis also allows genetic counselling for members of the patient's family (Sang et al., 2018; Verpoest, Okutman, Van Der Kelen, Sermon, & Viville, 2023). In addition, this research is leading to a better understanding of the physiology of female fertility, and thus to an overall improvement in the proposed treatments for ovarian stimulation and embryo culture. As in other fields of medical genetics, the ethical aspect of this research should not be neglected. While other considerations such as reproductive autonomy, the right (not) to know and privacy issues are still at play here, the profound effect of the presence of variants leading to infertility in patients with a child wish needs careful reflection (Verpoest et al., 2023).

Specific recommendations include:

- Continuing efforts to identify further genes responsible for an OZEMA phenotype.
- Developing gene therapies for identified genes. The first gene therapy studies have begun, with convincing results for some genes and failures for others, emphasizing the need to continue these studies (Sang et al., 2018).

11. A better understanding of embryo implantation through in vitro models and genetic studies

Implantation failure is the situation where a high-quality embryo is not implanting after transfer to the uterus (ESHRE Working Group on Recurrent Implantation Failure et al., 2023).
Even good quality embryos resulting from mature oocytes often fail to implant and result in pregnancy. A significant portion of this failure is due to chromosomal aberrations, such as aneuploidies, that are uniformly present within the embryo and most commonly inherited from the female gamete (Capalbo, Poli, Jalas, Forman, & Treff, 2022; Hassold & Hunt, 2001). However, even when using preimplantation genetic testing for aneuploidies (PGT-A) to identify euploid embryos for transfer, still half of them fail to implant and lead to a successful pregnancy, explaining why IVF remains inefficient in a significant proportion of patients (Cimadomo et al., 2023; Tiegs et al., 2021).

New approaches to address the black box of embryo implantation are continuously being developed. One such approach is embryo outgrowth, which involves extending the culture of an embryo up to day 14 of in vitro development (Popovic et al., 2019). The development of organoids mimicking the endometrial environment that allow human embryos to initiate implantation in vitro have taken implantation models to a new level (Rawlings et al., 2024; Santamaria et al., 2023). Combined with the use of stem cell derived embryo models (Rivron et al., 2023) that alleviate the scarcity of human embryos for research and are unencumbered by the 14-day rule for embryo culture, new powerful in vitro models applicable at large scale become available. These models are amenable to large-scale genome editing, which can be valuable for studying the impact of lethal genes, helping to elucidate specific pathways associated with implantation and their impact on its correct fulfilment (Cacheiro et al., 2024; Kline et al., 2021; Zhang, Yin, & Zhou, 2023).

Specific recommendations include:

- Investing in research focused on genome editing tools is a prerequisite to be able to carry out functional studies into genetic variants causing infertility.
- Making use of in vitro models to study genetic variants associated with poor implantation.

12. Improved knowledge of the causes and risk factors of (recurrent) pregnancy loss

Pregnancy loss is defined as the spontaneous demise of a pregnancy before the foetus reaches viability (Bender Atik et al., 2023). A significant proportion of pregnancies ends in a pregnancy loss. This holds for both spontaneous and assisted conceptions. Accordingly, every year more than 30 million pregnancy losses happen. The authors of The Lancet miscarriage series 2021 (Coomarasamy, Dhillon-Smith, et al., 2021; Coomarasamy, Gallos, et al., 2021; Quenby et al., 2021) called for a complete rethink of the narrative around pregnancy loss and a comprehensive overhaul of medical care and advice offered to individuals with recurrent pregnancy loss.
The ESHRE recurrent pregnancy loss guideline concludes similarly that evidence-based understanding is sparse and evidence-based treatments are lacking (Bender Atik et al., 2023). Simultaneously, there is an increasing demand from patients and society to provide answers on why a pregnancy loss happened and what can be done to avoid another loss.

Studies have shown a mental burden for the patients, an increasing risk of losing a pregnancy with each consecutive pregnancy loss, and an increasing association with diseases such as diabetes, cardiovascular, autoimmune, and mental diseases and mental health issues 10-15 years after pregnancy loss. It is evident that part of the problem is due to foetal conditions that are incompatible with life but for about half of pregnancy losses no such condition is identified, and the cause of the pregnancy loss could be a range of disturbances where the womb rejects a potentially viable pregnancy. Future research is needed to understand the causes of recurrent pregnancy loss and to identify risk factors that can inform a preventative approach through prognostic tools to increase the chances of a live birth in these patients. It will also lead to new insights on fertility and infertility.

Specific recommendations include:

- Investigating causes of and risk factors for (recurrent) pregnancy loss and the underlying mechanisms through large and in-depth population studies.
- Increasing the understanding of the processes involved in early pregnancy and foetal-maternal interactions through fundamental research.

References

Aitken, R. J. (2024). Paternal age, de novo mutations, and offspring health? New directions for an ageing problem. *Human Reproduction, 39*(12), 2645–2654. doi:10.1093/humrep/deae230

Anderson, R. A., Amant, F., Braat, D., D'Angelo, A., Chuva de Sousa Lopes, S. M., Demeestere, I., . . . Vermeulen, N. (2020). ESHRE guideline: female fertility preservation. *Hum Reprod Open, 2020*(4), hoaa052. doi:10.1093/hropen/hoaa052

Avery, J. C., Deslandes, A., Freger, S. M., Leonardi, M., Lo, G., Carneiro, G., . . . Hull, M. L. (2024). Non-invasive diagnostic imaging for endometriosis part 1: a systematic review of recent developments in ultrasound, combination imaging, and artificial intelligence. *Fertil Steril, 121*(2), 164–188. doi:10.1016/j.fertnstert.2023.12.008

Becker, C. M., Bokor, A., Heikinheimo, O., Horne, A., Jansen, F., Kiesel, L., . . . Vermeulen, N. (2022). ESHRE guideline: endometriosis. *Hum Reprod Open, 2022*(2), hoac009. doi:10.1093/hropen/hoac009

Bender Atik, R., Christiansen, O. B., Elson, J., Kolte, A. M., Lewis, S., Middeldorp, S., . . . Goddijn, M. (2023). ESHRE guideline: recurrent pregnancy loss: an update in 2022. *Hum Reprod Open, 2023*(1), hoad002. doi:10.1093/hropen/hoad002

Cacheiro, P., Lawson, S., Van den Veyver, I. B., Marengo, G., Zocche, D., Murray, S. A., . . . Smedley, D. (2024). Lethal phenotypes in Mendelian disorders. *Genet Med, 26*(7), 101141. doi:10.1016/j.gim.2024.101141

Capalbo, A., Buonaiuto, S., Figliuzzi, M., Damaggio, G., Girardi, L., Caroselli, S., . . . Kahraman, S. (2022). Maternal exome analysis for the diagnosis of oocyte maturation defects and early embryonic developmental arrest. *Reprod Biomed Online, 45*(3), 508–518. doi:10.1016/j.rbmo.2022.05.009

Capalbo, A., Poli, M., Jalas, C., Forman, E. J., & Treff, N. R. (2022). On the reproductive capabilities of aneuploid human preimplantation embryos. *Am J Hum Genet, 109*(9), 1572–1581. doi:10.1016/j.ajhg.2022.07.009

Capalbo, A., Poli, M., Riera-Escamilla, A., Shukla, V., Kudo Høffding, M., Krausz, C., . . . Simon, C. (2021). Preconception genome medicine: current state and future perspectives to improve infertility diagnosis and reproductive and health outcomes based on individual genomic data. *Hum Reprod Update, 27*(2), 254–279. doi:10.1093/humupd/dmaa044

Cedars, M. I., Taymans, S. E., DePaolo, L. V., Warner, L., Moss, S. B., & Eisenberg, M. L. (2017). The sixth vital sign: what reproduction tells us about overall health. Proceedings from a NICHD/CDC workshop. *Human Reproduction Open, 2017*(2), hox008. doi:10.1093/hropen/hox008

Cheng, P. J., Pastuszak, A. W., Myers, J. B., Goodwin, I. A., & Hotaling, J. M. (2019). Fertility concerns of the transgender patient. *Transl Androl Urol, 8*(3), 209–218. doi:10.21037/tau.2019.05.09

Chi, P., Ou, G., Qin, D., Han, Z., Li, J., Xiao, Q., . . . Deng, D. (2024). Structural basis of the subcortical maternal complex and its implications in reproductive disorders. *Nat Struct Mol*

Biol, 31(1), 115–124. doi:10.1038/s41594–023–01153–x

Children's Alliance. (2023). *A preconception care strategy*. Retrieved from https://childrensalliance.org.uk/wp-content/uploads/2023/05/2–Preconception-care-strategy-report-University-of-Southampton.pdf

Cimadomo, D., Rienzi, L., Conforti, A., Forman, E., Canosa, S., Innocenti, F., . . . Capalbo, A. (2023). Opening the black box: why do euploid blastocysts fail to implant? A systematic review and meta-analysis. *Hum Reprod Update, 29*(5), 570–633. doi:10.1093/humupd/dmad010

Collins, M. E. (2019). The Impact of Infertility on Daily Occupations and Roles. *J Reprod Infertil, 20*(1), 24–34.

Colpi, G. M., Francavilla, S., Haidl, G., Link, K., Behre, H. M., Goulis, D. G., . . . Giwercman, A. (2018). European Academy of Andrology guideline Management of oligo-astheno-teratozoospermia. *Andrology, 6*(4), 513–524. doi:10.1111/andr.12502

Coomarasamy, A., Dhillon-Smith, R. K., Papadopoulou, A., Al-Memar, M., Brewin, J., Abrahams, V. M., . . . Quenby, S. (2021). Recurrent miscarriage: evidence to accelerate action. *Lancet, 397*(10285), 1675–1682. doi:10.1016/s0140–6736(21)00681–4

Coomarasamy, A., Gallos, I. D., Papadopoulou, A., Dhillon-Smith, R. K., Al-Memar, M., Brewin, J., . . . Quenby, S. (2021). Sporadic miscarriage: evidence to provide effective care. *Lancet, 397*(10285), 1668–1674. doi:10.1016/s0140–6736(21)00683–8

Cox, C. M., Thoma, M. E., Tchangalova, N., Mburu, G., Bornstein, M. J., Johnson, C. L., & Kiarie, J. (2022). Infertility prevalence and the methods of estimation from 1990 to 2021: a systematic review and meta-analysis. *Hum Reprod Open, 2022*(4), hoac051. doi:10.1093/hropen/hoac051

Crawshaw, M. (2018). Direct-to-consumer DNA testing: the fallout for individuals and their families unexpectedly learning of their donor conception origins. *Human Fertility, 21*(4), 225–228. doi:10.1080/14647273.2017.1339127

Dougherty, M. P., Poch, A. M., Chorich, L. P., Hawkins, Z. A., Xu, H., Roman, R. A., . . . Layman, L. C. (2023). Unexplained Female Infertility Associated with Genetic Disease Variants. *N Engl J Med, 388*(11), 1055–1056. doi:10.1056/NEJMc2211539

ECDC. (2024). STI cases on the rise across Europe. Retrieved from https://www.ecdc.europa.eu/en/news-events/sti-cases-rise-across-europe

Ekechi, C. (2021). Addressing inequality in fertility treatment. *Lancet, 398*(10301), 645–646. doi:10.1016/s0140–6736(21)01743–8

Encalada Soto, D., Rassier, S., Green, I. C., Burnett, T., Khan, Z., & Cope, A. (2022). Endometriosis biomarkers of the disease: an update. *Curr Opin Obstet Gynecol, 34*(4), 210–219. doi:10.1097/gco.0000000000000798

ESHRE. (2024). Factsheet on environmental exposure and male reproductive health. Retrieved from https://www.eshre.eu/Press-Room/Resources/Fact-sheets

ESHRE Working Group on Recurrent Implantation Failure, Cimadomo, D., de los Santos, M. J., Griesinger, G., Lainas, G., Le Clef, N., . . . Macklon, N. (2023). ESHRE good practice recommendations on recurrent implantation failure†. *Human Reproduction Open,*

2023(3), hoad023. doi:10.1093/hropen/hoad023

European Commission. (2024). Horizon Europe Work Programme 2023–2025 4. Health. Retrieved from https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021–2027/horizon/wp-call/2023–2024/wp–4–health_horizon–2023–2024_en.pdf

Fang, Y., Wang, Y., Peng, M., Xu, J., Fan, Z., Liu, C., . . . Zhang, H. (2020). Effect of paternal age on offspring birth defects: a systematic review and meta-analysis. *Aging (Albany NY), 12*(24), 25373–25394. doi:10.18632/aging.104141

Feinberg, J. I., Bakulski, K. M., Jaffe, A. E., Tryggvadottir, R., Brown, S. C., Goldman, L. R., . . . Feinberg, A. P. (2015). Paternal sperm DNA methylation associated with early signs of autism risk in an autism-enriched cohort. *Int J Epidemiol, 44*(4), 1199–1210. doi:10.1093/ije/dyv028

Fjeldstad, J., Qi, W., Mercuri, N., Siddique, N., Meriano, J., Krivoi, A., & Nayot, D. (2024). An artificial intelligence tool predicts blastocyst development from static images of fresh mature oocytes. *Reprod Biomed Online, 48*(6), 103842. doi:10.1016/j.rbmo.2024.103842

Gameiro, S., Boivin, J., Dancet, E., de Klerk, C., Emery, M., Lewis-Jones, C., . . . Vermeulen, N. (2015). ESHRE guideline: routine psychosocial care in infertility and medically assisted reproduction-a guide for fertility staff. *Hum Reprod, 30*(11), 2476–2485. doi:10.1093/humrep/dev177

Gameiro, S., & Finnigan, A. (2017). Long-term adjustment to unmet parenthood goals following ART: a systematic review and meta-analysis. *Hum Reprod Update, 23*(3), 322–337. doi:10.1093/humupd/dmx001

Gartrell, N., Bos, H., & Koh, A. (2018). National Longitudinal Lesbian Family Study - Mental Health of Adult Offspring. *N Engl J Med, 379*(3), 297–299. doi:10.1056/NEJMc1804810

Golombok, S., Blake, L., Slutsky, J., Raffanello, E., Roman, G. D., & Ehrhardt, A. (2018). Parenting and the Adjustment of Children Born to Gay Fathers Through Surrogacy. *Child Development, 89*(4), 1223–1233. doi:https://doi.org/10.1111/cdev.12728

Golombok, S., Zadeh, S., Imrie, S., Smith, V., & Freeman, T. (2016). Single mothers by choice: Mother–child relationships and children's psychological adjustment. *Journal of Family Psychology, 30*(4), 409–418. doi:10.1037/fam0000188

Hariton, E., Pavlovic, Z., Fanton, M., & Jiang, V. S. (2023). Applications of artificial intelligence in ovarian stimulation: a tool for improving efficiency and outcomes. *Fertil Steril, 120*(1), 8–16. doi:10.1016/j.fertnstert.2023.05.148

Hassold, T., & Hunt, P. (2001). To err (meiotically) is human: the genesis of human aneuploidy. *Nat Rev Genet, 2*(4), 280–291. doi:10.1038/35066065

Hudson, N. (2022). The missed disease? Endometriosis as an example of 'undone science'. *Reprod Biomed Soc Online, 14*, 20–27. doi:10.1016/j.rbms.2021.07.003

Humphries, L. A., Chang, O., Humm, K., Sakkas, D., & Hacker, M. R. (2016). Influence of race and ethnicity on in vitro fertilization outcomes: systematic review. *Am J Obstet Gynecol, 214*(2), 212.e211–212.e217. doi:10.1016/j.ajog.2015.09.002

Inhorn, M. C., & Patrizio, P. (2015). Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. *Hum Reprod Update, 21*(4),

411–426. doi:10.1093/humupd/dmv016

International Infertility Counselling Organisation. (2024). IICO Statement about Psychosocial Counselling and Professional Support

related to involuntary childlessness, including Implications over the life-course. In.

Jenkins, J., van der Poel, S., Krüssel, J., Bosch, E., Nelson, S. M., Pinborg, A., & Yao, M. M. W. (2020). Empathetic application of machine learning may address appropriate utilization of ART. *Reprod Biomed Online, 41*(4), 573–577. doi:10.1016/j.rbmo.2020.07.005

Kasman, A. M., Del Giudice, F., & Eisenberg, M. L. (2020). New insights to guide patient care: the bi-directional relationship between male infertility and male health. *Fertil Steril, 113*(3), 469–477. doi:10.1016/j.fertnstert.2020.01.002

Katz, P., Millstein, S., & Pasch, L. (2002). The social impact of infertility. *Fertil Steril, 78*, S28. doi:10.1016/S0015–0282(02)03454–4

Kekäläinen, J. (2021). Genetic incompatibility of the reproductive partners: an evolutionary perspective on infertility. *Human Reproduction, 36*(12), 3028–3035. doi:10.1093/humrep/deab221

Keller, E., Botha, W., & Chambers, G. M. (2023). Does in vitro fertilization (IVF) treatment provide good value for money? A cost-benefit analysis. *Front Glob Womens Health, 4*, 971553. doi:10.3389/fgwh.2023.971553

Kiconco, S., Tay, C. T., Rassie, K. L., Azziz, R., Teede, H. J., & Joham, A. E. (2022). Where are we in understanding the natural history of polycystic ovary syndrome? A systematic review of longitudinal cohort studies. *Human Reproduction, 37*(6), 1255–1273. doi:10.1093/humrep/deac077

Kline, J., Vardarajan, B., Abhyankar, A., Kytömaa, S., Levin, B., Sobreira, N., . . . Jobanputra, V. (2021). Embryonic lethal genetic variants and chromosomally normal pregnancy loss. *Fertil Steril, 116*(5), 1351–1358. doi:10.1016/j.fertnstert.2021.06.039

Kraaij, V., Garnefski, N., Fles, H., Brands, A., & van Tricht, S. (2016). Effects of a Self-Help Program on Depressed Mood for Women with an Unfulfilled Child Wish. *Journal of Loss and Trauma, 21*(4), 275–285. doi:10.1080/15325024.2015.1057451

Leone Roberti Maggiore, U., Chiappa, V., Ceccaroni, M., Roviglione, G., Savelli, L., Ferrero, S., . . . Spanò Bascio, L. (2024). Epidemiology of infertility in women with endometriosis. *Best Practice & Research Clinical Obstetrics & Gynaecology, 92*, 102454. doi:https://doi.org/10.1016/j.bpobgyn.2023.102454

Levine, H., Jørgensen, N., Martino-Andrade, A., Mendiola, J., Weksler-Derri, D., Jolles, M., . . . Swan, S. H. (2023). Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries. *Hum Reprod Update, 29*(2), 157–176. doi:10.1093/humupd/dmac035

Lv, R., Huang, Y., Huang, S., Wu, S., Wang, S., Hu, G., . . . Yuan, C. (2024). Associations between parental adherence to healthy lifestyles and cognitive performance in offspring: A prospective cohort study in China. *Chin Med J (Engl), 137*(6), 683–693. doi:10.1097/cm9.0000000000002861

Makieva, S., Fraire-Zamora, J. J., Mincheva, M., Uraji, J., Ali, Z. E., Ammar, O. F., . . . Massarotti, C.

(2023). #ESHREjc report: failed fertilization: is genetic incompatibility the elephant in the room? *Human Reproduction, 38*(2), 324–327. doi:10.1093/humrep/deac265

McLernon, D. J., Maheshwari, A., Lee, A. J., & Bhattacharya, S. (2016). Cumulative live birth rates after one or more complete cycles of IVF: a population-based study of linked cycle data from 178,898 women. *Hum Reprod, 31*(3), 572–581. doi:10.1093/humrep/dev336

Mercuri, N. D., & Cox, B. J. (2022). The need for more research into reproductive health and disease. *Elife, 11*. doi:10.7554/eLife.75061

Nik Hazlina, N. H., Norhayati, M. N., Shaiful Bahari, I., & Nik Muhammad Arif, N. A. (2022). Worldwide prevalence, risk factors and psychological impact of infertility among women: a systematic review and meta-analysis. *BMJ Open, 12*(3), e057132. doi:10.1136/bmjopen–2021–057132

Noventa, M., Scioscia, M., Schincariol, M., Cavallin, F., Pontrelli, G., Virgilio, B., . . . Ambrosini, G. (2019). Imaging Modalities for Diagnosis of Deep Pelvic Endometriosis: Comparison between Trans-Vaginal Sonography, Rectal Endoscopy Sonography and Magnetic Resonance Imaging. A Head-to-Head Meta-Analysis. *Diagnostics (Basel), 9*(4). doi:10.3390/diagnostics9040225

Pedro, J., Brandão, T., Schmidt, L., Costa, M. E., & Martins, M. V. (2018). What do people know about fertility? A systematic review on fertility awareness and its associated factors. *Upsala Journal of Medical Sciences, 123*(2), 71–81. doi:10.1080/03009734.2018.1480186

Picchetta, L., Caroselli, S., Figliuzzi, M., Cogo, F., Zambon, P., Costa, M., . . . Capalbo, A. (2022). Molecular tools for the genomic assessment of oocyte's reproductive competence. *J Assist Reprod Genet, 39*(4), 847–860. doi:10.1007/s10815–022–02411–5

Popovic, M., Dhaenens, L., Taelman, J., Dheedene, A., Bialecka, M., De Sutter, P., . . . Heindryckx, B. (2019). Extended in vitro culture of human embryos demonstrates the complex nature of diagnosing chromosomal mosaicism from a single trophectoderm biopsy. *Hum Reprod, 34*(4), 758–769. doi:10.1093/humrep/dez012

Quenby, S., Gallos, I. D., Dhillon-Smith, R. K., Podesek, M., Stephenson, M. D., Fisher, J., . . . Coomarasamy, A. (2021). Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet, 397*(10285), 1658–1667. doi:10.1016/s0140–6736(21)00682–6

Randeva, H. S., Tan, B. K., Weickert, M. O., Lois, K., Nestler, J. E., Sattar, N., & Lehnert, H. (2012). Cardiometabolic aspects of the polycystic ovary syndrome. *Endocr Rev, 33*(5), 812–841. doi:10.1210/er.2012–1003

Raperport, C., Chronopoulou, E., Homburg, R., Khan, K., & Bhide, P. (2023). Endogenous progesterone in unexplained infertility: a systematic review and meta-analysis. *J Assist Reprod Genet, 40*(3), 509–524. doi:10.1007/s10815–022–02689–5

Rawlings, T. M., Tryfonos, M., Makwana, K., Taylor, D. M., Brosens, J. J., & Lucas, E. S. (2024). Endometrial Assembloids to Model Human Embryo Implantation In Vitro. In M. Zernicka-Goetz & K. Turksen (Eds.), *Embryo Models In Vitro: Methods and Protocols* (pp. 63–74). New York, NY: Springer US.

Rice, L. W., Cedars, M. I., Sadovsky, Y., Siddiqui, N. Y., Teal, S. B., Wright, J. D., . . . del Carmen, M. G.

(2020). Increasing NIH funding for academic departments of obstetrics and gynecology: a call to action. *American Journal of Obstetrics & Gynecology, 223*(1), 79.e71–79.e78. doi:10.1016/j.ajog.2020.03.022

Riegler, M. A., Stensen, M. H., Witczak, O., Andersen, J. M., Hicks, S. A., Hammer, H. L., . . . Haugen, T. B. (2021). Artificial intelligence in the fertility clinic: status, pitfalls and possibilities. *Hum Reprod, 36*(9), 2429–2442. doi:10.1093/humrep/deab168

Rivron, N. C., Martinez-Arias, A., Sermon, K., Mummery, C., Schöler, H. R., Wells, J., . . . Kato, K. (2023). Changing the public perception of human embryology. *Nature Cell Biology, 25*(12), 1717–1719. doi:10.1038/s41556–023–01289–4

Rodriguez-Wallberg, K. A., Hao, X., Marklund, A., Johansen, G., Borgström, B., & Lundberg, F. E. (2021). Hot Topics on Fertility Preservation for Women and Girls-Current Research, Knowledge Gaps, and Future Possibilities. *J Clin Med, 10*(8). doi:10.3390/jcm10081650

Rowbottom, B., Galhardo, A., Donovan, E., & Gameiro, S. (2022). Feasibility randomized controlled trial of a self-guided online intervention to promote psychosocial adjustment to unmet parenthood goals. *Human Reproduction, 37*(10), 2412–2425. doi:10.1093/humrep/deac168

Sang, Q., Li, B., Kuang, Y., Wang, X., Zhang, Z., Chen, B., . . . Wang, L. (2018). Homozygous Mutations in WEE2 Cause Fertilization Failure and Female Infertility. *Am J Hum Genet, 102*(4), 649–657. doi:10.1016/j.ajhg.2018.02.015

Santamaria, X., Roson, B., Perez-Moraga, R., Venkatesan, N., Pardo-Figuerez, M., Gonzalez-Fernandez, J., . . . Simon, C. (2023). Decoding the endometrial niche of Asherman's Syndrome at single-cell resolution. *Nature Communications, 14*(1), 5890. doi:10.1038/s41467–023–41656–1

Senapati, S., Asch David, A., Merchant Raina, M., Rosin, R., Seltzer, E., Mancheno, C., & Dokras, A. (2022). The Fast Track to Fertility Program: Rapid Cycle Innovation to Redesign Fertility Care. *NEJM Catalyst, 3*(10), CAT.22.0065. doi:10.1056/CAT.22.0065

Sousa-Leite, M. (2024). *'What if we never make it!? What's going to happen to us?': Routine Psychosocial Care to Promote Patients' Adjustment to the End of Unsuccessful Fertility Treatment.* (Doctorate of Philosophy in Psychology). Cardiff University, Cardiff University Repository. Retrieved from https://orca.cardiff.ac.uk/id/eprint/168829

Stewart, E., Cookson, C., Gandolfo, R., & Schulze-Rath, R. (2017). Epidemiology of uterine fibroids: a systematic review. *BJOG: An International Journal of Obstetrics & Gynaecology, 124*(10), 1501–1512. doi:https://doi.org/10.1111/1471–0528.14640

Stewart, E. A., Laughlin-Tommaso, S. K., Catherino, W. H., Lalitkumar, S., Gupta, D., & Vollenhoven, B. (2016). Uterine fibroids. *Nat Rev Dis Primers, 2*, 16043. doi:10.1038/nrdp.2016.43

Teede, H. J., Tay, C. T., Laven, J., Dokras, A., Moran, L. J., Piltonen, T. T., . . . International, P. N. (2023). Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome†. *Human Reproduction, 38*(9), 1655–1679. doi:10.1093/humrep/dead156

The European I. V. F. Monitoring Consortium for the European Society of Human Reproduction and Embryology, Calhaz-Jorge, C., Smeenk, J., Wyns, C., De Neubourg, D., Baldani, D. P., . . . Goossens, V. (2024). Survey on ART and IUI: legislation, regulation, funding, and

registries in European countries—an update. *Human Reproduction, 39*(9), 1909–1924. doi:10.1093/humrep/deae163

The European I. V. F. Monitoring Consortium for the European Society of Human Reproduction and Embryology, Smeenk, J., Wyns, C., De Geyter, C., Kupka, M., Bergh, C., . . . Goossens, V. (2023). ART in Europe, 2019: results generated from European registries by ESHRE†. *Human Reproduction, 38*(12), 2321–2338. doi:10.1093/humrep/dead197

The Guideline Group on Unexplained Infertility, Romualdi, D., Ata, B., Bhattacharya, S., Bosch, E., Costello, M., . . . Le Clef, N. (2023). Evidence-based guideline: unexplained infertility†. *Human Reproduction, 38*(10), 1881–1890. doi:10.1093/humrep/dead150

Theilgaard Lassen, J., Fly Kragh, M., Rimestad, J., Nygård Johansen, M., & Berntsen, J. (2023). Development and validation of deep learning based embryo selection across multiple days of transfer. *Sci Rep, 13*(1), 4235. doi:10.1038/s41598–023–31136–3

Tiegs, A. W., Tao, X., Zhan, Y., Whitehead, C., Kim, J., Hanson, B., . . . Scott, R. T., Jr. (2021). A multicenter, prospective, blinded, nonselection study evaluating the predictive value of an aneuploid diagnosis using a targeted next-generation sequencing-based preimplantation genetic testing for aneuploidy assay and impact of biopsy. *Fertil Steril, 115*(3), 627–637. doi:10.1016/j.fertnstert.2020.07.052

Tran, D., Cooke, S., Illingworth, P. J., & Gardner, D. K. (2019). Deep learning as a predictive tool for fetal heart pregnancy following time-lapse incubation and blastocyst transfer. *Hum Reprod, 34*(6), 1011–1018. doi:10.1093/humrep/dez064

United Nations. (2015). *Transforming our world: The 2030 agenda for sustainable development*. Retrieved from https://sdgs.un.org/sites/default/files/publications/21252030%20Agenda%20for%20Sustainable%20Development%20web.pdf

Van Der Kelen, A., Okutman, Ö., Javey, E., Serdarogullari, M., Janssens, C., Ghosh, M. S., . . . Viville, S. (2023). A systematic review and evidence assessment of monogenic gene-disease relationships in human female infertility and differences in sex development. *Hum Reprod Update, 29*(2), 218–232. doi:10.1093/humupd/dmac044

VerMilyea, M., Hall, J. M. M., Diakiw, S. M., Johnston, A., Nguyen, T., Perugini, D., . . . Perugini, M. (2020). Development of an artificial intelligence-based assessment model for prediction of embryo viability using static images captured by optical light microscopy during IVF. *Hum Reprod, 35*(4), 770–784. doi:10.1093/humrep/deaa013

Verpoest, W., Okutman, Ö., Van Der Kelen, A., Sermon, K., & Viville, S. (2023). Genetics of infertility: a paradigm shift for medically assisted reproduction. *Hum Reprod, 38*(12), 2289–2295. doi:10.1093/humrep/dead199

Vizheh, M., Muhidin, S., Behboodi Moghadam, Z., & Zareiyan, A. (2021). Women empowerment in reproductive health: a systematic review of measurement properties. *BMC Womens Health, 21*(1), 424. doi:10.1186/s12905–021–01566–0

Wang, A., Huang, S., Liu, M., Wang, B., Wu, F., Zhu, D., & Zhao, X. (2021). Clinical exome sequencing identifies novel compound heterozygous mutations of the WEE2 gene in primary infertile women with fertilization failure. *Gynecol Endocrinol, 37*(12), 1096–1101. doi:10.1080/09513590.2021.1916458

Wang, X., Zhu, H., He, Y., Zeng, J., Zhao, J., Xia, Q., . . . Li, Y. (2022). A novel homozygous mutation in

the PADI6 gene causes early embryo arrest. *Reprod Health, 19*(1), 190. doi:10.1186/s12978-022-01495-7

West, R., Coomarasamy, A., Frew, L., Hutton, R., Kirkman-Brown, J., Lawlor, M., . . . Miller, D. (2022). Sperm selection with hyaluronic acid improved live birth outcomes among older couples and was connected to sperm DNA quality, potentially affecting all treatment outcomes. *Hum Reprod, 37*(6), 1106–1125. doi:10.1093/humrep/deac058

WHO. (2013). Preconception care: Maximizing the gains for maternal and child health [PowerPoint slides]. Retrieved from https://cdn.who.int/media/docs/default-source/mca-documents/maternal-nb/preconception_care_presentation_slides.pdf?sfvrsn=c2a5dde6_5

WHO. (2021). WHO laboratory manual for the examination and processing of human semen. In (Sixth ed.). Geneva: World Health Organisation.

WHO. (2023). *Polycystic ovary syndrome [fact sheet]*. Retrieved from https://www.who.int/news-room/fact-sheets/detail/polycystic-ovary-syndrome

Widbom, A., Sydsjö, G., & Lampic, C. (2022). Psychological adjustment in disclosing and non-disclosing heterosexual-couple families following conception with oocytes or spermatozoa from identity-release donors. *Reprod Biomed Online, 45*(5), 1046–1053. doi:10.1016/j.rbmo.2022.06.011

Yao, Z., Zeng, J., Zhu, H., Zhao, J., Wang, X., Xia, Q., . . . Wu, L. (2022). Mutation analysis of the TUBB8 gene in primary infertile women with oocyte maturation arrest. *J Ovarian Res, 15*(1), 38. doi:10.1186/s13048-022-00971-9

Zadeh, S., Ilioi, E. C., Jadva, V., & Golombok, S. (2018). The perspectives of adolescents conceived using surrogacy, egg or sperm donation. *Human Reproduction, 33*(6), 1099–1106. doi:10.1093/humrep/dey088

Zegers-Hochschild, F., Adamson, G. D., Dyer, S., Racowsky, C., de Mouzon, J., Sokol, R., . . . van der Poel, S. (2017). The International Glossary on Infertility and Fertility Care, 2017†‡§. *Human Reproduction, 32*(9), 1786–1801. doi:10.1093/humrep/dex234

Zhang, Y. R., Yin, T. L., & Zhou, L. Q. (2023). CRISPR/Cas9 technology: applications in oocytes and early embryos. *J Transl Med, 21*(1), 746. doi:10.1186/s12967-023-04610-9