

TITLE: Identification of research priorities in infertility and assisted reproduction: an international, multicenter study in partnership with patients

RUNNING TITLE: Research priorities in infertility

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EXTENDED ABSTRACT:

STUDY QUESTION: Which are the main research interests among patients of assisted reproductive technologies (ART)?

SUMMARY ANSWER: Patients identified as research priorities that deserve further investigation: success rates and risks of ART, side-effects of treatments, resources to cope with infertility, effectiveness of alternative therapies, lifestyle habits to protect fertility, oocyte quality and ovarian reserve, and causes of genetic or hereditary infertility.

WHAT IS KNOWN ALREADY: The involvement of patients and caregivers in setting research agendas in medicine has gathered significant momentum in the last decade. Patients' involvement in setting research priorities offers several benefits: improved patient knowledge and awareness of their condition; greater understanding of the medical professionals of the impact of the condition on patients' quality of life; reduced costs associated with redundant research activities. This is may be also applicable to research in infertility and ART, where patients' interests have never been explored before.

STUDY DESIGN, SIZE, DURATION: This is a cross-sectional study that consists of an anonymous online survey, which was sent up to three times to 2112 patients from 11 fertility centers in 5 countries between January-December 2018. The study design was based on the James Lind Alliance priority setting partnership model, which comprises the identification of patients groups, the exploration of the research agenda, the analysis of collected data and identification of priorities.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Overall, 2112 patients were contacted, and 945 surveys were answered (RR: 44.7%). Patients were asked to identify research questions relevant to them in the areas of infertility causes and prevention, fertility treatments (medication and ART), and the emotional aspects of infertility. Answers were categorized in topics and ranked by frequency. A long list of the top-30 research topics was

extracted from the aggregate results, from which, a short list of the top-10 research topics was created. At the end, 10 research questions related to each of the 10 research topics were constructed, based on the answers given by patients.

MAIN RESULTS AND THE ROLE OF CHANCE: Female (845, 89.4%) and male (100, 10.6%) patients were included. The mean age of patients was 37.8 (SD 1.74). Most of the patients did not have children at the time of the survey (523, 59%), while 51 (5.7%) were pregnant. Sixty (6.3%) patients did not start treatment, 579 (61.3%) were performing a treatment with their own gametes and 304 (32.2%) were treated through gamete donation. Patients were mainly interested in the effectiveness of ART -especially per clinical profile-, side effects of drugs, protection of fertility and prevention of infertility –especially through diet and exercise-, and psychological aspects of the infertility journey. The top-10 research questions (and weight) obtained were: 1) What are the side-effects of ART treatments? (41.6%); 2) What are the most effective methods to cope with infertility from the psychological point of view? (37.2%); 3) What effects could diet have on fertility? (25.9%); 4) What are ART success rates per clinical profile? (25.9%); 5) Are there habits and lifestyle factors that could prevent infertility? (20.0%); 6) What are the long-term risks associated to ART? (18.5%); 7) Are alternative therapies such as acupuncture, yoga, and meditation effective to treat/prevent infertility? (18.5%); 8) What is the impact of exercise on fertility? (15.4%); 9) How does oocytes quantity and quality affect fertility? (9.5%); 10) What are the genetic patterns or hereditary conditions causing/related to infertility? (9.5%).

LIMITATIONS, REASONS FOR CAUTION: Although all respondents had attended a fertility center, not all of them were diagnosed as infertile (i.e. single women) and had started treatment at the time of response, while a few were pregnant; their priorities for research might have been influenced by their infertility journey. Also, all participants attended private fertility centers: areas of interest may be different in public settings.

WIDER IMPLICATIONS FOR THE FINDINGS: Researchers and clinicians should keep in mind that, in addition to improvement of treatments' success rates and side-effects, patients greatly value research on causes, prevention and emotional aspects of infertility. As their views might differ from those of medical professionals, patients' voices should be incorporated in setting infertility research priorities.

KEY WORDS:

Patients involvement; research interests; ART treatments; treatment personalization; psychological effects; healthy habits; fertility protection; infertility prevention; lifestyle; diet.

INTRODUCTION

In several medical fields and over the last decade, the involvement of patients and caregivers in setting research agendas had gathered significant momentum. Patient involvement in healthcare research offers a number of perceived benefits, including improved patient awareness and knowledge of their condition, and greater understanding of medical professionals about the implication of the condition on the patient quality of life (Brett, Staniszewska et al. 2014). Moreover, setting a correct and relevant research agenda for patients has been proposed as an efficient way to reduce costs associated with redundant research activities (Chalmers, Bracken et al. 2014).

One technique employed in recent years to establish research priorities is the one championed by the James Lind Alliance (JLA) in the UK, called the JLA priority setting partnership model (<http://www.jla.nihr.ac.uk/>). The original model comprises four phases of priority setting: 1) exploration, during which patients groups are identified; 2) consultation and prioritization, during which the research agenda is explored in more detail through surveys, interview and/or review of published literature; 3) integration, which analyzes the data collected and integrates the priorities identified; and 4) follow-up, which involves determining to which extent the patient views were incorporated into recommendations.

These priority setting exercises carried out in several patient populations have consistently reported significant differences in the perceived importance of research questions for researchers and academics compared to patients, which are ultimately the consumers of the research outcomes. Usually, the highest priorities are shared, for instance, improving treatment to achieve higher probability of cure, which is a high priority for all stakeholders. However, research into improving quality of life and lifestyle support consistently receives higher importance by patients and caregivers than by clinicians (Barnieh, Jun et al. 2015).

Although priority setting partnerships have been used to identify research priorities for patients with several chronic diseases like Parkinson's (Deane, Flaherty et al. 2014), stroke (Pollock, St George et al. 2014), or spinal cord injury (van Middendorp, Allison et al. 2016) no such exercises have been carried out in the general context of infertility. Nevertheless, infertility has been estimated to affect up to one in eight women and one in ten men attempting to conceive (Datta, Palmer et al. 2016), and the ageing Western population, together with reports of overall decrease in gamete fitness, indicates that the number of people needing treatment to conceive will increase in the future.

As it becomes urgent to include infertile patients in the research agenda decision making at both international and local level, we carried out a survey based on the principles of the JLA priority setting partnership model. The objective of this survey was to identify a list of patient needs in infertility research through a priority setting partnership with people accessing ART.

MATERIALS AND METHODS

This international, multicenter, cross-sectional study consists of an anonymous online survey among people attending a fertility center for an ART consultation. The survey was sent to all patients having attended a visit with a physician in one of the nine participant centers in Spain, Italy, Denmark, Brazil and Colombia between January and December 2018.

The study design was based in the James Lind Alliance priority setting partnership model. We first performed a pilot study to test the survey. Then we ran the main study, and research priorities were gathered from the collected data. We identified a long list of the top-30 main interest areas, from which a short list of top-10 interest areas was extracted. Finally, 10 research questions related to these main interest areas and based on real patients' questions were constructed. These phases of the study are further described below.

Survey

An online survey was specifically designed for this study by two of the authors (RV, DG), taking into account the main areas of the infertility experience: infertility causes and prevention, fertility treatments (medication and ART), and emotional aspects of infertility. Survey preparation was based on the JLA recommendations and similar surveys developed for different diseases, such as spinal cord injury (van Middendorp, Allison et al. 2016) or Parkinson's (Deane, Flaherty et al. 2014). The survey was prepared through the platform "Google Forms". The expected fill in time was about 20 minutes. Survey questions are presented as Supplementary material.

Pilot Study

A pilot study was run to evaluate whether the proposed survey was an appropriate tool to identify research priorities in infertility, based on whether participants would answer by identifying questions, and the variability in their answers. For instance, since infertility do not usually represent a significant physical burden for the patient, it might happen that all responses were centered on just one area of research, for instance success rates, narrowing too much the scope of the survey. The proposed survey was tested on a group of 100 individuals, randomly selected among all patients who attended a first visit in 2017 at one of the participating centers. The survey resulted in no modification following the analysis of the pilot study results. An initial categorization of patient's answers was extracted, and the authors agreed with the categorization of possible answers for the main study.

Main study

During this phase, the survey (translated into Spanish, Portuguese, French, Italian, Danish and Catalan) was sent to patients attending the participant centers in Brazil, Spain, Denmark, Italy, and Colombia during the study period. Depending on legal and ethical requirement of each participating country, patients were contacted retrospectively (Spain, Italy, Colombia) or

prospectively (Spain, Denmark, and Brazil). Patients attending the center or planning for a visit in 2018 at the moment of sending the survey were invited to participate. When patients were in couples, the survey was open to both partners. When necessary, patients were informed about the study face-to-face or by telephone, prior to send them the link to the survey by e-mail. Two reminders were sent to all the patients, two and four weeks after the initial sending, respectively.

Data analysis

Individual patient's answers were collected, translated into English, analyzed, and categorized by two authors at each study center together with the first author. Categorized answers of each center were aggregated by two of the authors (DG and SB). All identifiable research uncertainties in the survey were binned according to their theme and overall questions. Care was provided to strike a balance between over-binning (too much granularity) and under-binning (too few broad areas), according to the JLA criteria and published methodology. The aggregated categorized answers were ranked according to their frequency and a long list of the top-30 research topics was extracted and discussed among the authors to agree the top-10 topics of main interest. For the selection of the short list, some items closely related (e.g. general side effects and long-term side effects) were grouped. At the end, ten research questions related to each of the top-10 research topics were constructed, based on the real answers given by patients.

Ethical approval

The study obtained all the approvals legally required at each participant center prior to study initiation.

RESULTS

Study population

Overall, 2,112 patients were contacted, and 945 surveys were answered (RR: 44.7%). Female (845, 89.4%) and male (100, 10.6%) patients were included. Mean age of patients was 37.8 (SD

1.74). Most of the patients did not have children at the time of the survey (523, 59%), while 51 (5.7%) were pregnant. Sixty (6.3%) patients had not started treatment, 579 (61.3%) performed a treatment with their own gametes and 304 (32.2%) resorted to gametes donation.

Long list of research priorities

The long list of research priorities with the top-30 main topics highlighted by participants is displayed in Table I.

Overall, the main interests were related to protection of fertility, prevention of infertility and improvement of treatment success, by instance modifiable habits and lifestyle (diet, exercise). Some examples of answers given by patients regarding these aspects are: *"Is there a diet that can improve fertility/sperm quality, are there any dietary supplement we should take?"*, *"Can nutrition help improve sperm quantity?"*, *"Is there any food, vitamin that helps in prevention?"*, *"Do pineapple and coconut water actually help the embryo in the uterus?"*, *"How much exercise I am allowed to do and which types, can exercise improve fertility?"* These interests were even greater than success rates and safety of ART.

Regarding success rates, patients were interested in absolute values of ART results for different clinical profiles: *"How big a percentage of a specific age group gets pregnant"*, *"Percentage of completed pregnancies dependent on the techniques used"*. In regard to safety, concerns about risks associated to ART and the side effects of drugs and procedures (in mother and child) were common: *"How safe is the medication for the mother and the child"*, *"Which pathologies are related to fertilization treatments"*, *"Does the biopsy cause any problems for the embryo?"*, *"What are the risks for my child, are ART children more likely to suffer from some diseases/conditions?"*, the main concern being the risk of cancer: *"Can the drugs for ovarian hyperstimulation lead to future cancer?"*, *"I would like to know the actual risks of getting cancer because of the treatment and if people with a family history of cancer are more likely to get the disease if they do IVF"* Evidence in alternative therapies was often inquired: *"Does*

acupuncture help?” “It should be interesting be informed about the value of acupuncture, osteopathy, homeopathy, etc... following ART (with supporting studies)”

Psychological aspects of infertility and its treatment were important to participants too, for example, one patient wrote: *“I wonder if the medication used during treatment affects the emotional side. I feel that I become more emotional and less patient, but I often believe it is due to the anxiety that the treatment ungratefully generates. Is there any evidence of mood swings with the use of these medications?”* Patients also demand more skills to cope with infertility and suggest more emotional support (individual or couple support and group therapy), for example: *“What is the best therapeutic approach in psychology to treat aspects of infertility?”, “We would like to know more about techniques to avoid depression/anxiety during treatment”, “How can you talk to you partner about it, and what should you talk about before starting treatment”.*

Participants wondered about infertility causes, especially genetic or hereditary causes: *“Is infertility hereditary?”, “Is Infertility a process that you develop or is already defined by our DNA?”*, ovarian reserve: *“Why are not my eggs fertile”*, male factor: *“I’d like more research on DNA fragmentation and its effect on fertility”*, effect of stress on fertility: *“How anxiety can affect treatment (if hormones release such as cortisol could change the response to IVF medications)”*, miscarriages origin: *“I wonder if anxiety and panic disorder can affect pregnancy establishment or cause miscarriage”*, accurate impact of female age: *“More knowledge and information about how female age influences infertility”, “What is the age we should think about prevention? Already when we have the first menstruation or when we initiate sexual life?”*, *“It could be interesting to know in a personalized way the consecutive phases of the fertility decrease with time in a given person”*, concomitant diseases: *“I have hypothyroidism and I don’t know it does affects more my infertility?”, “Does celiac disease affect male fertility?”*,

Importantly, participants’ answers along the survey indicate a necessity of bigger efforts on treatment personalization (personalized success rates, therapies adapted to individual patients),

by instance: *“Which one is the most effective treatment against infertility and the most adapted to my situation”*, *“Actual success rates of treatment taking into account the particular case”*, *“Which treatment is the best for us, is it possible to customize dose of medication by measuring parameters in blood?”* Finally, participants would like a broaden diagnosis tests available (infertility tests, ovarian reserve tests): *“Which tests should be requested by professionals so that infertility could be diagnosed earlier?”*, *“Is there any embryonic analysis that can detect if the embryo will have infertility problems in the future?”*

Short list of research priorities

The short list of research priorities with the top-10 main topics extracted from the initial long list of 30 items is displayed in Table II.

Finally, the top-10 research priority questions formulated with the short list of research priorities were: 1) What are the side-effects of ART treatments? 2) What are the most effective methods to cope with infertility from the psychological point of view 3) What effects could diet have on fertility? 4) What are ART success rates per clinical profile? 5) Are there habits and lifestyle that could prevent infertility? 6) What are the long-term risks associated to ART? 7) Are alternative therapies as acupuncture, yoga, and meditation effective to treat/prevent infertility? 8) What is the impact of exercise on fertility? 9) How does oocytes quantity and quality affect fertility? 10) What are the genetic patterns or hereditary conditions causing/related to infertility?

DISCUSSION

To the best of our knowledge, this is the first time that a list of priorities in infertility research according ART patients' needs has been developed through collaborative engagement. We present here, in the form of ten relevant research questions, the research topics that patients wish to see investigated, based on their answers.

Unsurprisingly, the main concern of patients is safety of ART, including short-term side effects of the drugs, long-term side-effects for the mother and the child, and risks associated to techniques. We could expect to find success rates of ART ranks second, next to safety, however safety and efficacy are not always together and in our study success rates ranks fourth. There are some other aspects of treatment that appear to patients more important than success rates, in line with previous studies showing that success rates were relatively more important to physicians than to patients (van Empel, Nelen et al. 2010). Meaningfully, how to cope with infertility and its treatment, which can generate high levels of distress (Massarotti, Gentile et al. 2019), especially in patients with multiple treatment failures (Verhaak, Smeenk et al. 2007) or poor ovarian response (Gonda, Domar et al. 2018). We have to keep in mind that some infertile patients in our study had already undergone several previous failed treatments.

While counselling has been judged by ART patients as useful prior to treatment (Dancet, Nelen et al. 2010) and necessary during treatment (van Empel, Nelen et al. 2010), more research on the effectiveness of alternative therapies aimed to reduce distress around treatment is needed (ranked seventh priority). A systematic review of complementary therapies (mainly acupuncture, mind-body and cognitive techniques) showed the effectiveness of these techniques on decreasing anxiety in women under IVF, indicating they might help women to cope with distress (LoGiudice and Massaro 2018). However, reproductive outcomes after acupuncture were found to be increased when compared with no adjunctive controls, but no significant differences were identified when compared to sham controls (Smith, Armour et al. 2019). Similarly, elevated levels of negative emotions have been associated to using complementary and alternative medicines (Bardaweel, Shehadeh et al. 2013). These medicines can be viewed as natural, enhancing or low-cost treatments, but their efficacy and safety are inconclusive (Porat-Katz, Eldar-Geva et al. 2015). More research (and dissemination of research results) is needed in order to make clear to patients and professionals which habits and complementary/alternative medicines and therapies may help (or not) in preventing infertility and add to fertility treatments.

A healthy lifestyle to prevent certain diseases and improving quality of life is a subject currently gaining importance. This is reflected in the questions reported by patients in our study, with a special interest on the impact of diet on infertility and its treatment (ranked third). Although recent published studies about diet and fertility (Chiu, Chavarro et al. 2018; Nassan, Chavarro et al. 2018) and different diet patterns and IVF outcomes indicate a keen interest in this topic (Karayiannis, Kontogianni et al. 2018; Sugawa, Okubo et al. 2018), in our survey the relative importance of diet appears unexpectedly high. This could be due to the relatively low difficulty in modifying this factor, for example by introducing food supplements or so called “superfoods”, in comparison to other lifestyle changes more difficult to maintain, such as changing unhealthy habits or introducing regular physical activity in one’s routine.

In addition to research in the aspects commented above, there is still room for research in the causes of infertility. Genetic and hereditary causes were a concern for 1 in 10 patients, which wondered if they could have done something to prevent infertility or not, and more importantly, if infertility could be transmitted to their offspring. Although not related to treatment’s safety, this aspect is related to the ever-present preoccupation for the health of the future child. Among other possible infertility causes, causes related to ovarian reserve and oocyte quality were the most frequently interrogated, while interest in male factor was probably underrepresented as 10.6% of respondent were men, as well as an historical lack of focus on male factor diagnosis and treatment.

We acknowledge some limitations of this study. First, although all respondents had attended a fertility center, not all had already started treatment at the time of response, while a few were pregnant; priorities for research in different groups of participants might have been influenced by their infertility journey. Second, participants were recruited in private fertility centers, and areas of research interest may vary in different public settings (for instance, patients in private setting might feel more confident that pregnancy rates are already as high as possible in the clinic environment, and thus focus their question on other areas of treatment). Third, the survey

was mainly sent to women, so male patients are present, but underrepresented. Lastly, all patients attended a first visit in one of the participating centers, but not all of them were diagnosed with infertility (for instance single women). Therefore, some participants might not have answered the survey because they did not consider themselves concerned with infertility, lowering the response rate of the study, or skewing some of the answers towards questions related to techniques and drugs, rather than, for instance, infertility causes.

Following our study, the next steps in setting the research agenda for infertility research should be translating the results to all stakeholders, which are more and more interested in approaching research to patients needs. In this line, the European Medicines Agency (EMA) has recently published a booklet about the European procedure of human medicines authorization (EMA 2019), where it is highlighted how patients take part together with healthcare professionals in scientific advisory groups (one in five groups in 2017 involved patients). In these groups, patients are involved as experts who provide their views on whether a medicine can address their needs, describing their experience and their personal balance of the risk/benefit ratio for a given treatment (93% of procedures in 2017 were adapted to patients' advice).

In conclusion, researchers and clinicians should keep in mind that, in addition to improvement of treatments' success rates and side-effects of fertility treatments, patients greatly value research on causes, prevention and emotional aspects of infertility. As their views might differ from those of medical professionals, patients' voices should be incorporated in setting infertility research priorities.

AUTHORS ROLES

DG, RV and AR were involved in study design, database analysis and expert knowledge. All authors were involved in sending the surveys, analyzing the answers and manuscript preparation.

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CONFLICT OF INTEREST

The authors have nothing to declare.

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Table I. Long list of research priorities (30 items)

Topics	Frequency
- Impact of diet on fertility and ART success	25,9%
- Success rates of ART	24,8%
- How to cope with infertility (general)	20,1%
- Healthy habits (general)	20,0%
- Alternative therapies	18,5%
- Risks associated to ART	18,5%
- Long-term side effects	17,2%
- Side effects (general)	16,4%
- Impact of exercise on fertility and ART success	15,4%
- General psychological support	12,1%
- Safety (general)	10,1%
- Individual psychological support	9,6%
- Genetic or hereditary causes	9,5%
- Oocyte quality, ovarian reserve	9,5%
- Impact of nervousness, stress, anxiety	9,4%
- Implantation failures (miscarriages)	8,8%
- Early infertility diagnosis	8,4%
- Male factor infertility reasons	7,7%
- Treatment personalization	7,5%
- Idiopathic infertility (not identifiable) reasons	6,8%
- Woman's age	6,7%
- Diseases (not STDs) related to infertility	6,6%
- Composition, action mode of drugs used in ART	6,5%
- Efficacy of drugs used in ART	5,1%
- Impact of environmental pollution on fertility	5,0%
- Cancer risk in the future due to drugs used in ART	4,4%
- Group psychological support	4,2%
- How to cope with the couple relationship	4,2%
- How to cope with infertility in society	4,1%
- Availability of diagnostic tests (infertility, ovarian reserve)	4,0%

Table II. Short list of research priorities (10 items)

Topic	Frequency
- Side-effects of treatments (short-term and long-term)	51,6%
- Coping with infertility (general and specific situations)	35,7%
- Impact of diet on fertility and ART success	25,9%
- Success rates of ART	24,8%
- Healthy habits (general)	20,0%
- Risks associated to ART	18,5%
- Alternative therapies	18,5%
- Impact of exercise on fertility and ART success	15,4%
- Oocyte quality, ovarian reserve	9,5%
- Genetic or hereditary causes	9,5%

Supplementary figure 1. Study survey

You are:

- Male
- Female

In which country do you live?

How old are you?

Do you have children?

- Yes
- No

Which of the following best describes you? Please tick all that apply

- I (or my partner) cannot get pregnant naturally
- I have had infertility treatment in the past
- I will probably have infertility treatment in the future
- My own gametes (eggs or sperm) were used for my treatment
- The gametes of a donor (eggs or sperm) were used for my treatment

How does infertility affect your daily life? Please tell us about physical, emotional and social effects.

Examples: Do you feel different from other people? Do you experience pain that prevents you from doing certain things? Did you change your social interactions because of infertility?

How do the treatments that you receive affect your daily life? Please tell us about physical, emotional and social effects.

Examples: Do hormonal stimulation make you feel bloated? Do injections disrupt your work schedule? Did you change vacation plans because of treatment? Do you find it hard to see your doctor for treatment?

There are many things that we do not know about infertility, and we would like to hear what are the aspects that are more important to you, so that we can focus our research efforts better.

Are there any questions that you think are important to be studied so that we can find the answer? Here we propose a few examples for you to reflect on, please let us know in the space provided what would you like to see investigated.

1. Do you have any questions about what causes infertility?

Examples: A similar survey in people with kidney disease identified that they wanted to know if certain errors in the DNA can cause their disease.

2. Do you have any questions about what can be done to prevent infertility?

3. Do you have any questions about the day-to-day life of people living with infertility?

Examples: In a similar survey, people with depression wanted to know how best they could identify a crisis before it happened.

4. Do you have any questions about the medication used for fertility treatment?

Examples: In a similar survey, people with diabetes asked about what kind of insulin was the safest and had the fewest side-effects.

5. Do you have any questions about the emotional aspects of infertility and fertility treatments?

Examples: People who had experienced cancer wanted to know whether personalized psychological support would improve their recovery.

6. Do you have any questions about the outcomes of infertility treatment?

Examples: People who broke their legs might want to know which surgical technique would have them go back to walk again faster.

7. Do you have any questions about the safety of infertility treatment for the mother and the conceived child?

8. Do you have any questions about other aspects of treatment (for instance aspects such as diet, exercise or alternative medicine) of infertility?

Examples: People who had experienced a muscle lesion wanted to know whether acupuncture might speed up their recovery.

9. Do you have any questions that you feel are important for researchers to answer but do not fall into the areas specified above?

Example: People who had experienced a stroke wanted to know whether stem cells research could be beneficial.