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Why Prospectively Randomized Clinical Trials Have Been Rare in Reproductive Medicine and Will Remain So?

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Abstract

There is almost unanimity that modern medicine should be "evidence based." In this context, lack of prospectively randomized clinical trials (RCTs) is widely lamented in reproductive medicine. Some leading voices, indeed, increasingly suggest that only RCT-based clinical conclusions should be integrated into clinical practice, since lower levels of evidence are inadequate. We have argued that reproductive medicine requires special considerations because, like clinical oncology, fertility treatments (especially in older women) are time dependent. Unlike clinical oncology, reproductive medicine, however, does not receive substantial financial research support from government or industry and, at least in the United States, has, therefore, to be primarily funded via patient revenues. Given a 50% chance of receiving placebo, infertility patients are, understandably, reluctant to fund their own RCTs. We here selectively review this subject, contrasting opposing opinions recently published in the literature by a prominent reproductive scientist and one of the world's leading experts on evidence-based medicine. Placing these recent publications into the evolving context of infertility practice, as also addressed in this journal in recent publications, we conclude that objective reasons explain why relatively few RCTs are performed in reproductive medicine and predict that this will not change in the foreseeable future. Reproductive medicine, therefore, has to find ways to develop satisfactory clinical evidence in other ways, satisfying patients' rights to easy access to potentially beneficial medical treatments with low costs and low risks. The RCTs should be reserved for relatively high risk and/or high cost treatments.

Keywords

clinical trial, reproductive medicine, RCT, Pharma industry, randomized clinical trials

Introduction

We commented almost 5 years ago on the, in our opinion, often excessive emphasis on prospectively randomized clinical trials (RCTs) in reproductive medicine.[1] These comments were not meant to deny the importance of RCTs in clinical research. Indeed, RCTs are universally recognized as the gold standard of study design in all areas of medicine. We, however, suggested that reproductive medicine faces obstacles to the conduct of RCTs, which do not exist in other medical specialty areas.

Interest in this subject recently experienced resurgence, as a number of publications addressed this subject, at times reaching opposing opinions. We in this editorial focus on 2 such opposing opinions voiced in print by a prominent reproductive endocrinologist[2] and a leading expert on evidence-based medicine[3] and in detail discuss as an example some of the practical obstacles associated with investigations of the increasingly popular technique of local endometrial injury, also recently addressed in the pages of this journal.[4,5]

This editorial is, thus, not meant to offer a comprehensive review of the subject but to point out surprising differences of opinion by leading authorities in the field and to suggest potential unifying conclusions.

The Purist's Approach

Hans Evers, MD, a leading reproductive scientist and current Editor-in-Chief of *Human Reproduction*, recently commented on a "well-designed, meticulously performed and carefully reported study" in his journal, reemphasizing the importance

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of RCTs, while lamenting their scarcity in reproductive medicine.[2] He was, of course, correct in decrying the scarcity of RCTs in reproductive medicine. The study he chose to make the point with, however, also well demonstrated one of the major reasons why RCTs are so scarce in reproductive medicine.

The quoted study by Yeung et al[6] was, indeed, a well-designed and executed RCT. It, however, was logistically and budget-wise relatively easy to execute. Ease of execution and availability of funding reflect the practical realities of clinical research and, ultimately, determine the practicability of RCTs in daily clinical research practice.

By asking the rather simple question, whether endometrial injury in an unselected patient population undergoing in vitro fertilization (IVF) affects outcomes, Yeung et al had, with appropriate informed consent, practically the center's patient population at their disposition. In addition, study costs were, likely, paid by routine IVF cycle reimbursements. Most IVF centers of average size will have enough unselected consecutive patients to conduct a study like this with reasonable statistical power and within a reasonably short time frame. Simple study questions, minimal costs, and easy access to an adequate-size patient population define a relatively easy to execute RCT.

When study design does not allow participation of consecutive patients, the situation, however, becomes more complex. The relevance of this point comes into better focus, when the history of investigations of endometrial injury in association with IVF is considered: First suggested in 2003 by Barash et al,[7] and recently also addressed in the pages of this journal,[4,5] these authors (in contrast to Yeung et al) selectively investigated endometrial injury only in patients enriched for a diagnosis of implantation failure (defined as at least one prior IVF failure in, otherwise, good prognosis patients).

Yeung et al, to their full credit, noted this important difference in their discussion.[6] While Barash et al, therefore, investigated endometrial injury in women with implantation difficulties (the diagnosis of implantation failure is, of course, still a ''black box''), Yeung et al investigated whether endometrial injury affects IVF outcomes in mostly normal patients. This difference in study design has to be recognized and acknowledged because it, to a significant degree, differentiates between easy and more difficult to perform RCTs, with the latter requiring much larger patient numbers (we will return to the subject of large patient numbers later).

Evers[2] failed to comment on this difference in study design between Barash et al[7] and Yeung et al.[6] What, however, may appear as only a subtle difference in study design has, of course, highly significant clinical consequences for the subsequent interpretation of study results as well as practicability (and likelihood) of conducting a proper RCT.

Without denigrating the laudable research effort of Yeung et al,[6] had they, like Barash et al,[7] investigated endometrial scratching in women enriched for a diagnosis of implantation failure, timely completion of their RCT would have been substantially more difficult since they would have had access to only a minority of their center's patient population. The study, therefore, would have required more time and/or collaboration from other centers. Most likely, as therefore a common practice in reproductive medicine, the study would have been published as a single center RCT with inadequate power, often producing misleading results. Underpowered RCTs, therefore, are widely considered an inferior study format to other study formats of lower evidence levels.

Discussion of the Purist's Approach

Based on how patients have to be selected and how RCTs can be financed recognizing the different levels of complexity in execution of RCTs, is, therefore, of importance when considering why RCTs are sparse in reproductive medicine. Reproductive medicine is, of course, also one of the least funded specialty areas in medicine, with IVF in the United States actually being excluded from all federal funding.[8]

A currently registered RCT of dehydroepiandrosterone (DHEA) supplementation in the United Kingdom demonstrates how difficult design and execution of RCTs can be in reproductive medicine.[9] Women with low functional ovarian reserve (LFOR) are prospectively difficult to randomize because they, understandably, are hesitant to lose limited conception time to placebo treatments. We, for example, had to cancel 2 RCTs in patients with LFOR, which attempted to investigate the utility of DHEA supplementation.[10]

By noting in the public registration that the number of patients to be recruited into the study, likely, would be insufficient, this British-registered RCT a priori acknowledged this difficulty.[9] All these pilot studies, therefore, will likely produce yet another underpowered RCT with absolutely no value for clinical practice. We, therefore, would argue that in the absence of any ability to conduct properly powered RCTs, registration and conduct of underpowered RCTs should actually be discouraged.

In the United States, where IVF often is an out-of-pocket expense, we assumed patient recruitment difficulties into RCTs were primarily financially motivated. This, however, proved incorrect when a DHEA RCT in Europe also had to be cancelled because of inability to recruit, even though most patients were covered by third party insurances.[10] While a degree of financial motivation cannot be ruled out, failure to enroll infertility patients in RCTs, therefore, does not primarily appear financially motivated. More likely, women with LFOR are primarily driven by the recognition that they no longer have enough reproductive lifespan to consent to randomization.

Clinical research in reproductive medicine, thus, faces a multitude of objective practical obstacles, which prevent increased utilization of RCTs, and will continue to prevent their use in the foreseeable future. For the field of reproductive medicine this, in our opinion, raises the principal question, what there is to be done when RCTs cannot be performed, and/or are not likely to be performed in a foreseeable future.

Purists, like Evers,[2] reject this question as inappropriate because in their opinion almost all clinical evidence to support

medical interventions should be exclusively based on RCTs. The logical conclusion from such a position is to reject all treatment interventions, which are not based on RCTs. To quote from an editor's recent manuscript rejection letter, we have become privy to "Such treatments should not be used in clinical practice since that would, in essence, be a license for treating patients with whatever somebody considers might do them good, throwing out the rule book, and doing whatever one wants, a vote for poor/no science and a dismissal of the need for evidence and evidence-based decision making in patient treatment."

As the famously infamous published metaanalysis of RCTs of parachute jumping by Smith and Pell[11] so well demonstrated, to assume that every clinical activity can or should be RCT-based, is, however, very obviously nonsensical.

All of medicine (not only reproductive medicine) has to reach consensus what there is to be done about established medical practices, widely considered clinically effective, though RCT unproven. While purists will likely argue that all such practices, ultimately, should be RCT confirmed, such an effort realistically appears unachievable and, therefore, is really a useless goal.

David Eddy, who coined the term "evidence-based medicine," initially estimated that only approximately 15% of medical practice was evidence based.[12] More recent data suggest that the current percentage of evidence-based clinical practice is significantly higher than that,[13] Which leaves us with newly proposed treatments: Whether for such treatments RCT-driven evidence is unobtainable or, likely, for a foreseeable future unobtainable, medicine has under such circumstances to find alternative methods of accumulating clinically sufficient evidence to initiate new treatments. This is not only a relevant issue in reproductive medicine but also represents an essential determination for all medical specialties.

Similar time constraints, as faced by elderly infertility patients trying to conceive with use of their own oocytes, also exist in other medical specialties. In clinical oncology, time is of essence to safe lives, and considerable discussion has recently ensued about either modifying RCTs and/or providing earlier access to experimental drugs for patients with cancer.[14-17] Similar discussions also took place during the recent Ebola outbreak,[18,19] and media widely reported on the use of "unapproved" treatments of patients with Ebola infection who were in danger of dying.

Particular attention should, in this context, be given to the following statement by one of the leading medical ethicists in the United States and his coworkers: "We maintain that there are alternative trial designs that can do so as well (as RCTs) and that sometimes these are preferable to RCTs."[19]

Older infertile women but also younger females with occult primary ovarian insufficiency (premature ovarian aging) often have limited time left to conceive with use of their own eggs. Though the threat of death, ethically, of course outweighs every other potential threat, loss of genetic motherhoods warrants similar considerations.

Table 1. Five Reasons Why Evidence Based Medicine is "In Crisis"[a]

- The evidence based "quality mark" has been misappropriated by vested interests
- The volume of evidence, especially clinical guidelines, has become unmanageable
- Statistically significant benefits may be marginal in clinical practice
- Inflexible rules and technology driven prompts may produce care that is management driven rather than patient centered
- Evidence based guidelines often map poorly to complex multimorbidity

[a]Modified from Greenhalgh et al,[3] with permission.

The Realist's Approach

The second article we referred to earlier by Trisha Greenhalgh (and colleagues), Dean for Research Impact at the London School of Medicine and Dentistry, and one of the world's leading experts on evidence-based medicine, in this context also deserves attention since it offers a rather remarkable recent analysis of evidence-based medicine, concluding that evidence-based medicine for 5 principal reasons (all summarized in Table 1) is now a "movement in crisis."[3]

Here only so much of her thinking: She, for example, makes the points that vested economic interest "have moved evidence based quality marks to serve (their own) economic interests," a very obvious observation in reproductive medicine, when big Pharma on purpose closes its eyes to differences in effectiveness of fertility drugs in different patient populations to maximize market size for their medications; when preimplantation genetic screening is marketed to patients (and fertility centers) as effective in improving IVF outcomes without any supportive evidence and without consideration of patient age and/or ovarian function for exactly the same reason and when industry aggressively promotes extremely costly closed incubation systems with time-lapse photography to the IVF market with unsupported claims of improving IVF outcomes.

Her, likely, most important point is, however, that in clinical practice, statistically significant benefits in most cases are only marginal. This is, of course, a hugely important observation because detection of beneficial treatment effects, even in well-designed RCTs, therefore, in such cases will require very large patient numbers (the smaller a beneficial effect, the largest the number of required study subject to reach adequate power to detect such an effect). Such trials in reproductive medicine are not only beyond the scope of individual centers but for lack of funding sources, even beyond the scope of multicenter efforts.

Discussion of the Realist's Approach

We, therefore, have to acknowledge the indisputable fact that many important studies in reproductive medicine for practical purposes cannot and will not be performed in the format of RCTs. To deprive infertility patients of treatments, which in their likely efficacy can also be established by studies of lower evidence levels, would in such circumstances, as also noted by Caplan et al,[19] have to be considered as unethical.

Table 2. The Definition of What "Real" Evidence-Based Medicine Should Be.[a]

- Makes the ethical care of the patient its top priority
- Demands individualized evidence in a format that clinicians and patients can understand
- Is characterized by expert judgment rather than mechanical rule following
- Shares decisions with patients through meaningful conversations
- Builds on a strong clinician–patient relationship and the human aspects of care
- Applies these principles at community level for evidence based public health

[a]Modified From Greenhalgh et al,[3] with permission.

As RCTs and a meta-analysis were not required to establish that parachutes save lives when jumping out of a plane,[11] most of current infertility treatments, including most IVF applications, do no longer require RCTs to confirm their efficacy. In vitro fertilization is, indeed, a rather remarkable example of how a newly established at its initiation barely successful medical treatment on strength of its market success over more than 30 years without utilization of RCTs persistently improved outcomes. And, as noted before, it achieved this success in the United States without federal funding.[8]

Agreeing with Greenhalgh et al as to what evidence-based medicine really should be like (Table 2), we with Caplan et al[19] would argue that satisfactory evidence for minimal efficacy (or lack thereof) can in many instances probably equally well be obtained with studies of lower evidence levels. Especially if, in addition, appropriate animal models can support the clinical evidence, such an approach not only is more practical but, likely, also more cost-effective.

Practicability and cost-effectiveness considerations require that RCTs, clearly the gold standard of clinical research, be selectively utilized, so that this obviously highly limited resource is only applied to the most essential questions in medicine. Over-utilization as well as under-utilization of RCTs, indeed, would, therefore, appear equally unethically.

"Essential" questions that need to be addressed by RCTs need to be defined. Before doing so with an example, we, however, specifically want to point out our conflict statement in regard to supplementation with androgens (including DHEA) of women with LFOR.

Because supplementation with DHEA carries minimal costs and has minimal potential side effects,[10] we do not consider the determination of treatment efficacy of DHEA by RCTs in women with LFOR essential. We, however, find it quite scandalous that none of the gonadotropins on the market have so far been evaluated in age- and ovarian function-specific ways because gonadotropins, of course, are extremely costly and can cause significant side effects.

Similarly, we find it disturbing that the profession, almost without criticism, embraces very costly new IVF procedures, such as, indiscriminate of age and ovarian function, preimplantation genetic screening and closed embryo incubation systems with time-lapse photography, without even minimal evidence of efficacy and/or prior determinations of risks.

As Greenhalgh et al[3] and Caplan et al[19] noted, RCTs are not a universal solution to all questions in medicine. It, however, appears to us that a first priority in reproductive medicine should be the proper reappropriation of evidence-based "quality marks," which, as Greenhalgh et al so appropriately describe in their article, have been for too long misappropriated by vested interests under the false disguise of evidence-based medicine (Table 1).[3]

Conclusion

Even purists, therefore, have to realize that medicine can not only rely on RCTs in deciding what is acceptable medical care. Purists and realists are in agreement that high-quality medical care achieves balance between under- and overutilization of treatments. Responsible clinicians do not want to utilize ineffective therapies. Especially when time is of essence, they, however, also do not want to withhold effective care.

The American Society for Reproductive Medicine (ASRM) recently exercised this balance well when declaring oocyte preservation no longer experimental for women threatened by permanent sterility from impending toxic medical treatments to their ovaries, while maintaining the experimental status of social egg freezing.[20] ASRM in this circumstance, ethically correctly, assessed relativity of risk/benefit considerations before them before issuing this very balanced and nuanced opinion.

We here suggest that the same approach should be taken for other clinical decisions in reproductive medicine, where costs and risks are low, a demand for costly RCTs is not only unrealistic but appears unethical, since it deprives patients of potential low cost and low-risk benefits without exposing them to either significant risks or costs. The RCTs should be reserved for high risk and/or high cost treatments, where potential harm to patients, indeed, can be substantial, whether physical or financial.

Authors' Note

N.G. contributed to study concept and writing of initial manuscript. N.G., V.A.K., and D.H.B. contributed to literature review. N.G., V.A.K., and D.H.B. contributed to substantial manuscript revisions. All authors approved the final manuscript version.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Conflict statement: N.G. and D.H.B. are listed as co-inventors on a number of US patents, which claim therapeutic benefits from androgen supplementation (including supplementation with DHEA) in women with LFOR. Both receive royalties for some of these patents from Fertility Nutraceuticals, LLC, a company, which produces fertility-related nutritional supplements. N.G. is also a shareholder in that company. N.G. and D.H.B. are also listed as co-inventors on other patents, unrelated to here discussed subjects. All 3 authors have in the past received travel funds, speakers' honoraria and research support from various pharmaceutical and medical device companies, none related to here discussed subjects. All 3 authors are also shareholders in other companies,

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