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**ESHRE Pages**

# ESHRE's key research priorities in infertility: maximizing impact on science, people and society†

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## ABSTRACT

**STUDY QUESTION:** Which research topics in the area of infertility should be prioritized in the allocation of research resources?

**SUMMARY ANSWER:** Twelve research priorities were formulated, spanning the following areas: preventing infertility and preserving fertility, gynaecological diseases, male infertility, optimizing fertility treatments, optimizing psychosocial support and deepening knowledge on preimplantation development and early pregnancy.

**WHAT IS KNOWN ALREADY:** Many research gaps related to infertility and its management remain understudied and underfunded, making it important to set priorities to ensure appropriate allocation of research resources.

**STUDY DESIGN, SIZE, DURATION:** The European Society of Human Reproduction and Embryology (ESHRE) appointed a multidisciplinary working group, including a patient representative, to develop a list of research priorities related to infertility, which are relevant to researchers and institutions that fund research.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** A list of research topics was collated based on the recommendations for future research formulated in ESHRE's evidence-based guidelines and suggestions submitted by ESHRE's Special Interest Groups as call topics for the ESHRE research grants. A scoring tool was developed to assess the expected impact of research on each topic on

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individuals, society and scientific advancement. Topics were scored independently by the working group members and the 12 topics with the highest scores were selected for presentation in this paper.

**MAIN RESULTS AND THE ROLE OF CHANCE:** Using our newly developed scoring tool, we have identified 12 research priorities that broadly fall under six areas. These are preventing infertility and preserving fertility, gynaecological diseases, male infertility, optimizing fertility treatments (two priorities per area selected), optimizing psychosocial support (one priority selected) and deepening knowledge on preimplantation development and early pregnancy (three priorities selected).

**LIMITATIONS, REASONS FOR CAUTION:** The impact scoring tool would benefit from further testing and refinement in future projects. The scoring of some impact indicators is heavily based on the judgment and expertise of the scorers, which was accounted for by ensuring representation of knowledge and experience from all relevant disciplines and subject areas as well as the patient perspective within the working group.

**WIDER IMPLICATIONS OF THE FINDINGS:** This paper may serve to stimulate further thought and discussion within the infertility research community on the potential impact of proposed and ongoing research. It will furthermore inform and encourage policy makers involved in research funding allocation and contribute to a more efficient and purposeful allocation of research resources towards infertility research.

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## Introduction

Infertility is defined as 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).

Globally, it is estimated that infertility at any moment during 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 affect their wellbeing in the long-term (Gameiro and Finnigan, 2017; Nik Hazlina *et al.*, 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 difficulties with social participation (Katz *et al.*, 2002). Furthermore, evidence suggests that diminished reproductive health may be a marker for that individual's general health, including cardiovascular and metabolic health (Cedars *et al.*, 2017). Infertility-related distress and time spent on fertility care may contribute to lower work productivity, resulting in economic losses at both individual and societal level (Collins, 2019). Economic losses are even more pronounced with chronic diseases underlying an infertility diagnosis, such as endometriosis, that also have a major impact on quality of life (Darbà and Marsà, 2022; Maulenkul *et al.*, 2024). Thus, providing fertility care to help people fulfil their reproductive plans not only offers perspectives at the personal level, but it also eventually benefits society, the economy and therefore the individual taxpayer (Keller *et al.*, 2023), as does providing healthcare in any other field.

While the underlying cause of infertility in heterosexual couples is equally often due to male or female factors (Carson and Kallen, 2021), the physical burden of the treatment mostly lies on the woman. Women, particularly those with lower incomes, have reported a greater impact of infertility on their relationships and wellbeing than have men (Katz *et al.*, 2002). Other groups that are disproportionately impacted by infertility include cancer patients, whose reproductive capacity may be impaired by gonadotoxic treatments (e.g. chemotherapy), and members of the LGBTQIA+ community, who may lack the capacity to reproduce with their partners or have undergone treatments impacting on their fertility, such as gender transition (Cheng *et al.*, 2019). Fertility treatment outcomes also differ between groups, as evidenced by lower live birth rates after in vitro fertilization (IVF) among minoritized ethnic groups compared to white patients (Humphries *et al.*, 2016). Therefore, addressing infertility can contribute to reducing societal inequalities.

Despite the high prevalence of infertility and its known effects 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). In their Sustainable Development Goals (SDGs), the United Nations (UN) have set ambitious targets related to good health and wellbeing (SDG3) and gender equality (SDG5) to be achieved by 2030 (United Nations, 2015). Investing into infertility research can contribute to achieving these goals both directly and indirectly, by building the foundation for more effective infertility prevention and better care and support for those who are affected.

In the face of limited resources for infertility research, not all research topics can receive funding and a prioritization is necessary. This paper aims to determine research gaps related to infertility where further research is anticipated to have a particularly high and beneficial impact in three areas: first for basic and

clinical science in the field of reproductive medicine, second for individuals seeking to fulfil their child wish and third for society as a whole.

## Materials and methods

### Working group

The research priorities presented in this paper were identified by the ESHRE working group on research gaps and priorities. The working group (K.S. (Chair), G.C., I.D., C.F., S.G., A.P., A.O., J.T., N. V.) included experts with research experience in different areas of human reproduction (genetic research, basic embryological research, clinical research, psychosocial research and research on fertility education), as well as a representative from the patient organization Fertility Europe, an umbrella organization of 31 patient associations from 28 different countries. Additional topic experts were invited to support the working group in drafting the text for the specific research gaps.

### List of research gaps

As a starting point to identify research gaps in infertility, all recommendations for further research formulated in ESHRE's evidence-based guidelines published until March 2023 were compiled along with all suggestions proposed by ESHRE's Special Interest Groups (SIGs) to inform the 2022 call topics for the ESHRE research grant programme. The highly specific topics on this list were merged into broader, overarching topics by the working group members, leading to a shortlist of 24 research gaps.

### Impact scoring

For the purpose of this project, impact was defined as 'the extent to which research on a particular topic is expected to generate significant positive or negative, intended or unintended, higher-level effects' (adapted from OECD, 2023). To assess the potential impact of research on a particular topic, an impact scoring tool was developed that includes 11 indicators across three dimensions: impact on individuals who could benefit from the outcomes of the research, such as new or improved treatment and care strategies, impact on society as a whole, and impact on science in the field of reproductive medicine. The indicators for individual impact were newly developed by the working group to account for the specific desired impacts of infertility research on individuals, whereas the indicators for societal and scientific impact were based on the indicators applied by the European Commission to assess the impact of the Horizon Europe research framework programme and the UN SDGs. Table 1 displays the final impact indicators.

The potential impact of research on each topic was scored independently by all working group members. Each indicator was scored with 0 (low), 1 (medium) or 2 (high). Working group members were asked to leave any indicators on which they perceived that they lacked the necessary expertise to judge the anticipated impact blank, and these were not taken into account in the calculation of average scores. The calculation of total impact scores for each topic followed a three-step process. As a first step, average scores from the different working group members were calculated per indicator. Second, dimension subtotals were calculated by summing up the average indicator scores from the same dimension and multiplying this sum with a dimension-specific weighting factor. Finally, total scores were obtained by adding up the dimension subtotals. The purpose of the dimension-specific weighting factors was to provide for the same maximum subtotal score per dimension, thereby ensuring that each dimension had an equal weight in the total impact score despite having a different number of indicators. A maximum subtotal score of 33.33 per dimension was chosen in order to provide for a maximum total impact score of 100 to facilitate interpretation.

Out of the 24 shortlisted topics that were scored, the 12 topics with the highest impact scores were selected for presentation in this paper. For each topic, two to three experts who are actively engaged in research on the topic were asked to describe the current state of the art of research on this topic and the specific research gaps. The order in which the topics are presented is not based on the impact scores but on the logical flow of the text, grouping related topics together. The list and description of topics was revised and approved by ESHRE's European Affairs Committee and Executive Committee.

## Results

The full list of scored research topics with the total impact scores and subtotals per dimension is presented in Supplementary Table S1. An overview of the 12 selected topics is provided in Fig. 1 and each topic is described in detail below.

### 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 not only 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, and thereby have 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.

#### *Topic 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, i.e. before a person is aware of their 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

Table 1. Impact indicators used for the selection of topics.

| Dimension | Indicators |
|---|---|
| **Individual/Patient impact** | **Preventing infertility:** Extent to which research on the topic will contribute to preventing an individual from experiencing infertility |
| | **Quality of life 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 infertility 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 wellbeing' |
| | **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 |

studies on fertility awareness consistently indicate that the general population lacks knowledge about the factors influencing fertility (Pedro *et al.*, 2018). Unfortunately, the time allocated to education on reproductive health in schools is non-existent or under pressure at best. In addition to the traditional focus on preventing STIs, 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).
- Optimizing 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 impact of preconception interventions on fertility outcomes of fertility patients and the underlying biological and/or mechanistic processes.

### *Topic 2: optimized 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 oocytes 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 optimization (Rodriguez-Wallberg *et al.*, 2021). Future research should be focused on the clinical application of these techniques, which may benefit children, and additionally make fertility preservation available and efficient for adults who, 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:

- Optimizing ovarian and testicular tissue cryopreservation, including the management of stored materials.
- Optimizing technology for obtaining mature oocytes and sperm from immature cells (i.e. in vitro maturation protocols).
- Promoting 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 profound impacts on health and well-being, including their ability to conceive and carry a pregnancy to term (Leone Roberti Maggiore *et al.*, 2024).

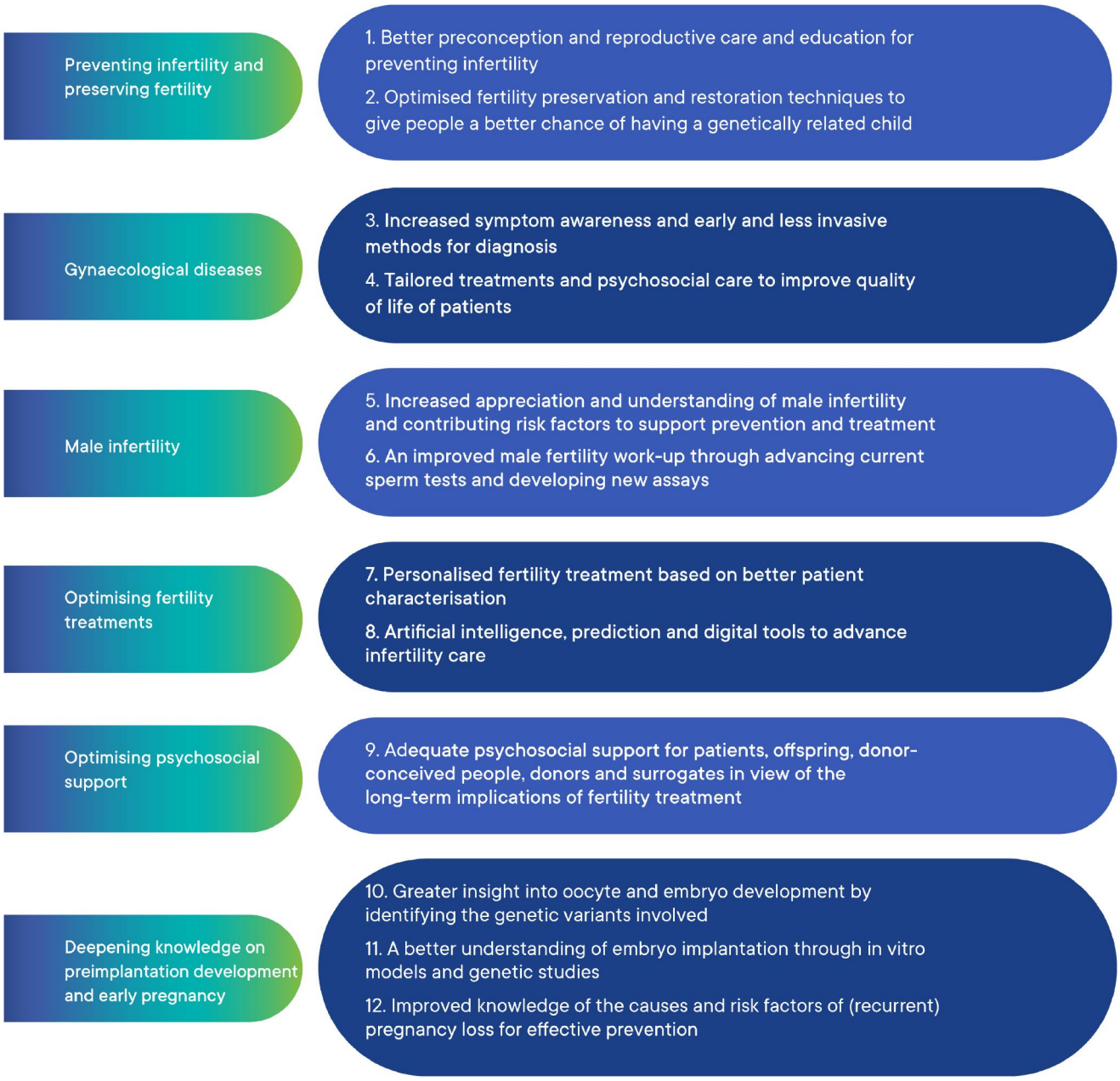


**Figure 1. Twelve key topics on infertility on which research is expected to have a particularly high and beneficial impact.**

Endometriosis affects approximately 176 million women globally, or about 10% of women of reproductive age (Vizheh *et al.*, 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 and Cox, 2022; Teede *et al.*, 2023). Uterine fibroids are present in up to 68% of women (Stewart *et al.*, 2017). In approximately 30% of those affected, these benign tumours cause severe symptoms like heavy bleeding, pain and infertility (Stewart *et al.*, 2016).

Research on gynaecological diseases has historically been underfunded and undervalued, while patient's complaints have often been overlooked, as is the case for menstrual pain in patients with endometriosis (Rice *et al.*, 2020; Hudson, 2022). 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 diagnosis, as well as appropriate treatment and counselling, for those affected.

### *Topic 3: increased symptom awareness and early and less invasive methods for diagnosis*

A big challenge in relation to gynaecological diseases lies in their 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 and 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 of enhancing 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, symptom recognition 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 a deeper understanding of disease characteristics through radiomics, i.e. the extraction of large numbers of features from radiographic medical images using data-characterization algorithms.

### *Topic 4: tailored treatments and 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 (Vizheh *et al.*, 2021; Kiconco *et al.*, 2022; Mercuri and Cox, 2022; 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, i.e. investigating new pharmacological and non-pharmacological interventions to manage the symptoms of PCOS and endometriosis and to maximize 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 for 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 to 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 their 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 in the offspring 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 what steps 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 early mortality (Kasman *et al.*, 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.

### *Topic 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, with one example being a possible link between healthy diet and offspring intelligence, as 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 (Fang *et al.*, 2020; Aitken, 2024).

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, and 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).

### *Topic 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 sperm head, containing the acrosome and nucleus, allows for the interaction with the oocyte and the transmission of paternal genetic and epigenetic material after fertilization, while 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 fertilization 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:

- Standardizing 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 development and offspring health 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.

## Optimizing fertility treatments

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

### *Topic 7: personalized fertility treatment based on better patient characterization*

A first aspect of personalized 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 oocyte 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 (Romualdi *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 standardized 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 personalized 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 optimize 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, 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.

### *Topic 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 *et al.*, 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 (Tran *et al.*, 2019; VerMilyea *et al.*, 2020; Theilgaard Lassen *et al.*, 2023; Fjeldstad *et al.*, 2024). 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.*, 2022).

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 healthcare 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 potential to lead to a healthy child.
- Developing automated decision-making AI-driven tools and evaluate these tools 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, for personalization of psychosocial care to patients undergoing fertility treatment.
- Developing methodological approaches to better evaluate the effectiveness of AI-driven tools that address potential/current biases in fertility care.
- Developing understanding about the ethical implications and the real-world impact of AI-tools.

## Optimizing 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 child(ren) they desire and on how to support all different parties involved in third-party reproduction.

### *Topic 9: adequate psychosocial support for patients, offspring, donor-conceived people, 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, exacerbating its high physical and

mental burden (McLernon *et al.*, 2016; Smeenk *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; Calhaz-Jorge *et al.*, 2024).

Evidence from a 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 and sadness and a profound existential crisis, taking, on average, 2 years to overcome (Gameiro and 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 focusing on this patient group have been developed and evaluated (Kraaij *et al.*, 2016; Rowbottom *et al.*, 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 a genetic link between donor-conceived people (DCP) and their parent(s) can impact relationships and creates challenges for disclosing donor conception (Golombok *et al.*, 2018; Zadeh *et al.*, 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 DCP and their donors, as well as between DCP from the same donor, often referred to as 'half-siblings' (Crawshaw, 2018; Widbom *et al.*, 2022; Gilman *et al.*, 2024). 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 and DCP that need addressing (Golombok *et al.*, 2016; Gartrell *et al.*, 2018). 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, offspring, DCP, donors, surrogates and their families. Therefore, professional organizations 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, offspring, DCP, gamete donors and surrogates, 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 trajectories for those exploring other options (adoption, fostering, life without children) instead of or after fertility treatment, and understanding their experiences and needs.
- Mapping the full range of individual and social impacts experienced because of different trajectories and outcomes of fertility treatment on patients, offspring, DCP, gamete donors, surrogates 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, offspring, DCP, gamete donors, surrogates and their families.
- Developing and evaluating models of care, tools and psychosocial interventions that use cutting-edge knowledge and technology (e.g. AI, telemedicine, big data, wearables) to promote healthy adjustment across the life course for fertility patients, offspring, DCP, gamete donors, surrogates and their families.
- Developing care models to support planning and value-based decisions for all possible fertility treatment options and resulting families, 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 monitoring 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 (Randeva *et al.*, 2012; Inhorn and Patrizio, 2015; Dougherty *et al.*, 2023; Raperport *et al.*, 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, fertilization failures and embryo development arrest, i.e. issues that would remain undetected in spontaneous pregnancies and would therefore be classified as idiopathic or unexplained infertility. Some patients experience recurring patterns of embryonic developmental issues across multiple cycles (Capalbo *et al.*, 2022a), suggesting genetic causes rather than random factors like laboratory conditions or hormonal influences (Cimadomo *et al.*, 2023b).

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.

### *Topic 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 have been the last causes to remain 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 (Wang *et al.*, 2021; Wang *et al.*, 2022; Yao *et al.*, 2022; Chi *et al.*, 2024). Genes responsible for premature ovarian failure (POI) have been known for several years, and more recently, three

additional phenotypes, i.e. Oocyte Maturation Defect (OMD), fertilization failure and 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 21 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, which is indispensable for correctly executed meiosis; as well as fertilization 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/personalized treatments. A genetic diagnosis also allows genetic counselling for members of the patient's family (Sang *et al.*, 2018; Verpoest *et al.*, 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 the 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).

### *Topic 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 (Cimadomo *et al.*, 2023a). 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 (Hassold and Hunt, 2001; Capalbo *et al.*, 2022b). 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 (Tiegs *et al.*, 2021; Cimadomo *et al.*, 2023b).

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 (Santamaria *et al.*, 2023; Rawlings *et al.*, 2024). 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 (Kline *et al.*, 2021; Zhang *et al.*, 2023; Cacheiro *et al.*, 2024).

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.

### *Topic 12: improved knowledge of the causes and risk factors of (recurrent) pregnancy loss for effective prevention*

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 *et al.*, 2021a,b; 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, for 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.

## Discussion

There are many research gaps related to infertility, making it important to set priorities to ensure appropriate allocation of research resources. This paper identifies 12 key topics where further research is expected to have a particularly high and beneficial impact for individuals, society and scientific advancement.

Several previous papers have put forward research priorities related to infertility, usually presenting lists of top 10 research priorities for different sub-areas of infertility (Horne *et al.*, 2017; Prior *et al.*, 2017; Duffy *et al.*, 2020; Teede *et al.*, 2024). The contributions of this paper are twofold. First, it makes research priorities on infertility more accessible to a non-specialist audience such as research funders with a general scope on health research, since it covers various disciplines and sub-areas of infertility in one short but comprehensive list and provides a description and explanation of the importance of each topic. Second, this paper puts forward a list of criteria for research prioritization, which can complement the use of consensus-building methods as applied in previous priority-setting initiatives.

The impact scoring tool applied in this paper would benefit from further testing and refinement in future projects. One limitation is that the scoring of some impact indicators is heavily based on the judgment and expertise of the scorers. This was accounted for by ensuring representation of knowledge and experience from all relevant disciplines and subject areas as well as the patient perspective within the working group, but this limitation should be taken into account in future projects aiming to use the presented impact criteria.

This paper may serve to stimulate further thought and discussion within the infertility research community on the potential impact of proposed and ongoing research and to contribute to a more efficient and purposeful allocation of research resources moving forward.

## Supplementary data

Supplementary data are available at *Human Reproduction* online.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding authors.

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## Authors' roles

K.S. led the working group and oversaw the project. G.C., I.D., C.F., S.G. and A.P. were members of the working group and contributed to designing the scoring tool, scoring the topics and drafting the manuscript. J.T., A.O. and N.V. provided overall support to the working group. J.T. drafted the paper. The other authors contributed to the drafting of sections on specific research gaps. All authors reviewed and approved the final version of the manuscript.

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A.C. reports employment at Juno Genetics. Y.C. reports a grant from Guerbet and honoraria from Ferring, Merck, Abbot, Nordic Pharma and Organon. G.C. reports consulting fees from Gedeon Richter and honoraria from Cooper Surgical. S.G. reports the development of www.myjourney.pt licensed under a CC BY-NC-SA 4.0 licence. J.K.-B. reports grants from the NIHR Evaluation and Studies Coordinating Centre, the Gates Foundation, the Economic and Social Research Council, BAYER Consumer Health and MRC Confidence in Concept; honoraria from Ferring and Cooper Surgical; travel support from Ferring, Cooper Surgical, Congressworks LLP, Deutsche Gesellschaft für Andrologie e. V., BAYER, University of Munster and ESHRE; a patent for microchannel sperm cell preparation; and a leadership or fiduciary role in the Association of Clinical and Reproductive Scientists. A. P. reports grants (to her institution) and consulting fees from Gedeon Richter, Ferring, Merck A/S and Cryos; honoraria from Gedeon Richter, Ferring, Merck A/S and Organon; and travel support (to her institution) from Gedeon Richter. H.S.N. reports grants from Freya Biosciences ApS, Ferring Pharmaceuticals, BioInnovation Institute, Ministry of Education, Novo Nordic Foundation, Augustinus Fonden, Oda og Hans Svenningsens Fond, Demant Fonden, Ole Kirks Fond, and the Independent Research Fund Denmark; speaker's fees from Ferring, Merck A/S, Astra Zeneca, Cook Medical, Gedeon Richter, Ibsa Nordic, Novo Nordisk A/S; co-development of an app with the Maternity Foundation; and co-founding a project with Lulu Health. The remaining authors (J.T., A.A., I.D., C.F., M.G., A.S.L., M.M.-R., V.N., A.O., N.R., M.S.-L., P.T., N.V., S.V. and K.S.) have nothing to declare.

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Human Reproduction, 2025, 00, 1–14
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