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Top 10 priorities for future infertility research: an international consensus development study*,†

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Submitted on May 11, 2020; resubmitted on July 5, 2020; editorial decision on July 22, 2020; published online November 30, 2020.

* This article has not been externally peer reviewed.

† This article has been published simultaneously in Human Reproduction.

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Fertility and Sterility® Vol. 115, No. 1, January 2021 0015-0282

https://doi.org/10.1016/j.fertnstert.2020.11.014

Study Question: Can the priorities for future research in infertility be identified?
Summary Answer: The top 10 research priorities for the four areas of male infertility, female and unexplained infertility, medically assisted reproduction, and ethics, access, and organization of care for people with fertility problems were identified.
What is Known Already: Many fundamental questions regarding the prevention, management, and consequences of infertility remain unanswered. This is a barrier to improving the care received by those people with fertility problems.
Study Design, Size, Duration: Potential research questions were collated from an initial international survey, a systematic review of clinical practice guidelines, and Cochrane systematic reviews. A rationalized list of confirmed research uncertainties was prioritized in an interim international survey. Prioritized research uncertainties were discussed during a consensus development meeting. Using a formal consensus development method, the modified nominal group technique, diverse stakeholders identified the top 10 research priorities for each of the categories male infertility, female and unexplained infertility, medically assisted reproduction, and ethics, access, and organization of care.
Participants/Materials, Setting, Methods: Healthcare professionals, people with fertility problems, and others (healthcare funders, healthcare providers, healthcare regulators, research funding bodies and researchers) were brought together in an open and transparent process using formal consensus methods advocated by the James Lind Alliance.
Main Results and the Role of Chance: The initial survey was completed by 388 participants from 40 countries, and 423 potential research questions were submitted. Fourteen clinical practice guidelines and 162 Cochrane systematic reviews identified a further 236 potential research questions. A rationalized list of 231 confirmed research uncertainties were entered into an interim prioritization survey completed by 317 respondents from 43 countries. The top 10 research priorities for each of the four categories male infertility, female and unexplained infertility (including age-related infertility, ovarian cysts, uterine cavity abnormalities, and tubal factor infertility), medically assisted reproduction (including ovarian stimulation, IUI, and IVF), and ethics, access, and organization of care, were identified during a consensus development meeting involving 41 participants from 11 countries. These research priorities were diverse and seek answers to questions regarding prevention, treatment, and the longer-term impact of infertility. They highlight the importance of pursuing research which has often been overlooked, including addressing the emotional and psychological impact of infertility, improving access to fertility treatment, particularly in lower resource settings, and securing appropriate regulation. Addressing these priorities will require diverse research methodologies, including laboratory-based science, qualitative and quantitative research, and population science.
Limitations, Reasons for Caution: We used consensus development methods, which have inherent limitations, including the representativeness of the participant sample, methodological decisions informed by professional judgement, and arbitrary consensus definitions.
Wider Implications of the Findings: We anticipate that identified research priorities, developed to specifically highlight the most pressing clinical needs as perceived by healthcare professionals, people with fertility problems, and others, will help research funding organizations and researchers to develop their future research agenda.
Study Funding/ Competing Interest(s): The study was funded by the Auckland Medical Research Foundation, Catalyst Fund, Royal Society of New Zealand, and Maurice and Phyllis Paykel Trust. Geoffrey Adamson reports research sponsorship from Abbott, personal fees from Abbott and LabCorp, a financial interest in Advanced Reproductive Care, committee membership of the FIGO Committee on Reproductive Medicine, International Committee for Monitoring Assisted Reproductive Technologies, International Federation of Fertility Societies, and World Endometriosis Research Foundation, and research sponsorship of the International Committee for Monitoring Assisted Reproductive Technologies from Abbott and Ferring. Siladitya Bhattacharya reports being the Editor-in-Chief of Human Reproduction Open and editor for the Cochrane Gynaecology and Fertility Group. Hans Evers reports being the Editor Emeritus of Human Reproduction. Andrew Horne reports research sponsorship from the Chief Scientist's Office, Ferring, Medical Research Council, National Institute for Health Research, and Wellbeing of Women and consultancy fees from Abbvie, Ferring, Nordic Pharma, and Roche Diagnostics. M. Louise Hull reports grants from Merck, grants from Myovant, grants from Bayer, outside the submitted work and ownership in Embrace Fertility, a private fertility company. Neil Johnson reports research sponsorship from Abb-Vie and Myovant Sciences and consultancy fees from Guerbet, Myovant Sciences, Roche Diagnostics, and Vifor Pharma. José Knijnenburg reports research sponsorship from Ferring and Theramex. Richard Legro reports consultancy fees from Abbvie, Bayer, Ferring, Fractyl, Insud Pharma and Kindex and research sponsorship from Guerbet and Hass Avocado Board. Ben Mol reports consultancy fees from Guerbet, iGenomix, Merck, Merck KGaA and ObsEva. Ernest Ng reports research sponsorship from Merck. Craig Niederberger reports being the Co Editor-in-Chief of Fertility and Sterility and Section Editor of the Journal of Urology, research sponsorship from Ferring, and retains a financial interest in NexHand. Jane Stewart reports being employed by a National Health Service fertility clinic, consultancy fees from Merck for educational events, sponsorship to attend a fertility conference from Ferring, and being a clinical subeditor of Human Fertility. Annika Strandell reports consultancy fees from Guerbet. Jack Wilkinson reports being a statistical editor for the Cochrane Gynaecology and Fertility Group. Andy Vail reports that he is a Statistical Editor of the Cochrane Gynaecology & Fertility Review Group and of the journal Reproduction. His employing institution has received payment from HFEA for his advice on review of research evidence to inform their 'traffic light' system for infertility treatment 'add-ons'. Lan Vuong reports consultancy and conference fees from Ferring, Merck and Merck Sharp and Dohme. The remaining authors declare no competing interests in relation to the present work. All authors have completed the disclosure form.
Trial Registration Number: Not applicable. (Fertil Steril® 2021;115:180-90. ©2020 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key words: Consensus science methods, infertility, modified Delphi method, modified Nominal Group Technique, reproductive medicine, and research priorities

INTRODUCTION

The ultimate aim of infertility research is to improve clinical practice and optimize the chances of people with fertility problems achieving parenthood. For this to be possible, research needs to address questions that are pertinent to people with infertility, be conducted using appropriate methods, and be reported in a comprehensive, transparent, and accessible manner (6). The first step in research production is to identify appropriate questions. Traditionally, research funding organizations and researchers have identified, refined, and prioritized their own research agenda. It is unlikely that such prioritization has used formal consensus methods, engaged wider stakeholders, including people with fertility problems, and was independent of commercial interests. There has been modest improvement in some countries, including The Netherlands, UK, and the USA, which has emphasized the importance of including patients and the public in developing research priorities (11).

Sir Iain Chalmers, founder of the Cochrane Collaboration, has advocated for research priorities to be jointly identified by healthcare professionals, patients, and communities (4). He established the James Lind Alliance, which brings together healthcare professionals, patients, and others, in priority setting partnerships. Using formal consensus methods, each priority setting partnership engages in an open and transparent process to identify and prioritize unanswered research questions, known as research uncertainties, in a particular area of health care (13). The expectation is that prioritized research uncertainties will establish the future research agenda of funding organizations and researchers. As a result, it is hoped that the gap will close between what research is needed and what research is pursued (25).

An international collaboration has brought health care professionals, people with fertility problems, and others together within a Priority Setting Partnership for Infertility to develop future research priorities for male infertility, female and unexplained infertility, medically assisted reproduction, and ethics, access, and organization of care.

MATERIALS AND METHODS

An international multidisciplinary steering group, including healthcare professionals, people with fertility problems, and researchers was established to provide a diverse range of perspectives to inform key methodological decisions. The steering group was convened during the development of the study protocol, before the launch of the initial survey and interim prioritization survey, and before the consensus development meeting. A systematic review of registered, progressing, and completed priority setting research settings was completed to assist with the planning and delivery of the study (11).

Research uncertainties related to infertility associated with endometriosis, miscarriage, and polycystic ovary syndrome were not considered because of other current or completed research prioritization initiatives (12, 24).

Research priorities were developed in a three-stage process using consensus methods advocated by the James Lind Alliance (13). Potential research uncertainties were gathered through an online survey of healthcare professionals, people with fertility problems, and others. Healthcare professionals, including embryologists, fertility specialists, and gynecologists, were recruited through the British Fertility Society, Core Outcomes in Women's Health (CROWN) initiative, Cochrane Gynaecology and Fertility Group, Fertility and Sterility Forum, Reproductive Medicine Clinical Study Group, and Royal College of Obstetricians and Gynecologists. People with fertility problems were recruited through Fertility Europe, an umbrella organization of more than 20 European patient organizations, including Fertility Network UK and Freya, Fertility New Zealand, RESOLVE: The National Infertility Association, and the Women's Voices Involvement Panel hosted by the Royal College of Obstetricians and Gynecologists. Other people could register to participate, including healthcare funders, healthcare regulators, and researchers. Recruitment was supported by an active social media campaign. Potential participants received an explanatory video abstract, a plain language summary, and survey instructions. Before completing the survey, participants provided demographic details, including age, gender, and geographical location, and information pertaining to their professional or personal experience of infertility. Participants were invited to suggest up to five research questions related to infertility that they considered unanswered.

After the survey had closed, the survey responses were examined in detail within an iterative process. Individual responses were reviewed by at least two members of the steering group. Responses were excluded if they included questions that did not fit the scope of the study, were not answerable by research, related to a specific person or situation, or were ambiguous. Incomplete responses were also excluded. The remaining responses were formatted into appropriate research questions.

In addition, research recommendations were identified from a systematic review of clinical practice guidelines and Cochrane systematic reviews. Clinical practice guidelines relevant to infertility were identified by searching bibliographical databases, including Embase, International Guideline Library, and MEDLINE, from 2007 to July 2017. Research recommendations were extracted verbatim from clinical practice guidelines. Using a data extraction tool available to the Cochrane Gynaecology and Fertility Group, research recommendations were extracted from individual Cochrane reviews evaluating potential fertility treatments. Research recommendations from clinical practice guidelines and Cochrane systematic reviews were reviewed by two members of the steering group and formatted into appropriate research questions. Differences in opinion were resolved by discussion with the steering group.

The long list of potential research questions was organized by allocating individual research questions in four categories: male infertility; female and unexplained infertility, including age-related infertility, ovarian cysts, uterine cavity abnormalities, and tubal factor infertility; medically assisted reproduction including ovarian stimulation, IUI, and IVF; and ethics, access, and organization of care. These categories were identified in consultation with the steering group. Duplicate research questions were removed. Research questions

were checked against the published research evidence, including clinical practice guidelines, Cochrane systematic reviews, and randomized trials, and those questions considered to be already answered were removed.

The long list of confirmed research uncertainties was entered into an interim prioritization survey. Initial survey participants were invited to participate in the survey. In addition, healthcare professionals, people with fertility problems, and others were recruited using the same methods as the initial survey. Before completing the survey, participants provided demographic details, including age, gender, and geographical location, and information pertaining to their professional or personal experience of infertility. Participants were invited to select the research uncertainties they considered most important. After the survey had closed, questions were ranked based on the frequency they had been chosen by participants.

The top 15 research uncertainties in each category were discussed during a consensus development meeting (data are presented in the Supplementary Table S1). A formal consensus development method, the modified nominal group technique, was used to identify the top 10 research uncertainties for each category (13). Healthcare professionals, people with fertility problems, and others who had completed the initial or interim prioritization survey were invited to participate. The modified nominal group technique does not depend on statistical power. In consultation with the steering group, the aim was to recruit between 15 and 30 participants, as this number has yielded sufficient results and assured validity in other settings (18).

Before the consensus development meeting, participants provided demographic details, including age, gender, and geographical location, and information pertaining to their professional or personal experience of infertility. Following an introductory session, participants were assigned to one of two groups, each with a facilitator, to discuss the ranking of prioritized research uncertainties. The assignments were pre-specified to ensure a mixture of healthcare professionals, people with fertility problems, and others. The groups were provided with a set of cards with an individual research uncertainty printed on each. Each participant was asked to contribute their opinions on the research uncertainties they felt most and least strongly about. Following this initial discussion, participants were invited to discuss the ordering of the research uncertainties. By the end of the session the research uncertainties were placed in ranked order. The rankings from the two groups were aggregated into a single ranking order and presented to the entire group. Participants were invited to discuss the ordering of the research uncertainties. By the end of the discussion the research uncertainties were placed in a final ranked order.

The National Research Ethics Service, UK, advised the study did not require formal review.

RESULTS

The initial survey was completed by 179 healthcare professionals (46%), 153 people with fertility problems (39%), and 56 others (14%), from 40 countries (Table 1). Four hundred and twenty-three responses were submitted (Fig. 1). Following review, 136 responses (32%) were excluded. Clinical practice guidelines relevant to infertility were identified by searching bibliographical databases; the search strategy identified 3,680 records. After excluding 731 duplicate records, 2,949 titles and abstracts were screened. Thirty-two potentially relevant clinical practice guidelines were evaluated. Fourteen clinical practice guidelines met the inclusion criteria, including two guidelines related to infertility in general (17, 19), five guidelines related to male infertility (2, 14, 15), five guidelines related to uterine anomalies (1, 3, 16, 21, 23), and two guidelines related to medically assisted reproduction (20, 22). Thirteen research recommendations were extracted from the clinical practice guidelines. The Cochrane Gynaecology and Fertility Group provided research recommendations from 162 Cochrane systematic reviews. Two hundred and twenty-three potential research questions were extracted from these research recommendations. A long list of 533 potential research uncertainties were reviewed, 241 duplicate research uncertainties were removed and 51 research uncertainties which had been answered by research were also removed.

A rationalized list of 231 confirmed research uncertainties was developed, which included 34 research uncertainties related to male infertility, 48 research uncertainties related to female and unexplained infertility, 101 research uncertainties related to medically assisted reproduction, and 48 research uncertainties related to ethics, access, and organization of care. These confirmed research uncertainties were entered into an interim prioritization survey, which was completed by 143 healthcare professionals, 119 people with fertility problems, and 55 others, from 43 countries.

Nineteen health care professionals, 14 people with personal experience of infertility, and eight others, from 11 countries, participated in the consensus development meeting. The modified nominal group technique was used to prioritize the top 10 research uncertainties for male infertility, female and unexplained infertility, medically assisted reproduction, and ethics, access, and organization of care. Fifteen highly prioritized research uncertainties for each category were discussed during the consensus development meeting (Supplementary Table S1). The 15 highly prioritized research uncertainties were initially discussed by two separate groups and at the end of the discussion they ranked the research uncertainties. The first-round ranking is presented in Supplementary Table S1. The rankings from the two groups were aggregated into a single ranking order and discussed by the entire group (Supplementary Table S1). Participants were encouraged to discuss and finalize the rank order of the research priorities. The top 10 research priorities are presented in Fig. 2.

DISCUSSION

The Priority Setting Partnership for infertility has brought together healthcare professionals, people with fertility problems, and others to identify the top 10 research priorities for future infertility research. These research priorities are diverse

TABLE 1

Characteristics of the participants in a survey to identify the priorities for future infertility research.

	Survey 1 Initial survey n = 388	Survey 2 Interim prioritization n = 317	Consensus meeting Final prioritization n = 41
Stakeholder group, n			
People with fertility problems	153	119	14
Healthcare professionals	179	143	19
Embryologists	39	26	4
Fertility specialists	71	64	6
Gynaecologists	44	28	6
Others	25	25	3
Researchers	28	28	7
Others	15	10	1
Prefer not to say	13	17	0
Gender, n			
Female	223	176	25
Male	129	119	16
Prefer not to say	36	22	0
Age (years), n			
Below 30	47	26	2
30 to 39	118	85	12
40 to 49	61	60	5
50 to 59	73	61	13
Over 60	42	29	5
Prefer not to say	47	56	4
Geographical location, n			
Africa	15	14	0
Asia	57	34	3
Australia and New Zealand	61	51	22
Europe	115	117	13
North America	82	54	3
South America	27	19	0
Prefer not to say	31	28	0

Duffy. Priorities for future infertility research. Fertil Steril 2020.

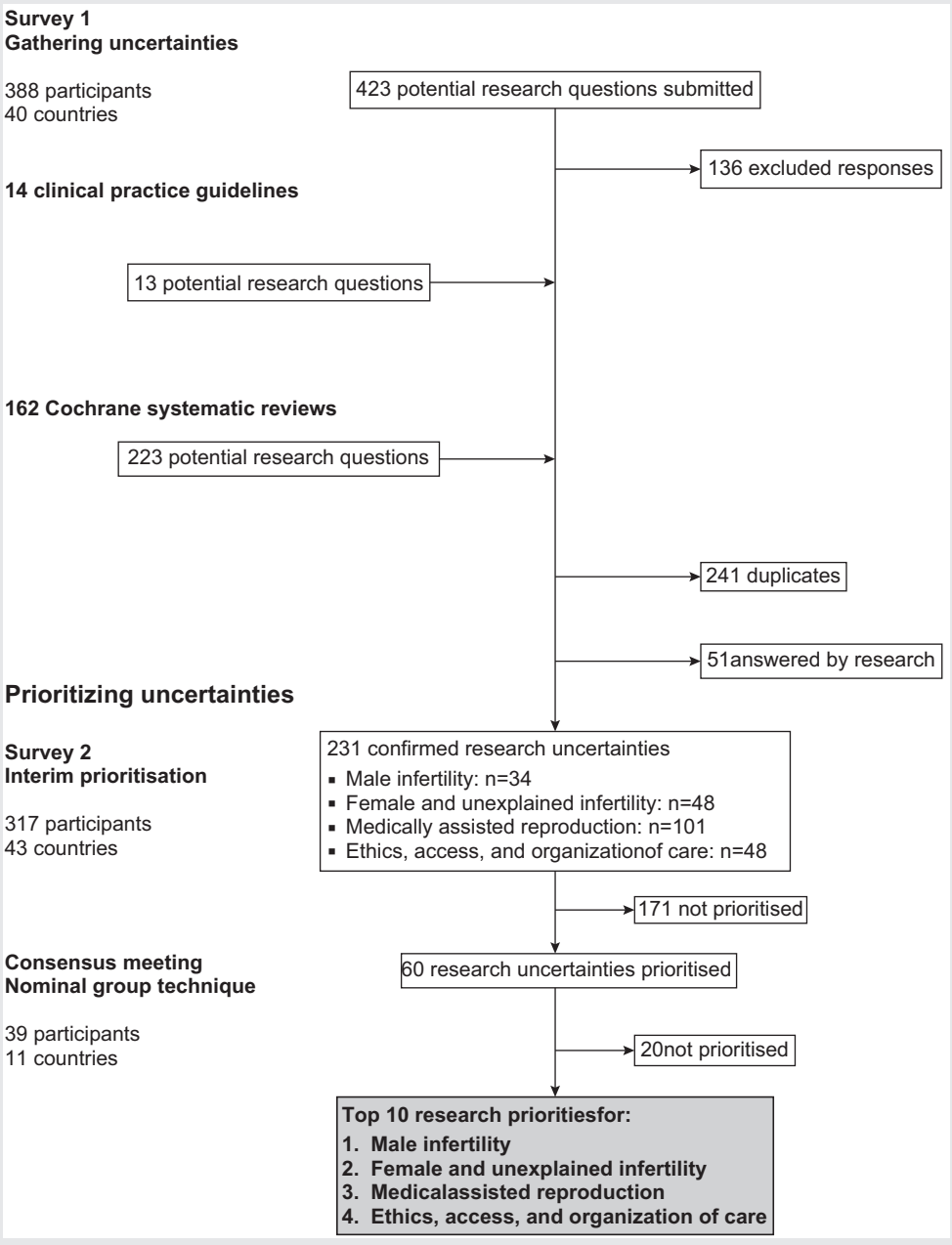
and seek answers to questions regarding prevention, treatment, and the longer-term impact, as well as wider contextual issues related to access and public health policy. They highlight the importance of pursuing research which has often been overlooked, including addressing the emotional and psychological impact of infertility, improving access to fertility treatment, particularly in lower resource settings, and securing appropriate regulation. Addressing these priorities will require diverse research methodologies, including laboratory-based science, qualitative and quantitative research, and population science.

Strengths and Limitations

The James Lind Alliance has published guidance to inform the design of research priority setting studies (13). This study has followed this guidance to ensure the research priorities were developed using a clear and transparent process using formal consensus development methods. The study design, development, and delivery was also informed by a systematic review of research priority setting studies relevant to women's health (11). With 388 respondents from 40 countries participating in the initial survey, 317 respondents from 43 countries participating in the interim prioritization survey, and 41 participants from 11 countries included in the consensus development meeting, the global participation achieved in this study should secure the generalizability of the results within an international context. The study included people with fertility problems and they were able to suggest potential research uncertainties during the initial survey, share their views regarding the importance of research uncertainties during the interim prioritization survey, and participate fully in the consensus development meeting which prioritized the final research priorities.

This consensus study is not without limitations. Consideration should be given to the representativeness of the study's participants. For example, when considering the initial survey, there was a higher response from participants who identified as living in Europe (115 participants; 30%). To participate in the initial survey and interim prioritization survey, English proficiency and literacy, a computer, and internet access were required. We appreciate that limitations in the representativeness of the sample could impact upon the research uncertainties suggested and prioritized. There is uncertainty regarding the optimal consensus development method to prioritize research uncertainties, and methodological research is required to evaluate different approaches to priority setting and the use of different consensus methods. Further contextual information, including the number of people the research priority impacts upon, the feasibility of answering the research priority, and the resources required to address the research uncertainty could have assisted participants to prioritize research uncertainties. Future methodological research should evaluate the use of contextual information in research priority studies.

FIGURE 1



Overview of the process of identifying research uncertainties.

Duffy. Priorities for future infertility research. Fertil Steril 2020.

Reflections on the Research Priorities

Reproductive medical care for men has lagged behind that for women. Setting impactful and tractable priorities for male reproduction is consequently a critically important task. For diagnosis, the variation in morphology is extraordinary and counting sperm is challenging, severely limiting our ability to make predictions of male reproductive potential from the standard semen analysis, and begging the question: are there other, better tests of sperm? We need to explore how overall health affects male fertility and whether treating other diseases improves it. Because a man does not live in a vacuum, we need to understand how the environment affects male reproduction. When considering the treatment of male infertility, men often ask what they can do to improve their fertility, and well conducted studies into diet and nutraceuticals are essential. The endocrine system drives the making of

FIGURE 2

Top 10 research priorities for male infertility

1. Are sperm tests other than bulk parameters useful in evaluating male fertility? If so, which?
2. What is the emotional and psychological impact of male infertility? Can addressing it improve outcomes?
3. Do environmental factors cause male infertility? If so, which?
4. Does treating specific causes of male infertility improve outcomes?
5. Can we improve surgical sperm extraction outcomes by using endocrine stimulation protocols?
6. What modifiable risk factors cause male infertility?
7. Does treating modifiable risk factors improve outcomes?
8. What co-morbidities are associated with infertility?
9. Does treating co-morbidities improve outcomes?
10. Are nutraceuticals useful in improving male reproductive potential? If so, which?

Top 10 research priorities for female and unexplained infertility

1. Can age-related infertility be prevented?
2. Can a predictive model be developed, tested, and validated to compare the outcomes of different management strategies for couples with unexplained infertility?
3. In couples with unexplained infertility, what is the optimal ART?
4. Can a predictive model for fertility based upon ovarian reserve tests be developed, tested, and validated?
5. In women at risk of age-related infertility does standardized fertility assessment before attempting expectant management improve live birth rates?
6. What causes unexplained infertility?
7. In women with uterine fibroids what is the optimal management strategy to preserve fertility?
8. In women with otherwise unexplained infertility does hysteroscopic removal of an endometrial polyp increase live birth rates?
9. In women with mild intrauterine adhesions and otherwise unexplained infertility, does removal increase live birth rates?
10. In women with a uterine septum and otherwise unexplained infertility does hysteroscopic resection increase live birth rates?

Top 10 research priorities for medically assisted reproduction

1. What are the causes of implantation failure?
2. What is the optimal treatment for women who are poor responders undergoing IVF to increase live birth rates?
3. What is the optimal method of sperm selection in IVF cycles?
4. In couples with unexplained infertility does IUI increase live birth rates when compared with other ARTs, including IVF?
5. In couples with unexplained infertility what is the optimal number of IUI cycles before moving to IVF?
6. What is the optimal method of embryo selection in IVF cycles?
7. What are the factors which affect cycle to cycle variability in the number and quality of oocytes produced in an IVF cycle?
8. What is the optimal time interval between ovulation and IUI?
9. What is the emotional and psychological impact on children born using donor gametes?
10. What is the emotional and psychological impact of repeated fertility treatment failure?

Top 10 research priorities for ethics, access, and organization of care

1. Which public health interventions are effective in preventing infertility?
2. How can the cost of infertility treatment be reduced?
3. How can infertility treatment be made available in lower resource settings?
4. How should the information needs of people with infertility be met?
5. What age limit should be applied to women and men seeking infertility treatment?
6. What is the economic burden of infertility?
7. What is the minimum standard of care people with infertility should expect?
8. How should financial conflicts of interest be managed in clinical and research settings?
9. How should social egg freezing be regulated?
10. What are the optimal methods to report long term maternal and offspring outcomes across national and international settings?

The top 10 priorities for future infertility research in each of the four categories.

Duffy. Priorities for future infertility research. Fertil Steril 2020.

sperm and further evidence is required to understand if hormonal therapy could improve the production of sperm and improve live birth rates.

The priorities for unexplained infertility seek answers to several challenging and long-standing questions, including the prevention of age-related infertility and exploring the role of fibroids, polyps, intrauterine adhesions, and uterine septa in unexplained infertility. It is also surprising that it remains unclear what the first line treatment is for couples with unexplained infertility, IVF or IUI, and the timing of the superior treatment for that couple.

When considering medically assisted reproduction, new large prospective cohorts that consider all variables and use advance methodology will be required to addressed casual relationships related to implantation failure. Similar complexity will exist when studying oocyte yield and quality over subsequent IVF cycles, even though similar stimulation protocols have been used. The three research priorities concerning the effectiveness of IVF are seeking to identify optimal ovarian stimulation protocols in poor responders, sperm selection techniques, and embryo selection. These contrast with the research priorities which explore if, when, and how IUI should be used. To answer these effectiveness questions, well designed randomized controlled trials will be required (26). The psychological impact of fertility treatment is brought into sharper focus with research priorities related to the emotional and psychological impact of repeated fertility treatment failure and in children following gamete donation. Strong involvement of patient representatives, psychologists, and behavioral scientists will be required to establish the appropriate qualitative and quantitative studies to address these important priorities.

The research priorities for ethics, access, and organization of care broadly fall into two overarching themes: access and infertility as a public health issue. When considering access, cost is a major barrier to appropriate care, which is reflected in the research priorities aiming to explore interventions to reduce the cost of fertility treatment and increase the availability of fertility treatment in lower resources settings. Turning to infertility as a public health issue, prevention of infertility should be a key priority for public health initiatives. We need to determine the minimum standard of care that people with fertility problems should expect, especially if we are seeking reimbursements for this care.

Wider Context

A prioritized list of research uncertainties, developed to specifically highlight the most pressing clinical needs as perceived by healthcare professionals, people with fertility problems, and others, should help funding organizations and researchers to set their future research agenda. The selected list of research uncertainties should serve to focus a discussion regarding the allocation of limited resources.

Many of the research priorities will require national and international collaboration. Several countries, including China, the Netherlands, UK, and the USA, have developed national networks to undertake infertility research (5). Further development of national infrastructure is required. Collaboration should spread beyond national boundaries and develop within an international context. It is hoped the development of a prioritized research agenda could be an important enabler to deepen international collaboration. Development of generic infrastructure could help foster collaboration, including the use of minimum data sets, known as core outcome sets, low cost data repositories, and standardized approaches to the reporting of research. A core outcome set has recently been developed for future infertility trials (7). Over 400 healthcare professionals, researchers, and patients, from 40 countries, have used formal consensus development methods to identify a core outcome set for infertility (9). Consensus definitions have also been agreed for individual core outcomes (10). It is hoped the core outcome set will provide generic tools to collect outcomes during research, provide concise guidance regarding statistical analysis, and standardize the approach to research reporting (8).

Research priorities identified in this study correspond with research priorities identified by the Priority Setting Partnership for Miscarriage, including determining the emotional and psychological impact of miscarriage, investigating the modifiable risk factors which cause miscarriage, and identifying specific co-morbidities which cause miscarriage (24). Other similarities exist when considering the research uncertainties prioritized by the Priority Setting Partnership for Endometriosis and International Polycystic Ovary Syndrome Network (12).

Answering the prioritized research questions would represent a significant step forward for our specialty. The steering group recognizes the important role of research which stems from the intellectual curiosity of individuals, fundamental research which does not have an immediate clinical application, and research which is funded by special interest groups raising funding for the topic of their particular interest. A blended research strategy should offer the optimal pathway to improving clinical care and patient outcomes.

Perhaps the most important part of this process has been the strengthening of relationships between partner organizations, health care professionals, and people with lived experience of infertility. The prioritized list of uncertainties that require research should help funding organizations and researchers to set their future research agenda. Our approach should ensure that future research has the necessary reach and relevance to inform clinical practice and to improve patient outcomes.

APPENDIX. PRIORITY SETTING PARTNERSHIP FOR INFERTILITY

Dr Hisham AlAhwany, University of Nottingham, UK; Ofra Balaban, CHEN: Patient Fertility Association, Israel; Faith Barton, UK; Dr Yusuf Beebeejaun, King's Fertility, Fetal Medicine Research Institute, UK; Professor Jacky Boivin, Cardiff University, UK; Professor Jan J. A. Bosteels, Imelda Hospital, Belgium; Professor Carlos Calhaz-Jorge, Faculdade de Medicina da Universidade de Lisboa, Portugal; Dr Arianna D'Angelo, Wales Fertility Institute, UK; Dr Leona F. Dann, Health Quality and Safety Commission, New Zealand; Professor Christopher J. De Jonge, University of Minnesota Medical Center, United States; Elyce du Mez, University of Auckland, New Zealand; Professor Rui A. Ferriani, University of Sao Paulo, Brazil; Dr Marie-Odile Gerval, Chelsea and Westminster Hospital NHS Foundation Trust, UK; Lynda J. Gingel, UK; Dr Ellen M. Greenblatt, Mount Sinai Fertility, University of Toronto, Toronto; Professor Geraldine Hartshorne, University of Warwick, UK; Charlie Helliwell, New Zealand; Charlotte Helliwell, New Zealand; Lynda J. Hughes, The Fertility Clinic, London Health Sciences Centre, Canada; Dr Junyoung Jo, Conmaul Hospital of Korean Medicine, Republic of Korea; Jelena Jovanović, Serbia; Professor Ludwig Kiesel, University of Münster, Germany; Dr Chumnan Kietpeerakool, Khon Kaen University, Thailand; Dr Elena Kostova, Cochrane Gynaecology and Fertility, New Zealand; Professor Tansu Kucuk, Acibadem Maslak Hospital, Turkey; Rajesh Kumar, National Foundation for the Deaf, New Zealand; Robyn L. Lawrence, The Liggins Institute, The University of Auckland, New Zealand; Nicole Lee, Canada; Katy E. Lindemann, UK; Professor Olabisi M. Loto, Obafemi Awolowo University, Nigeria; Associate Professor Peter J. Lutjen, Monash University, Australia; Michelle MacKinven, Fertility New Zealand; New Zealand; Dr Mariano Mascarenhas, Leeds Teaching Hospital NHS Trust, UK; Helen McLaughlin, Endometriosis UK, UK; David J. Mills, UK; Dr Selma M. Mourad, Isala Hospital Zwolle, The Netherlands; Linh K. Nguyen, Vietnam; Professor Robert J. Norman, Robinson Research Institute, University of Adelaide, Adelaide; Maja Olic, NGO Counselling Center for In Vitro Fertilisation, Serbia; Kristine L. Overfield, NISIG: National Infertility Support and Information Group, Ireland; Maria Parker-Harris, UK; David G. Ramos, Spain; Aleksandra Rendulic, Serbia; Sjoerd Repping, Amsterdam University Medical Centres, The Netherlands; Professor Roberta Rizzo, University of Ferrara , Italy; Professor Pietro Salacone, Italy; Catherine H. Saunders, The Dartmouth Institute for Health Policy and Clinical Practice, United States; Dr Rinku Sengupta, UK; Dr Ioannis A. Sfontouris, Eugonia: Assisted Reproduction Unit, Greece; Natalie R. Silverman, The Fertility Podcast, UK; Dr Helen L. Torrance, University Medical Center Utrecht, The Netherlands; Dr Eleonora P. Uphoff, UK; Dr Sarah A. Wakeman, Fertility Associates, New Zealand; Professor Tewes Wischmann, Heidelberg University, Germany; Dr Bryan J. Woodward, UK; and Mohamed A. Youssef, Cairo University, Egypt.

AUTHORS' ROLES

Study concept and design: JMND, SB, BC, CC, JLHE, RGF, SF, LCG, AWH, NPJ, YK, JMLK, RSL, SL, BWM, HN, EHYN, CN, ASO, LP, SRH, MS, JS, AS, CS, AV, MvW, MAV, NLV, AYW, RW, JW, and CMF. Acquisition of data: JMND, SB, KB, CB, CC, JLHE, RGF, AF, SF, LCG, AWH, NPJ, YK, JMLK, RSL, SL, BWM, EHYN, CN, ASO, LP, SRH, MS, JS, AS, CS, AV, MvW, MAV, NLV, AYW, RW, JW, and CMF. Analysis and interpretation of data: JMD, GDA, EB, SB, SB, MB, KB,

BC, CC, JLHE, RGF, AF, SF, LCG, EG, MH, AWH, MLH, NPJ, VJ, YK, JMLK, RSL, SL, JM, DM, BWM, DEM, HN, EHYN, CN, ASO, LP, SRH, LS, IS, MS, JS, AS, CS, AV, MvW, MV, NLV, AYW, RW, JW, KW, TW, and CMF. Drafting of the manuscript: JMD, BC, SL, HN, CN, MS, MvW, MV, RW, JW, and CMF. Critical revision of the manuscript for important intellectual content: GDA, EB, SB, SB, MB, BK, CC, JLHE, RGF, AF, SF, LCG, EG, MH, AWH, MLH, NPJ, VJ, YK, JMLK, RSL, JM, MM, DM, BWM, DM, EHYN, ASO, LP, SRH, LS, IS, JS, AS, CS, AV, NLV, AYW, KW, and TW. Statistical analysis: JMD, JW, and AV. Study supervision: CMF.

FUNDING

This research was funded by the Catalyst Fund, Royal Society of New Zealand, Auckland Medical Research Foundation, and Maurice and Phyllis Paykel Trust. The funders had no role in the design and conduct of the study, the collection, management, analysis, or interpretation of data, or manuscript preparation. Ben Mol is supported by a National Health and Medical Research Council Practitioner Fellowship (GNT1082548). Siladitya Bhattacharya was supported by the Auckland Foundation Seelye Travelling Fellowship.

CONFLICT OF INTEREST

Geoffrey Adamson reports research sponsorship from Abbott, personal fees from Abbott and LabCorp, a financial interest in Advanced Reproductive Care, committee membership of the FIGO Committee on Reproductive Medicine, International Committee for Monitoring Assisted Reproductive Technologies, International Federation of Fertility Societies, and World Endometriosis Research Foundation, and research sponsorship of the International Committee for Monitoring Assisted Reproductive Technologies from Abbott and Ferring. Siladitya Bhattacharya reports being the Editor-in-Chief of Human Reproduction Open and editor for the Cochrane Gynaecology and Fertility Group. Hans Evers reports being the Editor Emeritus of Human Reproduction. Andrew Horne reports research sponsorship from the Chief Scientist's Office, Ferring, Medical Research Council, National Institute for Health Research, and Wellbeing of Women and consultancy fees from Abbvie, Ferring, Nordic Pharma, and Roche Diagnostics. M. Louise Hull reports grants from Merck, grants from Myovant, grants from Bayer, outside the submitted work and ownership in Embrace Fertility, a private fertility company. Neil Johnson reports research sponsorship from Abb-Vie and Myovant Sciences and consultancy fees from Guerbet, Myovant Sciences, Roche Diagnostics, and Vifor Pharma. José Knijnenburg reports research sponsorship from Ferring and Theramex. Richard Legro reports consultancy fees from Abbvie, Bayer, Ferring, Fractyl, Insud Pharma and Kindex and research sponsorship from Guerbet and Hass Avocado Board. Ben Mol reports consultancy fees from Guerbet, iGenomix, Merck, Merck KGaA and ObsEva. Ernest Ng reports research sponsorship from Merck. Craig Niederberger reports being the Co Editor-in-Chief of Fertility and Sterility and Section Editor of the Journal of Urology, research sponsorship from Ferring, and retains a financial interest in NexHand. Jane Stewart reports being employed by a National Health Service fertility clinic, consultancy fees from Merck for educational events, sponsorship to attend a fertility conference from Ferring, and being a clinical subeditor of Human Fertility. Annika Strandell reports consultancy fees from Guerbet. Jack Wilkinson reports being a statistical editor for the Cochrane Gynaecology and Fertility Group. Andy Vail reports that he is a Statistical Editor of the Cochrane Gynaecology & Fertility Review Group and of the journal Reproduction. His employing institution has received payment from HFEA for his advice on review of research evidence to inform their 'traffic light' system for infertility treatment 'add-ons'. Lan Vuong reports consultancy and conference fees from Ferring, Merck and Merck Sharp and Dohme. The remaining authors declare no competing interests in relation to the present work. All authors have completed the disclosure form.

Acknowledgements: We would like to thank the initial survey, interim prioritization survey, and consensus development meeting participants, and colleagues at the Cochrane Gynaecology and Fertility Group, University of Auckland, New Zealand.

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Las 10 principales prioridades para la investigación de la infertilidad futura: un estudio de desarrollo de consenso internacional *

Pregunta de estudio: ¿Se pueden identificar las prioridades para la investigación futura en infertilidad?

Respuesta resumida: fueron identificadas las 10 principales prioridades de investigación para las cuatro áreas de infertilidad masculina, infertilidad femenina e inexplicable, reproducción médicamente asistida, ética, acceso y organización de la atención para personas con problemas de fertilidad.

Lo que ya se sabe: quedan sin respuesta muchas preguntas fundamentales relacionadas con la prevención, el manejo y las consecuencias de la infertilidad.. Esta es una barrera para mejorar la atención que reciben las personas con problemas de fertilidad.

Diseño, tamaño y duración del estudio: las posibles preguntas de investigación se recopilaron a partir de una encuesta inicial internacional, una revisión sistemática de guías de práctica clínica y revisiones sistemáticas Cochrane. Se priorizó una lista racionalizada de incertidumbres de investigación confirmadas en una encuesta internacional provisional. Las incertidumbres prioritarias de la investigación se discutieron durante una reunión de desarrollo de consenso. Usando un método de desarrollo de consenso formal, la técnica de grupo nominal modificado, diversas partes interesadas identificaron las 10 principales prioridades de investigación para cada una de las categorías de infertilidad masculina, infertilidad femenina e inexplicable, reproducción médicamente asistida y ética, acceso, y organización de la atención.

Participantes / Materiales, entorno, métodos: profesionales de la salud, personas con problemas de fertilidad y otros (financiadores de la salud, proveedores de atención médica, reguladores de la atención médica, organismos de financiación de la investigación e investigadores) se reunieron en un marco abierto y transparente utilizando métodos formales de consenso propugnados por James Lind Alliance.

Resultados principales y el papel del azar: La encuesta inicial fue completada por 388 participantes de 40 países, se enviaron 423 preguntas potenciales de investigación. Catorce guías de práctica clínica y 162 revisiones sistemáticas Cochrane identificaron unas 236 posibles preguntas de investigación.
Se ingresó una lista racionalizada de 231 incertidumbres de investigación confirmadas en una encuesta de priorización provisional completada por 317 encuestados de 43 países. Las 10 principales prioridades de investigación para cada una de las cuatro categorías de infertilidad masculina, Infertilidad femenina e inexplicable (incluida la infertilidad relacionada con la edad, quistes ováricos, anomalías de la cavidad uterina y factor tubárico infertilidad), reproducción médicamente asistida (incluida la estimulación ovárica, IIU e FIV), ética, acceso y organización de cuidado, se identificaron durante una reunión de desarrollo de consenso en la que participaron 41 participantes de 11 países. Estas prioridades de investigación eran diversas y buscaban respuestas a preguntas sobre prevención, tratamiento y el impacto a largo plazo de la infertilidad.
Ellos destacaron la importancia de realizar investigaciones que a menudo se han pasado por alto, incluido el tratamiento de los aspectos emocionales y impacto psicológico de la infertilidad, mejorando el acceso al tratamiento de fertilidad, particularmente en entornos de menores recursos, y asegurando una regulación apropiada. Abordar estas prioridades requerirá diversas metodologías de investigación, incluidos aspectos cientificos de laboratorio, investigación cualitativa y cuantitativa y aspectos cientificos poblacionales.

Limitaciones, motivos de precaución: utilizamos métodos de desarrollo de consenso, que tienen limitaciones inherentes, incluyendo la representatividad de la muestra de participantes, decisiones metodológicas informadas por juicio profesional y definiciones de consenso arbitrarias.

Implicaciones más amplias de los hallazgos: Anticipamos que las prioridades de investigación identificadas, desarrolladas para resaltar específicamente las más urgentes percibidas por los profesionales sanitarios Las necesidades clínicas según las, las personas con problemas de fertilidad y otros, ayudarán a las organizaciones de financiación de la investigación e investigadores para desarrollar una agenda futura de investigación.

Financiamiento del estudio / Intereses en competencia: El estudio fue financiado por la Fundación de Investigación Médica de Auckland, Catalyst Fund, Royal Sociedad de Nueva Zelanda y Maurice and Phyllis Paykel Trust. Geoffrey Adamson informa el patrocinio de investigación de Abbott, honorarios personales por parte de Abbott y LabCorp, un interés financiero en Advanced Reproductive Care, membresía del comité del Comité de FIGO sobre Medicina Reproductiva, Comité Internacional para el Monitoreo de Tecnologías de Reproducción Asistida, Federación Internacional de Fertility Societies y World Endometriosis Research Foundation, y patrocinio de investigación del Comité Internacional de Monitoreo de Tecnologías de reproducción asistida de Abbott y Ferring. Siladitya Bhattacharya informa que es el editor en jefe de Human Reproduction Open y editor del Grupo Cochrane de Ginecología y Fertilidad. Hans Evers informa ser el editor emérito de Human Reproduction. Andrew Horne informa el patrocinio de investigación de la Chief Scientist's office, Ferring, Consejo investigación médica, Instituto Nacional de Investigaciones en Salud, y Bienestar de las mujeres y honorarios de consultoría de Abbvie, Ferring, Nordic Pharma y Roche Diagnostics. M. Louise Hull informa subvenciones de Merck, subvenciones de Myovant, subvenciones de Bayer, fuera del presente trabajo y propiedad en Embrace Fertility, una empresa privada de fertilidad. Neil Johnson informa el patrocinio de investigación de Abb-Vie y Myovant Sciences y honorarios de consultoría de Guerbet, Myovant Sciences, Roche Diagnostics y Vifor Pharma. José Knijnenburg informa el patrocinio de investigación de Ferring y Theramex. Richard Legro informa los honorarios de consultoría de Abbvie, Bayer, Ferring, Fractyl, Insud Pharma y Kindex y patrocinio de investigación de Guerbet y Hass Avocado Board. Ben Mol informa honorarios de consultoría de Guerbet, iGenomix, Merck, Merck KGaA y ObsEva. Ernest Ng informa el patrocinio de investigación de Merck. Craig Niederberger informa que es coeditor en jefe de Fertility and Sterility y editor de sección de Journal of Urology, patrocinio de investigación de Ferring y mantiene un interés financiero en NexHand. Jane Stewart informa que está empleada por una Clínica de fertilidad del Servicio National de Salud, honorarios de consultoría de Merck para eventos educativos, patrocinio para asistir a una conferencia de fertilidad de Ferring y subeditor clínico de Human Fertility. Annika Strandell informa los honorarios de consultoría de Guerbet. Jack Wilkinson informa ser editor estadístico del Grupo Cochrane de Ginecología y Fertilidad. Andy Vail informa que es editor estadístico del Grupo Cochrane de Ginecología y Fertilidad y de la revista Reproduction. Su institución empleadora ha recibidopago de HFEA por su consejo sobre la revisión de la evidencia de la investigación para informar su sistema de "semáforo" para los "complementos" del tratamiento de la infertilidad. Lan Vuong informa los honorarios de consultoría y conferencias de Ferring, Merck y Merck Sharp and Dohme. Los autores restantes declaran no tener intereses contrapuestos en relación con el presente trabajo. Todos los autores han completado el formulario de divulgación.