Do à la carte menus serve infertility patients? The ethics and regulation of IVF add-ons.

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Running title: The ethics and regulation of IVF add-ons

Abstract

Add-on treatments are the new black. They are provided (most frequently, sold) to people undergoing in vitro fertilization on the premise that they will improve the chances of having a baby. However, the regulation of add-ons is consistently minimal, meaning that they are introduced into routine practice before they have been shown to improve the live birth rate. Debate over the adequacy of this light-touch approach rages. Defenders argue that demands for a rigorous approval process are paternalistic, since this would delay access to promising treatments. Critics respond that promising treatments may turn out to have adverse effects on patients and their offspring, contradicting the clinician's responsibility to do no harm. Some add-ons, including earlier versions of PGT-A, might even reduce the live birth rate, raising the prospect of desperate patients paying more to worsen their chances. Informed consent represents a solution in principle, but in practice there is a clear tension between impartial information and direct-to-consumer advertising. Because the effects of a treatment can't be known until it has been robustly evaluated, we argue that strong evidence should be required before add-ons are introduced to the clinic. In the meantime, there is an imperative to identify methods for communicating the associated risks and uncertainties of add-ons to prospective patients.

Capsule

How should IVF add-ons be regulated? Is it ethical to provide unproven treatments? How can we inform patients about the risks and uncertainties?

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Keywords: IVF, add-ons, regulation, informed consent, ethics

Introduction

The decision to seek treatment for infertility usually follows from a failure to conceive naturally, often after years of trying. The investment of the couple is physical, emotional, and in non-public health systems, financial. Nobody has IVF on a whim.

The likelihood that treatment will result in a live birth varies considerably depending on the patient's prognostic profile, and in some populations first line treatments such as intra-uterine insemination (for unexplained or mild-male infertility) or ovulation induction (for anovulatory infertility) have a high success rate (1, 2). Despite this, IVF is often employed as the default first line treatment for patients presenting with various kinds of subfertility, causing some commentators to suggest that it is overused (3). Unfortunately, IVF frequently doesn't result in a baby; the US national report of the Society for Assisted Reproductive Technologies (SART) puts the cumulative live birth rate per attempted egg retrieval at 37% (4). Although multiple IVF attempts may increase the cumulative chance of live birth, many patients do not have babies as a result of their treatment. Each time treatment fails, patients are faced with a choice: give up or try again. Patients may feel that they have to make this decision under time pressure, and that delays deliberating could very well cause them to lose their opportunity to conceive and have children. These concerns might be exaggerated, since material decline in fertility manifests over a timespan of years rather than months, but may be voiced by some treatment providers. Moreover, patients often have to decide which clinic to attend in order to maximise their chance of success.

This situation creates competition for patients, and IVF clinics frequently market themselves both by emphasising their superior performance (not always with veracity (5-7) and by offering to make

people's 'dreams come true' (8). Attempting to gain a competitive edge, or perhaps simply hoping to maintain parity with rivals, clinics offer optional add-on treatments to people undergoing IVF. These add-ons are non-essential interventions which may be offered to people undergoing IVF with the claim that they will increase the chance of success, such as endometrial scratching, embryo glue, steroids to suppress immunity, or preimplantation genetic testing for aneuploidy (PGT-A). While data on global patterns of add-on usage are limited, a UK survey of clinic-users initiated by the Human Fertilisation and Embryology Authority (HFEA) reported that 74% of respondents had used at least one add-on, that usage was growing, and that usage was greater with privately funded treatment (9). Add-ons should be distinguished from additional procedures that are rendered necessary by some diagnoses (such as intracytoplasmic sperm injection (ICSI) or surgical sperm retrieval for some couples with severe male factor infertility). They should also be distinguished from treatments that are integral to IVF. For example, although we can debate which ovarian stimulation protocol is most effective and safe, IVF typically requires some form of ovarian stimulation to be performed, and so we would not consider any particular protocol to constitute an 'add-on'. If add-on interventions were unequivocally effective (improving the cumulative live birth rate per started cycle), their sale would not pose an ethical quandary. However, robust supportive studies of the effectiveness of these procedures are lacking, with no add-on therapy being given the green light in a recent review of the evidence in the United Kingdom (10). Given the considerable uncertainty around whether add-ons work, questions arise regarding the appropriateness of offering them to patients who are often desperate, and believe that clinics rely on validated science for all treatments. Is it ever acceptable to offer, and sell, treatments of unclear effectiveness and safety? Under what circumstances? How should this be regulated and how should any regulation be implemented?

How are add on treatments regulated?

The regulation of IVF add-ons is consistently minimal (11). Usually, new fertility interventions are rapidly adopted on the basis of case reports, rather than following formal regulatory review (12). In the

United States, The Food and Drug Administration (FDA) only requires a full benefit/ risk evaluation when human cellular and tissue-based products are manipulated to a "more-than-minimal" degree (13) in (12). So far, no fertility intervention has been considered as meeting this criterion. In the United Kingdom, HFEA has limited power to prevent the sale of add-ons, or to control pricing (14). When considering a new treatment, HFEA can only refuse it on the grounds of safety; effectiveness is not a consideration. However, the UK regulator has issued a consensus statement in conjunction with industry and patient stakeholder groups outlining several principles of responsible innovation (15). These state that add-ons may be offered even when there is little or conflicting evidence provided that information about the current state of knowledge is given to patients. Where there is no evidence of efficacy and safety, the statement advises that treatments should only be offered as part of research. Both the HFEA and the Victorian Assisted Reproductive Treatment Authority (VARTA) in Australia provide information to consumers to make them aware that add-ons may not improve their chance of success (10, 16). However, there is no such regulatory body in the U.S, nor in most other countries.

Self-regulation, in conjunction with market forces, appears to represent the standard for regulation of IVF innovations in many parts of the world. This is not just true for Western nations (17) (18). Consequently, in markets such as the Netherlands, Belgium, and Slovenia where very little IVF is privately funded and most is delivered in state hospitals (19) use of add-ons is believed to be lower, although data are lacking.

How should IVF add-ons be regulated? Current proposals

While the status quo amounts to a self-regulated free-for-all driven largely by commercial pressures, it is unclear whether or not this will persist. Both executive and popular interest in add-ons has increased, partially as a result of high-profile media coverage of the topic in the UK (20), and this may lead to some form of regulatory response from policy makers.

However, support for changes to the regulatory framework surrounding new reproductive treatments is far from universal. Although arguments in favour of more stringent regulation have been advanced (12, 21-24), there have also been defences of current standards (25-27). A key argument in favour of reform states that self-regulation is an unsuitable model for IVF. A free market in goods and services relies upon consumers choosing not to buy useless products. If a mobile phone company were to produce a new high tech phone which did not work, then after an initial flurry of interest in the new product, its failings would become apparent and the market for it would disappear. Because there can be no guarantee that any cycle of IVF will lead to the birth of a baby, a cycle is more likely to fail than it is to work, and because patients only experience the outcome of their own situation, it is much harder for consumers of infertility services to tell for themselves whether an add-on treatment is worth purchasing. Rather than relying on individual patients 'voting with their feet' in order to crowd out useless interventions, it may be necessary instead for an expert regulator to make recommendations for them.

On the other side of the fence, proponents of the status quo emphasise the point that any regulatory delay might deprive patients of beneficial treatments (27). Supporters of this view generally frame the potential effects of add-ons as being neutral at worst. Under this framing, the call for tighter regulation is both paternalistic and perverse; patients are being "chided" by reformers for wanting to leave no stone unturned (27). It is an effective argumentative device; if it were true then there would be no debate to be had. It is, nonetheless, a red herring, because unfortunately some innovations do turn out to worsen patient outcomes. This can be true even of well-established treatments that are routinely used (28). For

example, many embryos that were reported to be abnormal (mosaic) following PGT-A were discarded, but we now know they can lead to normal pregnancies and they are frequently transferred. As a result, it now appears that many patients who paid for earlier versions of PGT-A reduced their chance of having a baby (29).

Except in cases where treatment effects are very large and stable (30-32), it is not known whether a treatment is beneficial or disadvantageous until it has been robustly evaluated, although this point sometimes gets lost amidst the excitement of having a new treatment to employ and a new product to sell. It can be difficult to remove an ineffective or harmful treatment from use once it has been widely adopted, both due to the enthusiasm of clinicians and the preferences of patients. For example, a recent large randomised controlled trial of the add-on treatment endometrial scratching suggested that the painful procedure has little or no effect on live birth rates (33), but this has been greeted with claims that it might work for some specific categories of infertile women (34). Intracytoplasmic sperm injection for non-male factor subfertility remains common, despite a lack of randomised evidence in its favour. If a trial had been mandated prior to the introduction of the techniques, the widespread provision of ineffective treatments could have been prevented.

Consequently, it has been argued that full regulatory review should be required before the introduction of a new reproductive treatment unless there are no more than minimal safety issues compared to the current standard, there is no risk of reduced live birth rates, and there are no risks of societal harm (12). Very few add-ons would meet all three of these conditions, particularly when potential risks to offspring are considered (12) (21) (22). An ideal paradigm for the development and introduction of new embryological techniques has been described, beginning with hypothesis-driven basic research and moving through stages of animal testing, research on donated human embryos, and clinical trials of increasing magnitude and scope, culminating in a thorough health technology assessment (21). The use

of animal models is unlikely to be applicable for many interventions, due to the fact that physiological differences may obfuscate effects in humans (see the example of ICSI, (21, 26)). On the other hand, with few exceptions, the clinical benefit of most interventions can and should be evaluated in a randomised trial (32).

Informed consent when effectiveness is questionable

Patient-centred, evidence-based medicine is a collaborative enterprise with patients and health professionals focused on the medical needs of the patient, and a relationship grounded in trust, fidelity, and veracity (35). Respecting the choices of patients who have made informed decisions about their medical preferences lies at the heart of informed consent and reflects the principle of autonomy in practice. Obtaining informed consent places duties on clinicians to ensure patients understand the risks and benefits of proceeding with an intervention by providing relevant information, as well as clarifying incomplete or misleading information, and ensuring that patients are making decisions without coercion or undue pressure (36). As informed consent is only possible if sufficient information on effectiveness and safety is available, there should be pressure on developers and suppliers of the add-on interventions to generate such information. Given concerns around add-on interventions in a low-regulation context, the challenges for patients are clear: effectiveness will rarely be known with certainty yet patients want, and often need, to make decisions now. Most add-on interventions are effectively experimental; the claims made on some fertility websites are not quantified and evidence is not cited to support such claims (7); and the potential risks for both women and offspring undergoing add-on interventions are unknown.

Neither can these concerns be seen in isolation to other relevant aspects: the social pressures on patients to have children; one's desperation to have a child of one's own (37), possible conflicts of interest between commercial providers and their obligation to act in the patient's best interests (38, 39), and the vulnerabilities of patients (including their financial welfare). Ensuring that patients are supported to make an informed choice that reflects their preferences and values may be especially challenging within this context. Concerns around financial conflict of interest are heightened by the prospect of corporatisation of reproductive care; some umbrella organisations representing several IVF clinics are listed companies, so their primary interest is shareholder profit. In a clinical setting, one way to expand a business is to treat to excess, which includes selling additional unnecessary treatments to patients and treating people who don't need to be treated (38). Informing people that they don't need to buy your product is antithetical to raising the stock price, and this is the core tension between informed patient choice and direct to consumer marketing.

Increasing the range of infertility treatment add-ons in recent years has created new ethical challenges. Is more choice necessarily a good thing for patients? Some may argue providing choices aligns with respecting patient autonomy. Yet autonomy's reach is limited and cannot be seen in isolation of the health professional's duty *not* to provide treatments that are ineffective, futile, or of questionable safety (40). Moreover, giving patients more choice may not always be in their best interests (41). Even where a patient may pay the full cost for an add-on intervention, it may be justifiable to limit their choices when the add-on's effects are unlikely to contribute to the goals of a successful pregnancy. Where there is a substantive possibility that the add-on may actually reduce the patient's chance of success, the principle of non-maleficence may be brought to bear (40).

Where do we go next?

In the absence of mandatory regulatory review of new reproductive interventions, and in light of the minimal restrictions on how clinics advertise their products, the question becomes how best to inform prospective patients so that they can make a genuinely well-informed, autonomous decision regarding how to be treated (36).

The establishment of consensus-based classifications of treatments might be one option. For example, a scoring tool has been developed by the ESHRE special interest groups in Ethics and Law, and Safety and Quality in ART to distinguish between experimental, innovative and established treatments (42). The tool incorporates four domains: efficacy, safety, procedural reliability and transparency and effectiveness. Treatments must pass a threshold in all four in order to achieve a higher classification. In addition to the criteria for categorising infertility interventions, there is a need to identify effective methods for communicating the risk and uncertainty of add-ons to prospective patients (such as the EPIC fertility add-ons project: https://lse.eu.qualtrics.com/jfe/form/SV_bdAnfkKd2YGp5qd). General proposals for conveying research results to lay audiences have been made (43) but have not been successful in this goal (43, 44).

It is likely that a bespoke approach to risk communication may be required for infertility treatments, since the multistage nature of IVF means that success rates can be presented using a variety of denominators (5). This can change both the impression of an intervention's effectiveness (the live birth rate for PGT-A looks better when calculated per transfer procedure, but worse when calculated per cycle started) as well as the meaning and relevance of the statistic. It is asking too much of patients to parse statistical subtleties, despite suggestions from some authors that patients "must be critical of the information they are exposed to" (45). Nevertheless, encouraging patients to ask the five questions

recommended by the Choosing Wisely campaign, before having any test, treatment or procedure, might help them make more informed decisions: 'Do I really need this test, treatment or procedure?'; 'What are the risks?'; 'Are there simpler, safer options?', 'What happens if I don't do anything'; and 'What are the costs' (www.choosingwisely.org.au). In the context of IVF, we might add 'how will this treatment affect my chances of a live birth?' Informed consent also requires that any uncertainties, for example around the size of an intervention's effect, are communicated to patients, since patients may have individual opinions about the monetary value of modest increases in birth rate. The quantification and reduction of this uncertainty is, of course, one of the principal motivations for conducting randomised controlled trials. The development of decision aids for patients, based on high-quality evidence, could be useful in this space.

Supposing a suitable mode of information can be identified, it remains to work out how this information should be passed to patients. It would be desirable for patients to have this information brought to their attention at the point of care, but the commercial setting might make impartial consultancy challenging. One proposal arising from a recent executive review is the development of "compliance standards for the provision of information in relation to adjuvant treatments, which includes a requirement to advise patients how to access the resources developed by the regulators" (46). The report goes on to recommend that these compliance standards should be included in the conditions of clinic registration. But of course, this will not be the only information that patients rely upon when deciding whether to pay for additional treatment services. People with infertility often report doing their own research before embarking on treatment, and this generally means gathering material online, often from blogs and Facebook groups, where the quality and accuracy of information may be distinctly variable (9).

Poor information provision about research leading to excessive intervention has been included in a recently proposed taxonomy of abuse in assisted reproductive technologies (47). It has become clear

that self-regulation cannot be relied upon to protect patients from ineffective and unnecessary treatment, particularly in settings where IVF is privately funded. While industry opposition is inevitable, stronger regulation appears to have broad support (48). Until that time comes, the best way to empower both consumers and caregivers is to find ways to translate our knowledge about add-ons in a way that does justice to any risks and uncertainties. Nonetheless, the moral imperative to reduce those risks and uncertainties remains strong.

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References

1. Gunn DD, Bates GW. Evidence-based approach to unexplained infertility: a systematic review. Fertil Steril 2016;105:1566-74 e1.

2. ESHRE Capri Workshop Group. A prognosis-based approach to infertility: understanding the role of time. Hum Reprod 2017;32:1556-9.

3. Kamphuis EI, Bhattacharya S, van der Veen F, Mol BW, Templeton A, Evidence Based IVFG. Are we overusing IVF? BMJ 2014;348:g252.

4. Society for Assisted Reproductive Technologies. National Summary Report 2017. In, 2019.

5. Wilkinson J, Vail A, Roberts SA. Direct-to-consumer advertising of success rates for medically assisted reproduction: a review of national clinic websites. BMJ open 2017;7:e012218.

6. Hammarberg K, Prentice T, Purcell I, Johnson L. Quality of information about success rates provided on assisted reproductive technology clinic websites in Australia and New Zealand. Aust N Z J Obstet Gynaecol 2018;58:330-4.

7. Spencer EA, Mahtani KR, Goldacre B, Heneghan C. Claims for fertility interventions: a systematic assessment of statements on UK fertility centre websites. BMJ open 2016;6:e013940.

8. Hawkins J. Selling ART: An Empirical Assessment of Advertising on Fertility Clinics' Websites. Indiana Law J 2013;88:1147-79.

9. Human Fertilisation and Embryology Authority. Pilot national fertility patient survey. 2018. https://www.hfea.gov.uk/media/2702/pilot-national-fertility-patient-survey-2018.pdf, accessed Aug 2019.

10. Human Fertilisation and Embryology Authority. Treatment add-ons. 2019. https://www.hfea.gov.uk/treatments/explore-all-treatments/treatment-add-ons/, accessed July 2019.

11. Nardo LG, El-Toukhy T, Stewart J, Balen AH, Potdar N. British Fertility Society Policy and Practice Committee: adjuvants in IVF: evidence for good clinical practice. Hum Fertil (Camb) 2015;18:2-15.

12. Hendriks S, Pearson SD. A proposed framework for strengthening regulatory review of innovative reproductive techniques in the United States. In: Fertil Steril Dialog, 2018.

13. Food and Drug Administration. Human cells, tissues, and cellular and tissue-based products; establishment registration and listing. Food and Drug Administration, HHS. Final rule. Fed Regist 2001;66:5447-69.

14. Human Fertilisation and Embryology Authority. HFEA statement on fertility treatment 'add-ons'. 2016. https://www.hfea.gov.uk/about-us/news-and-press-releases/2016-news-and-press-releases/hfea-statement-on-fertility-treatment-add-ons/, accessed July 2019.

15. Human Fertilisation and Embryology Authority. The responsible use of treatment add-ons in fertility services: a consensus statement. 2019. https://www.hfea.gov.uk/media/2792/treatment-add-ons-consensus-statement-final.pdf, accessed July 2019.

16. Victorian Assisted Reproductive Treatment Authority. What you need to know about IVF 'add-ons'. 2019. https://www.varta.org.au/resources/blogs/what-you-need-know-about-ivf-add-ons.

17. Horbst V. 'You cannot do IVF in Africa as in Europe': the making of IVF in Mali and Uganda. Reprod Biomed Soc Online 2016;2:108-15.

18. Simpson B. IVF in Sri Lanka: A concise history of regulatory impasse. Reprod Biomed Soc Online 2016;2:8-15.

19. European Society for Hum Reprod and Embryology. The funding of IVF treatment. 2017. https://www.eshre.eu/Press-Room/Resources, accessed July 2019.

20. Panorama. Inside Britain's Fertility Business. BBC, 2016, https://www.bbc.co.uk/programmes/b084ngkd, accessed July 2019.

21. Harper J, Magli MC, Lundin K, Barratt CLR, Brison D. When and how should new technology be introduced into the IVF laboratory? Hum Reprod 2012;27:303-13.

22. Harper J, Jackson E, Sermon K, Aitken RJ, Harbottle S, Mocanu E *et al.* Adjuncts in the IVF laboratory: where is the evidence for 'add-on' interventions? Hum Reprod 2017;32:485-91.

23. Wilkinson J, Bhattacharya S, Duffy J, Kamath MS, Marjoribanks J, Repping S *et al.* Reproductive medicine: still more ART than science? BJOG 2019;126:138-41.

24. Repping S. Evidence-based medicine and infertility treatment. Lancet 2019;393:380-2.

25. Murdoch A. Should the HFEA be regulating the add-on treatments for IVF/ICSI in the UK?: AGAINST: HFEA regulation of add-on IVF/ICSI. BJOG 2017;124:1849.

26. Cohen J, Alikani M. Evidence-based medicine and its application in clinical preimplantation embryology. Reprod Biomed Online 2013;27:547-61.

27. Macklon NS, Ahuja KK, Fauser B. Building an evidence base for IVF 'add-ons'. Reprod Biomed Online 2019;38:853-6.

28. Prasad VK, Cifu AS. Ending medical reversal : improving outcomes, saving lives. Baltimore: Johns Hopkins University Press, 2015.

29. Twisk M, Mastenbroek S, van Wely M, Heineman MJ, Van der Veen F, Repping S. Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection. The Cochrane database of systematic reviews 2006:CD005291.

30. Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. BMJ 2007;334:349-51.

31. Evers J. Do we need an RCT for everything? Hum Reprod 2017;32:483-4.

32. Braakhekke M, Mol F, Mastenbroek S, Mol BW, van der Veen F. Equipoise and the RCT. Hum Reprod 2017;32:257-60.

33. Lensen S, Osavlyuk D, Armstrong S, Stadelmann C, Hennes A, Napier E *et al.* A Randomized Trial of Endometrial Scratching before In Vitro Fertilization. New England Journal of Medicine 2019;380:325-34.

34. Lensen S, Venetis C, Ng EHY, Young SL, Vitagliano A, Macklon NS *et al.* Should we stop offering endometrial scratching prior to in vitro fertilization? Fertil Steril 2019;111:1094-101.

35. Singer P, Wells D. In vitro fertilisation: the major issues. J Med Ethics 1983;9:192-9.

36. Madeira JL, Coyne K, Jaeger AS, Parry JP, Lindheim SR. Inform and consent: more than just "sign here". Fertil Steril 2017;108:40-1.

37. Karpin I. Regulatory Responses to the Gendering of Transgenerational Harm. Aust Feminist Stud 2016;31:139-53.

38. Blakely B, Williams J, Mayes C, Kerridge I, Lipworth W. Conflicts of interest in Australia's IVF industry: an empirical analysis and call for action. Hum Fertil (Camb) 2017:1-8.

39. Mayes C, Blakely B, Kerridge I, Komesaroff P, Olver I, Lipworth W. On the fragility of medical virtue in a neoliberal context: the case of commercial conflicts of interest in reproductive medicine. Theor Med Bioeth 2016;37:97-111.

40. Dondorp W, de Wert G. Innovative reproductive technologies: risks and responsibilities. Hum Reprod 2011;26:1604-8.

41. Zolkefli Y. Evaluating the Concept of Choice in Healthcare. Malays J Med Sci 2017;24:92-6.

42. Provoost V, Tilleman K, D'Angelo A, De Sutter P, de Wert G, Nelen W *et al.* Beyond the dichotomy: a tool for distinguishing between experimental, innovative and established treatment. Hum Reprod 2014;29:413-7.

43. Glenton C, Santesso N, Rosenbaum S, Nilsen ES, Rader T, Ciapponi A *et al.* Presenting the results of Cochrane Systematic Reviews to a consumer audience: a qualitative study. Med Decis Making 2010;30:566-77.

44. Alderdice F, McNeill J, Lasserson T, Beller E, Carroll M, Hundley V *et al.* Do Cochrane summaries help student midwives understand the findings of Cochrane systematic reviews: the BRIEF randomised trial. Syst Rev 2016;5:40.

45. Zemyarska MS. Is it ethical to provide IVF add-ons when there is no evidence of a benefit if the patient requests it? J Med Ethics 2019;45:346-50.

46. Gorton M. Review of assisted reproductive treatment. In: Victorian Government, Australia, 2018.

47. Hodson N, Bewley S. Abuse in assisted reproductive technology: A systematic qualitative review and typology. Eur J Obstet Gynecol Reprod Bio 2019;238:170-7.

48. Hendriks S, Vliegenthart R, Repping S, Dancet EAF. Broad support for regulating the clinical implementation of future reproductive techniques. Hum Reprod 2018;33:39-46.