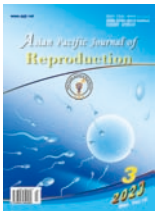

Letter to Editor

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Do not lose the moon while counting the stars: Conventional IVF *versus* add-on treatments

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When we look back at -more than four decades- the history of assisted reproductive treatments (ART), a continuous effort to optimise laboratory conditions and to improve treatment protocols can be seen. In basic terms, the aim of research about culture media and laboratory environments is to create as more physiological condition as possible, which means reducing the gap between the not-fully-known *in vivo* conditions and their *in vitro* counterparts. Apart from the modifications of standard protocols and improvements in laboratory variables, additional medications and interventions [the so called *in vitro* fertilization (IVF) add-ons] have also been proposed, creating excitement among practitioners and miraculous hope for patients. In general, compared with the conceivable investigation steps about the standard procedures, add-on techniques gain very high popularity even though there usually is a lack of robust evidence-based data about their efficiency[1]. Indeed, add-ons are a part of our daily IVF practice and almost all of us use one or more add-ons in our routine. Even though each add on may be a subject of an extended debate, in this brief commentary it was aimed to create an awareness about two key points: overusing the unproven IVF add-ons liberally and ignoring and underusing the more natural and proven conventional IVF (C-IVF) technique.

As a definition, an IVF add-on is any technique that is a variation of, or additional to a conventional IVF cycle, including clinical, laboratory and complementary treatments; add-ons construct a very long list which still keeps growing. Despite numerous add-on techniques and advancements in laboratory and clinical applications that emerged during the history of ART, only a limited increase has been achieved in live birth rates, which remains between 19%-22% per initiated cycle[2].

The story (emergence, adoption and application) of almost all of these add-ons is more or less similar: the first publications for each of them include a limited number of cases with miraculous results (some of them were even found to be effective by accident while searching for another issue) and they are believed to act with unknown or theoretical mechanisms of action. Most interestingly, the following well-designed publications reveal conflicting results and are not able to confirm the findings of the initial studies, resulting in confusion among IVF practitioners; a false hope in the infertile population and potential harm to the treatment outcome. As an example, endometrial scratching injury was first claimed to be effective after the report that eleven-out-of-twelve patients undergoing endometrial sampling for a "gap-junction protein research" conceived surprisingly at the following IVF cycle. Although it is very well known that the main actor during the implantation process is the embryo, this report created great attraction keeping researchers busy with clinical and histological studies aiming to clarify the effectiveness of this intervention. It took two decades to come to a conclusion that endometrial scratching injury does not result in a higher rate of live birth than no intervention among women undergoing IVF treatment. Despite the lack of evidence, 83% of the IVF practitioners still recommend endometrial scratching at a cost of nearly 500 USD with the hope of an unproven benefit with an unknown mechanism[3]. Furthermore, details of the scratching procedure are also not standardised, including timing, number of repetitions, and instrument and technique to be used.

Platelet rich plasma (PRP) can be denoted as another example of add-ons which has been used in some other disciplines (*e.g.* dentistry, dermatology, orthopedics) for several decades and has been gaining popularity in IVF recently. It has been offered mainly for thin endometrium and for poor ovarian reserve which are two of the most challenging problems in IVF practice for which many

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remedies have been tried for decades with little benefit if any. The first study about the use of PRP in women with thin endometrium was published in 2015 and included five patients only! Amazingly, all of these five patients whom had a history of failed IVF cycles due to poor endometrial response achieved pregnancy with the next IVF cycle just after PRP intervention[4]. Similarly, the first report about the use of PRP for poor ovarian reserve was published in 2018 and included just four patients. All four patients had lower serum follicle-stimulating hormone (FSH) levels and higher serum anti-Müllerian hormone (AMH) levels after intraovarian PRP injection compared with the pre-intervention serum FSH and AMH levels. However, based on the gathered knowledge from the existing literature so far, both intrauterine and intraovarian use of PRP are still considered to be experimental procedures[5].

It can be realised from the above examples that the individual timeline of emergence and evolution of most add-ons can be summarised mathematically with a parabolic curve: the first part, the ascending leg of the curve, represents the initial publication with unbelievably high efficacy, followed by a plateau resembling the studies with conflicting findings, while the last part is the descending leg showing the meta-analyses of all existing studies failing to reveal robust evidence. Last but not the least, there is always an additional cost which may be relatively low compared with the conventional treatment cost or may even exceed it at times. Considering all add-ons back-to-back in association with the history of IVF, their timeline can be depicted as a continuous sinusoidal wave as if one emerges as the predecessor fades away.

An online survey conducted in Australia showed that 82% of women having IVF had one or more IVF add-on usually (72%) with an additional cost and 66% experienced regret at their decision about add-on use. The authors suggested that the patients are not adequately informed about the benefits and risks of add-on procedures. Use of IVF add-ons was reported to be of a similar percentage in the European countries and it was assumed that their use may be greater in countries where majority of IVF treatments are not covered by national insurance systems[1].

Although add-ons are supposed to improve IVF outcomes, there are concerns about a potentially adverse effect on success rates. A recent analysis clearly shows that specific add-ons to ART, introduced into routine worldwide ART practice are likely causally related to steep declines in fresh non-donor live birth rates around the world[6]. Besides, this alarming loss in pregnancies has to be compensated for by performing more ART cycles, decreasing cost-effectiveness. Then, a critical question comes up based on the fundamental principle of "primum non nocere": if add-ons were to produce only similar results, what would be their purpose? Considering that at least one of the add-ons is used in more than two-thirds of IVF cycles[1], another critical question may be: what on earth have they been so widely used for? The practical answer to both questions maybe: the subjective and liberal use of add-ons by the practitioners makes a key-lock model with the hopeful exploration of the couples which easily push the patients to try at least one of them. In other words, commercialised IVF industry and patient panic industry collaborates for the creation of a therapeutic illusion (*i.e.* in many cases the women who conceive with add-ons actually will also do so without them).

It is worth noting that although there is a lack of sufficient resources providing evidence-based information regarding add-ons, a limited number of resources clearly state that only certain add-ons can be offered in selected patient groups or *via* research setting[7]. Human Fertility and Embryology Authority (HFEA), which is the fertility treatment regulator in United Kingdom, together with a range of professional societies and patient advocacy groups, developed and published a consensus statement in 2019 on the use of add-ons in ART[7]. Until recently, it was the only existing impartial source acting as a reference for the efficacy of a list of several IVF add-ons. Recently, European Society for Human Reproduction and Embryology (ESHRE) add-ons working group released a more comprehensive guideline entitled "Good practice recommendations for add-ons in reproductive medicine" which is currently under updating process based on the received comments[5].

In "Good practice recommendations for add-ons in reproductive medicine" of ESHRE, it is stated that "in some countries intracytoplasmic sperm injection (ICSI) is only performed when indicated, *i.e.*, in couples with diagnosed male factor infertility or fertilisation failure in the previous IVF cycle. In other countries or settings, ICSI is used in all couples, irrespective of the results of the fertility work-up and diagnostic interventions. As such, ICSI is not an add-on in the first setting, but should be considered so in the latter"[5]. Amongst the add-on pool, ICSI is worth being highlighted as the only one so far to have been proven to contribute to the clinical outcome, albeit in male factor infertility only. Despite ICSI having high popularity in the field of ART for all etiologic subgroups, C-IVF yields better fertilisation rates per collected cumulus-oocyte complexes (COCs) and similar or better implantation and pregnancy rates in patients diagnosed with non-male factor infertility[8]. Even in cases of poor ovarian response or advanced reproductive age, the choice of fertilisation method should be based primarily on semen quality[9]. Indeed, both American Society of Reproductive Medicine (ASRM) and ESHRE guidelines suggest reserving ICSI for male-factor infertility cases or maybe for patients with a history of fertilisation failure[10].

Apart from the fact that C-IVF and ICSI achieve similar clinical outcomes in couples diagnosed with non-male factor infertility, simplicity, cost-effectiveness, time-saving and steep learning curve of the laboratory staff are the additional prominent advantages of C-IVF. More frequent use of C-IVF would give in-depth information about fertilisation details and possibly provide solutions about the unexpected seldom fertilisation failures, which seem to be the apparently leading excuse practitioners put forward to prefer ICSI.

At a panoramic glance at the evolution of ARTs since the report of the first successful IVF delivery, it seems ironic that while

trying to optimise every step of the laboratory process [*e.g.* best sperm selection *via* microfluidic sorting, intracytoplasmic morhphologically selected sperm injection (IMSI), *etc*; artificial activation of the gametes; attempts to create a more natural environment], practitioners disregard the two crucial steps of natural fertilisation by ignoring C-IVF and using ICSI in non-male factor infertility cases: firstly, during ICSI, spermatozoon is selected artificially, sometimes amongst up to tens of millions of them, instead of a selection of the spermatozoa *via* C-IVF through the cross-talk between a cohort of sperm cells and COC. Secondly, the natural barriers of fertilisation are totally bypassed by directly injecting the spermatozoon into the ooplasm. Hence, C-IVF stands a natural and more efficient substitute for a combination of several add-ons and certainly will help the natural fertilisation process work meticulously in better harmony in non-male factor cases. Anyhow, particular add-on(s) can also be used in necessity on a rational basis alongside with a conventional IVF cycle.

In conclusion, we may realign our priorities by focusing on the efficient, simple, and cost-effective C-IVF technique and reconsider spending our efforts and sources for struggling with mostly unproven add-ons. In other words, instead of overusing ICSI in unnecessary indications and spending precious time and money with unproven add-on techniques, it will be more prudent to switch back to C-IVF which may contribute better to the effort of achieving higher success rates and safer long-term outcomes for ART individuals. Thus, for non-male factor infertility cases, sooner or later, IVF should be placed again in the right position it deserves.

Conflict of interest statement

The authors declare no conflicts of interest.

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