



Do à la carte menus serve infertility patients? The ethics and regulation of in vitro fertility add-ons

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1 Do à la carte menus serve infertility 2 patients? The ethics and regulation of IVF 3 add-ons.

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

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27

28 **Abstract**

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

43

44 **Capsule**

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

47 .

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

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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

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

99

100

101 *How are add on treatments regulated?*

102

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

105 United States, The Food and Drug Administration (FDA) only requires a full benefit/ risk evaluation
106 when human cellular and tissue-based products are manipulated to a “more-than-minimal” degree (13)
107 in (12). So far, no fertility intervention has been considered as meeting this criterion. In the United
108 Kingdom, HFEA has limited power to prevent the sale of add-ons, or to control pricing (14). When
109 considering a new treatment, HFEA can only refuse it on the grounds of safety; effectiveness is not a
110 consideration. However, the UK regulator has issued a consensus statement in conjunction with industry
111 and patient stakeholder groups outlining several principles of responsible innovation (15). These state
112 that add-ons may be offered even when there is little or conflicting evidence provided that information
113 about the current state of knowledge is given to patients. Where there is no evidence of efficacy and
114 safety, the statement advises that treatments should only be offered as part of research. Both the HFEA
115 and the Victorian Assisted Reproductive Treatment Authority (VARTA) in Australia provide
116 information to consumers to make them aware that add-ons may not improve their chance of success
117 (10, 16). However, there is no such regulatory body in the U.S, nor in most other countries.

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119

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

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128 *How should IVF add-ons be regulated? Current proposals*

129

130

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

135

136

137 However, support for changes to the regulatory framework surrounding new reproductive treatments is
138 far from universal. Although arguments in favour of more stringent regulation have been advanced (12,
139 21-24), there have also been defences of current standards (25-27). A key argument in favour of reform
140 states that self-regulation is an unsuitable model for IVF. A free market in goods and services relies
141 upon consumers choosing not to buy useless products. If a mobile phone company were to produce a
142 new high tech phone which did not work, then after an initial flurry of interest in the new product, its
143 failings would become apparent and the market for it would disappear. Because there can be no
144 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
145 work, and because patients only experience the outcome of their own situation, it is much harder for
146 consumers of infertility services to tell for themselves whether an add-on treatment is worth purchasing.
147 Rather than relying on individual patients 'voting with their feet' in order to crowd out useless
148 interventions, it may be necessary instead for an expert regulator to make recommendations for them.

149

150

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

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

162

163

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

175

176

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

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

189

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191

192 *Informed consent when effectiveness is questionable*

193

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

209

210

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

223

224

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

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236

237 *Where do we go next?*

238

239

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

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245

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

256

257

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

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

275

276

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

288

289

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

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

298

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302

303 **References**

304

- 305 1. Gunn DD, Bates GW. Evidence-based approach to unexplained infertility: a systematic
306 review. *Fertil Steril* 2016;105:1566-74 e1.
307
- 308 2. ESHRE Capri Workshop Group. A prognosis-based approach to infertility: understanding the
309 role of time. *Hum Reprod* 2017;32:1556-9.
310
- 311 3. Kamphuis EI, Bhattacharya S, van der Veen F, Mol BW, Templeton A, Evidence Based IVFG.
312 Are we overusing IVF? *BMJ* 2014;348:g252.
313
- 314 4. Society for Assisted Reproductive Technologies. National Summary Report 2017. In, 2019.
- 315 5. Wilkinson J, Vail A, Roberts SA. Direct-to-consumer advertising of success rates for medically
316 assisted reproduction: a review of national clinic websites. *BMJ open* 2017;7:e012218.
317
- 318 6. Hammarberg K, Prentice T, Purcell I, Johnson L. Quality of information about success rates
319 provided on assisted reproductive technology clinic websites in Australia and New Zealand. *Aust N Z*
320 *J Obstet Gynaecol* 2018;58:330-4.
321
- 322 7. Spencer EA, Mahtani KR, Goldacre B, Heneghan C. Claims for fertility interventions: a
323 systematic assessment of statements on UK fertility centre websites. *BMJ open* 2016;6:e013940.
324
- 325 8. Hawkins J. Selling ART: An Empirical Assessment of Advertising on Fertility Clinics' Websites.
326 *Indiana Law J* 2013;88:1147-79.
327

- 328 9. Human Fertilisation and Embryology Authority. Pilot national fertility patient survey. 2018.
329 <https://www.hfea.gov.uk/media/2702/pilot-national-fertility-patient-survey-2018.pdf>, accessed Aug 2019.
330
- 331 10. Human Fertilisation and Embryology Authority. Treatment add-ons. 2019.
332 <https://www.hfea.gov.uk/treatments/explore-all-treatments/treatment-add-ons/>, accessed July 2019.
333
- 334 11. Nardo LG, El-Toukhy T, Stewart J, Balen AH, Potdar N. British Fertility Society Policy and
335 Practice Committee: adjuvants in IVF: evidence for good clinical practice. *Hum Fertil (Camb)*
336 2015;18:2-15.
337
- 338 12. Hendriks S, Pearson SD. A proposed framework for strengthening regulatory review of
339 innovative reproductive techniques in the United States. In: *Fertil Steril Dialog*, 2018.
340
- 341 13. Food and Drug Administration. Human cells, tissues, and cellular and tissue-based products;
342 establishment registration and listing. Food and Drug Administration, HHS. Final rule. *Fed Regist*
343 2001;66:5447-69.
344
- 345 14. Human Fertilisation and Embryology Authority. HFEA statement on fertility treatment 'add-
346 ons'. 2016. [https://www.hfea.gov.uk/about-us/news-and-press-releases/2016-news-and-press-releases/hfea-](https://www.hfea.gov.uk/about-us/news-and-press-releases/2016-news-and-press-releases/hfea-statement-on-fertility-treatment-add-ons/)
347 [statement-on-fertility-treatment-add-ons/](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.
348
- 349 15. Human Fertilisation and Embryology Authority. The responsible use of treatment add-ons in
350 fertility services: a consensus statement. 2019. [https://www.hfea.gov.uk/media/2792/treatment-add-ons-](https://www.hfea.gov.uk/media/2792/treatment-add-ons-consensus-statement-final.pdf)
351 [consensus-statement-final.pdf](https://www.hfea.gov.uk/media/2792/treatment-add-ons-consensus-statement-final.pdf), accessed July 2019.
352
- 353 16. Victorian Assisted Reproductive Treatment Authority. What you need to know about IVF
354 'add-ons'. 2019. <https://www.varta.org.au/resources/blogs/what-you-need-know-about-ivf-add-ons>.
355
- 356 17. Horbst V. 'You cannot do IVF in Africa as in Europe': the making of IVF in Mali and Uganda.
357 *Reprod Biomed Soc Online* 2016;2:108-15.
358
- 359 18. Simpson B. IVF in Sri Lanka: A concise history of regulatory impasse. *Reprod Biomed Soc*
360 *Online* 2016;2:8-15.
361
- 362 19. European Society for Hum Reprod and Embryology. The funding of IVF treatment. 2017.
363 <https://www.eshre.eu/Press-Room/Resources>, accessed July 2019.
364
- 365 20. Panorama. Inside Britain's Fertility Business. BBC, 2016,
366 <https://www.bbc.co.uk/programmes/b084ngkd>, accessed July 2019.
367
- 368 21. Harper J, Magli MC, Lundin K, Barratt CLR, Brison D. When and how should new technology
369 be introduced into the IVF laboratory? *Hum Reprod* 2012;27:303-13.
370
- 371 22. Harper J, Jackson E, Sermon K, Aitken RJ, Harbottle S, Mocanu E *et al*. Adjuncts in the IVF
372 laboratory: where is the evidence for 'add-on' interventions? *Hum Reprod* 2017;32:485-91.
373
- 374 23. Wilkinson J, Bhattacharya S, Duffy J, Kamath MS, Marjoribanks J, Repping S *et al*.
375 Reproductive medicine: still more ART than science? *BJOG* 2019;126:138-41.
376
- 377 24. Repping S. Evidence-based medicine and infertility treatment. *Lancet* 2019;393:380-2.
378

- 379 25. Murdoch A. Should the HFEA be regulating the add-on treatments for IVF/ICSI in the UK?:
380 AGAINST: HFEA regulation of add-on IVF/ICSI. *BJOG* 2017;124:1849.
381
- 382 26. Cohen J, Alikani M. Evidence-based medicine and its application in clinical preimplantation
383 embryology. *Reprod Biomed Online* 2013;27:547-61.
384
- 385 27. Macklon NS, Ahuja KK, Fauser B. Building an evidence base for IVF 'add-ons'. *Reprod Biomed*
386 *Online* 2019;38:853-6.
387
- 388 28. Prasad VK, Cifu AS. Ending medical reversal : improving outcomes, saving lives. Baltimore:
389 Johns Hopkins University Press, 2015.
390
- 391 29. Twisk M, Mastenbroek S, van Wely M, Heineman MJ, Van der Veen F, Repping S.
392 Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in in vitro
393 fertilisation or intracytoplasmic sperm injection. *The Cochrane database of systematic reviews*
394 2006:CD005291.
395
- 396 30. Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary?
397 Picking signal from noise. *BMJ* 2007;334:349-51.
398
- 399 31. Evers J. Do we need an RCT for everything? *Hum Reprod* 2017;32:483-4.
400
- 401 32. Braakhekke M, Mol F, Mastenbroek S, Mol BW, van der Veen F. Equipoise and the RCT. *Hum*
402 *Reprod* 2017;32:257-60.
403
- 404 33. Lensen S, Osavlyuk D, Armstrong S, Stadelmann C, Hennes A, Napier E *et al.* A Randomized
405 Trial of Endometrial Scratching before In Vitro Fertilization. *New England Journal of Medicine*
406 2019;380:325-34.
407
- 408 34. Lensen S, Venetis C, Ng EHY, Young SL, Vitagliano A, Macklon NS *et al.* Should we stop
409 offering endometrial scratching prior to in vitro fertilization? *Fertil Steril* 2019;111:1094-101.
410
- 411 35. Singer P, Wells D. In vitro fertilisation: the major issues. *J Med Ethics* 1983;9:192-9.
412
- 413 36. Madeira JL, Coyne K, Jaeger AS, Parry JP, Lindheim SR. Inform and consent: more than just
414 "sign here". *Fertil Steril* 2017;108:40-1.
415
- 416 37. Karpin I. Regulatory Responses to the Gendering of Transgenerational Harm. *Aust Feminist*
417 *Stud* 2016;31:139-53.
418
- 419 38. Blakely B, Williams J, Mayes C, Kerridge I, Lipworth W. Conflicts of interest in Australia's IVF
420 industry: an empirical analysis and call for action. *Hum Fertil (Camb)* 2017:1-8.
421
- 422 39. Mayes C, Blakely B, Kerridge I, Komesaroff P, Olver I, Lipworth W. On the fragility of medical
423 virtue in a neoliberal context: the case of commercial conflicts of interest in reproductive medicine.
424 *Theor Med Bioeth* 2016;37:97-111.
425
- 426 40. Dondorp W, de Wert G. Innovative reproductive technologies: risks and responsibilities.
427 *Hum Reprod* 2011;26:1604-8.
428
- 429 41. Zolkefli Y. Evaluating the Concept of Choice in Healthcare. *Malays J Med Sci* 2017;24:92-6.

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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.