

# 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.

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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?

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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?

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101 *How are add on treatments regulated?*

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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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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*

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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.

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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.

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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).

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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.

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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).

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192 *Informed consent when effectiveness is questionable*

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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.

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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.

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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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237 *Where do we go next?*

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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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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](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).

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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](http://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.

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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).

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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.

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