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Review Article

IVF Add-ons: Fact, Fiction, Fake or Fortune?

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ABSTRACT

Since the development of IVF there have been many innovations which claim to improve success rates. These are known as 'add ons'. Fertility patients believe that these 'add ons' are safe and effective but the scientific evidence is strongly to the contrary or at best vague. Fertility clinics and manufacturers of 'add ons' derive considerable financial benefit from 'add ons' which only leads to the further proliferation of 'add ons'. This review discusses the current 'add ons' based on the current medical literature and in the context of 'fake science' which may provide 'evidence' for 'add ons'.

Keywords: Infertility; *In vitro* fertilization; Reproductive immunology

INTRODUCTION

'Rather than love, than money, than fame, give me truth'. Henry David Thoreau (1817-1862)

It is over 40 years since the first *in vitro* fertilization (IVF) baby was born [1]. This was the culmination of decades of scientific and medical research to understand how to safely bring together human gametes in the laboratory resulting in a human embryo which subsequently formed a healthy, normal human being. Since that time there have been over 8 million IVF babies born globally. Pregnancy rates seem steady at around 36% [2] or viewed by others, have declined to rates seen in the early 1990`s [3]. The predicted value of the IVF industry by 2026 is $36.2 billion [4] which is a doubling to what was seen in 2018. This will result in more Mergers & Acquisitions (M&A`s) to consolidate this still widely fragmented market. It is well known, and taught in elite business schools such as Harvard, that M&A`s fare worse in general than privately owned companies and that money comes mostly before quality [5]. This might also be reflected in the stagnation or even downward trend of reported assisted reproduction technologies (ART) success rates as well as in the rise of mainly low-quality scientific publications from such merged and consolidated clinic consortia, which depend on the good-will, money and "narrow" vision of their primarily money-driven shareholders. Merger and acquisition can result in owners having many clinics in their portfolio and such consortia could have the power to generate the critical mass of high-quality data needed to generate high-power publications with great impact. This is not seen so far on the landscape of ART in general and until today not at all in consortia of M&A`s. Neither publication in high impact journals nor in conferences such as ESHRE or ASRM is seen. Instead, most publications still end with sentences such as: "...Whether ART treatment (e.g. increases or decreases) ... needs further investigation".

Thus, even meta-analyses, which try hard to combine results from several single studies, often result in low quality data (including those assessing low-power, heterogeneous groups) and try to gain statistical power through increased sample size but mostly these fail. They fail especially in the fragmented field of ART but are still prevailing, adding no true value to solving urgently needed issues in ART. Meta-analyses of issues related to the patients and childhood safety and welfare may provide useful data. Fragmentation, which results in non-homogeneous/non-standardized scientific studies (even exponentially when doing multicentre trials for the sake to try to increase statistical power), could be solved by consolidation, where institutes could and should be working in a streamlined and thus homogeneous fashion. Nevertheless, this is not seen in the IVF-industry so far and probably not even in the long term. Additionally, single institutes, which are in negotiation with M&A`s, even manage to publish falsified scientific data [6] to increase their market value with minimal fear of prosecution. Such publications may end in meta-analyses which in turn fuels the "add ons" market.

A recent publication [7] demonstrates that randomized controlled trials (RCT) are needed to prevent things becoming even worse in the IVF world. If, for example, the RCT focuses on the 'take-home baby rate' with one single variable (e.g. blastocyst culture) it is important to remember that there are a vast number of variables in a non-unified setting. The non-unified setting prevails in the landscape of IVF clinics.

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In order for blastocyst culture, for example, to work effectively, a trained and competent team of doctors, scientists and nurses is needed along with the relevant Quality Management and administrative support. The choice of the 'right' patient is also very important. Many patients embark on IVF treatment even though other options could be as effective such as optimization of their physical and psychological wellbeing. These alternative treatment options are often ignored by IVF clinics. This is because IVF clinics exist for their primary purpose i.e. carrying out *in vitro* fertilization and selling their products such as IVF, ICSI and related treatments. This is where IVF clinics create their income and profit. There is no income or profit in trying to get couples pregnant by alternative methods such as life-style changes. IVF clinics have many staff on the payroll including doctors, scientists and nurses who drive the IVF business model which in turn provides the money for these salaries. IVF clinics do not earn a large income by providing consultations, which when done properly, may last hours. Equally IVF clinics do not earn a lot of income on subsequent consultations to check for improvements on the health status of the couples, which could take place over subsequent months or years.

When the consulting doctor in an IVF clinic sees 2-3 patients a day, he himself cannot handle the ultrasound scans for follicle monitoring, the oocyte collections, the embryo transfers and the communications with patients. The consulting doctor needs a team of doctors, nurses and scientists especially in the setting of strict day 5 embryo-transfer with culture of surplus slow growing embryos until day 6 or 7. From a logistical point of view a clinic using day 5 blastocyst culture and carrying out the oocyte collection on a Tuesday results in the embryo transfer taking place on a Saturday. Consideration has therefore to be given on the labour rights and the relevant working time law. Teamwork is the only way to effectively achieve such as service. All of the team members must have the appropriate training and competence and in all relevant procedures. There are also possible fluctuations in outcome for example when a certain doctor in the team works together with a certain biologist when performing the embryo transfer which may or may not be an indicator of good practice.

The availability of IVF on a global scale is related to the wealth of a country. This means that areas such as Sub-Saharan Africa have poor provision for fertility treatment [8]. The technology used in IVF today has changed completely from that used in 1978 making what was for an long in-patient treatment now a simple out-patient procedure [9] but still mostly with stagnating and overall disappointingly low success rates. The basic technology of IVF has nevertheless stood the test of time, but questions need to be asked about the safety and efficacy of new technologies [10] and the sometimes 'wobbly' evidence base for new reproductive technologies [11]. A possible increased risk of congenital heart defects in IVF/ICSI babies has recently been described [12] and the general consensus is that birth defects are more common in IVF babies [13]. In addition, there are possible concerns about the effect of IVF embryo culture (which usually varies from 3 to 5 days post-fertilization) on the epigenome [14].

The lead author of this paper gave a welcome statement in the PGDIS conference in 2012. He used the analogy of what has happened with the airplane industry from the pioneering state to today and what is seen with IVF since the pioneering work. In the early days of flying, many planes crashed, they were unsafe and technically in their infancy. Today we have safety when flying of >99.9% (at least with well-established companies) and travelling long distances is very easy and convenient. In contrast if IVF success rates stagnate somewhere around a 36% then this is little improvement from what was seen in the early days of IVF. IVF treatments were established for patients with a clear cause of infertility for example treating tubal factor infertility. Most patients today have a form of subfertility which might benefit more from other procedures such as life-style interventions and much too often end up with questionable IVF technologies including "add ons" which lack a sound scientific basis [11]. There are IVF clinics who fare better and others worse even when such clinics treat sub-fertile patients. All clinics use different protocols to prepare patients, different lab protocols, different culture media, where ingredients are not disclosed by the manufacturers. Some have specific embryo-transfer technologies. Many clinics use lead-follicle size measurements to predict optimal timing for ovulation induction. Various hormone formulations for luteal phase support are being used and administered at different starting points and inclusion parameters for patients to enter an IVF program *vs.* expectant management *vs.* artificial insemination or other treatment options are almost non-existent.

For example, is it truly advisable to start IVF treatment in obese or PCOS patients, where blood sugar levels are suboptimal and who would primarily benefit from life-style interventions? Do we truly neglect the male partner and his sperm, which might be of low quality because of his obesity or unhealthy lifestyle and rather jump straight onto IVF/ICSI with all the "add ons"? We also know that laboratory quality is of utmost importance when carrying out IVF [15].

To return to the analogy of the airplane industry technology such as IVF is quite often carried out in a comparatively 'blind' way. When a plane crashes we see the devastation and the resulting casualties. There are no such visible consequences in failed IVF apart from the pain and suffering of the patients.

In Austria, for example, all IVF centres have to report their success rates to the relevant authority and all IVF centres see their own results compared to the blinded competitors. There is no disclosure of these data. It is even forbidden to disclose a clinics' own results to a patient or the public, it can only be used for internal valuations. The analysis and comparisons of the various IVF centres is missing homogeneity as well as important data and thus comparisons are almost impossible. The same holds true for many other countries regarding their reporting systems to the authorities.

IVF patients may present with signs of depression, they may show signs of frustration and do not talk about their experience of unsuccessful 'trial and error' when trying to conceive through the help of reproductive technologies. This could be one major reason why many questionable technologies and unnecessary procedures can be sold to patients with relative ease.

If these patients were plane passengers, and they knew that the plane had a success rate of 36% to reach the destination, would they still be willing to pay extra fee for anything on the plane? Would they even be taking the risk to travel with such an aircraft? Even if the company or the pilot suggests that they should? Establishing a pregnancy using assisted reproduction technologies is even more difficult than that.

What about in patients with a "bumpy" endometrium, or with a "bumpy" body, with suboptimal oocyte quality and so on? Who truly tested these various components and variables rigorously?

If a plane crashes, there are thorough investigations to find out about the cause of the accident. Mostly it is not a single cause but a chain of events leading to a crash. When the cause is finally found, the aviation authority releases new directives to improve safety and future errors. This is not so when an IVF cycle fails. The patient is simply offered more of the same with the possible inclusion of untested 'add ons' to increase their chances of success.

The only approach to obtain meaningful data about IVF failure is to 'reboot' the system starting with the patient group for whom IVF was primarily meant to be, which were patients with tubal factor infertility and in the fertile age group of 25-32 years of age.

We only know that IVF works for about a third of patients with a true cause of infertility. Everything else already becomes blurry. Even the patient cohort with tubal infertility have not been further rigorously studied on any aspects be it variations in ethnicities, age or BMI.

Such studies could be viewed as starting point, from which to test each single "add on" rigorously. Using a homogenous group of patients receiving the same stimulation protocol and subsequent treatment will allow meaningful data to be collected.

Treatment for male infertility started using trial and error with the introduction of ICSI in the early 1990`s and parallel developments of surgical sperm retrieval techniques for men presenting with azoospermia were emerging in these early day. It was reported that sperm, which had to be first damaged and immobilized could fertilize an oocyte when directly injected. Until this time the opinion was: "don`t touch the oocyte"! This is why SUZI and other technologies prevailed until then because no one dared to touch the oocyte. Even Bob Edwards, who directed some of the very early research at Bourn Hall using SUZI with the second author of this paper, was very clear that no clinical embryologist should break the oolemma because the fear was oocyte damage and possible oocyte activation [16].

In this review we assess 'traditional add-on' treatment to IVF such as ICSI/IMSI. We also consider the more radical and unproven technologies used as 'add ons' in IVF and whether or not all of these additional treatments could reduce the safety and efficacy of IVF. It has recently been proposed that randomized studies to assess the impact of 'add ons' to the overall safety and efficacy of IVF should be carried out [17]. We will also consider the impact of patient pressure on the use of 'add-ons' and how 'add-ons' can be an easy additional revenue for some IVF clinics when treating vulnerable fertility patients.

Intracytoplasmic Sperm Injection (ICSI) and related technologies

The first ICSI births were reported in 1992 [18] as a treatment for severe male infertility. Ten years later a follow up of babies born following ICSI indicated that ICSI seemed to be a safe procedure although the authors did state that further studies are needed to ensure long-term safety [19]. More recently a review of ICSI showed that there are possible higher risks of major birth defects, a possible higher risk of autism and the possibility that ICSI conceived men have lower sperm count and motility when compared to naturally conceived peers [20]. It is clear that ICSI is the only route to treatment when there is severe male infertility (other than donor sperm or after oocyte freezing) and that it may or may not have long-term risks and these will only be known in the fullness of time. Our concern is the ever-increasing use of ICSI in patients without severe male infertility [21] with no real evidence base that these patients either benefit from, or may potentially be harmed by, the widespread contra-indicated use of ICSI. A randomised controlled trial of ICSI *vs.* IVF in non-male factor infertility is underway to try to resolve these difficult questions [22]. There is also some concern that there could be selective outcome reporting in IVF/ICSI randomized controlled trials which may be resulting in false or misleading data being used in clinical practice [23]. This should also be considered against the background of general fabrication and falsification of research data by some scientists [24] which unfortunately clouds the whole debate and could have a major, potentially damaging negative impact on clinical practice. In the UK it is reported that ICSI is used in anything from 20% to 80% of fertility treatments and in the higher percentage there was no increased live birth rate or an increased overall fertilisation rate suggesting that the use of ICSI in these cases makes no difference at all to the overall outcomes [25].

Many clinics also recommend ICSI to all patients with low numbers of oocytes (e.g.1-5) even when there are non-male factor infertility issues. This is thought to enhance the chances of fertilisation. There is no evidence base at all for this practice and indeed a recent European multicentre analysis states that the 'number of oocytes retrieved has no value in the selection of insemination procedure in case of non-male factor infertility' [26].

There is, of course, a financial incentive for clinics to carry out ICSI on as many cases as possible and this could fuel the overuse or inappropriate use of ICSI by some practitioners.

Intracytoplasmic Morphologically Selected Sperm Injection (IMSI)

IMSI was developed in 2008, as a modification to ICSI, in an attempt to increase embryo quality [27] and/ or subsequent live birth rate in patients who had previous failed ICSI treatment cycles [28,29]. A later randomized sibling oocyte study on IMSI reported that IMSI does not improve fertilization rate or embryonic development [30] suggesting that IMSI has no real benefit to patients despite it being offered as an expensive 'add on' to routine treatment. A recent meta-analysis on IMSI versus ICSI comes to the conclusion that there is not sufficient evidence to support the use of IMSI in IVF for male infertility [31] and this is supported by the most recent meta-analysis showing no difference between live birth rates and miscarriage rates in IMSI versus ICSI [32]. The UK Human Fertilisation and Embryology Authority (HFEA) states that IMSI is neither effective nor safe [33]. There are many factors in our opinion which drive the current use of IMSI despite negative literature evidence and regulatory authority opinion, such as:

- Patient pressure: these are patients with failed cycles using ICSI who seek a 'cure' to their problem and will try anything put forward by the clinic to achieve their aims. This is perhaps the most powerful driving force in this and all other 'add ons'. If a given clinic cannot offer what the patients believe is needed, then they will seek it out elsewhere.
- Manufacturers of the additional equipment and training needed to provide IMSI have a significant financial incentive to encourage the use of IMSI in their marketing.

Physiological Intracytoplasmic Sperm Injection (PICSI)

A second modification of ICSI, using hyaluronan to select sperm for injection (PICSI) is offered to some patients who have had prior failed cycle or miscarriage following ICSI. A recent parallel, two

group, randomized trial has shown that PICSI does not significantly improve live birth rates and is therefore not recommended for use to treat fertility patients [34]. Despite this, many clinics still offer PICSI with increased cost to the patient. The HFEA agree with this finding and state that PICSI is neither effective nor safe.

Sperm DNA fragmentation testing

Many IVF clinics offer male patients sperm DNA fragmentation testing in an attempt to assess a possible cause of male infertility. This technology represents a significant income source for many IVF clinics but the current opinion is that sperm DNA fragmentation studies should not be offered until randomised trials prove clinical efficacy [35]. Male patients with increased DNA fragmentation are often offered antioxidant medication in an effort to 'modify' their sperm DNA fragmentation. The current opinion states that such an approach 'may be useful' although the pregnancy rate in such patients is low [36]. There is currently conflicting evidence on the value of sperm DNA fragmentation testing and the results of this 'add on' are not thought to be important in the treatment plan of fertility patients.

Time-lapse video analysis of embryonic development (Embryoscope)

Time-lapse video analysis and un-interrupted culture (e.g. Embryoscope) of developing human embryos is now a routine in most IVF clinics and patient pressure to use the technology is high. There is, however, still controversy as to how much time-lapse and un-interrupted embryo culture actually produces better results in relation to the many other parameters involved in embryo culture [37]. The HFEA state that at present there is not enough evidence that time-lapse video analysis has any overall impact on live-birth rates and therefore the additional cost of the process is not worthwhile. Despite this, most patients want to use time-lapse technology in their treatment and may even change clinics if their current clinic cannot provide time-lapse technology. Further development in embryo morphokinetics and image analysis may in the future provide a benefit to patients [38] but at present such technology is unavailable.

Pre-implantation Genetic Screening (PGS) and Pre-implantation Genetic Diagnosis (PGD)

PGS, using polar body analysis, was first described in 1996 as a possible way to identify aneuploid embryos in older female patients and therefore possibly increase live birth rate in this patient group [39]. Subsequent developments in PGS utilised biopsy of the day 3 cleavage embryo (blastomeres) and also biopsy of the trophoblast of the blastocyst and many more patients, all in some clinics, were offered PGS on the principle that it will select the 'best' embryos for transfer. There is of course a significant cost implication to patients who decide to use PGS. More recent analysis of the data obtained from PGS and the resulting possible benefits to patients concludes that the overall hypothesis of PGS in clinical practice is increasingly difficult to maintain [3]. The HFEA state that there is conflicting evidence on the safety and efficacy of day 5 PGS and no evidence for the safety and efficacy of day 3 PGS. Most worrying is the recent report that 'abnormal' PGS embryos can actually go on to produce normal, healthy live births and that PGS therefore results in the disposal of many normal embryos [40]. One of the most recent publication on this topic [41] adds more to the confusion than it solves. This publication of Munné et al. 2019 was re-evaluated recently and with their calculations the authors state that preimplantation genetic testing for aneuploidy leads to an approximately 30% reduction of live-birth-rate for competent embryos and thus to embryo wastage [42].

PGD, the diagnosis of disease in embryos with a view to excluding serious inherited disease, is a very different story. So much so that it arguably should not be in a critical discussion of IVF 'add ons'. In theory it is possible to screen for any genetic disease where the genes are known and as of today at least 600 different genetic diseases can be screened for using PGD [43]. This enables families with known genetic disease to have healthy children. It is also possible to offer preimplantation tissue testing/HLA typing (PTT) in families where a 'saviour sibling' is needed to provide umbilical cord blood for transplantation [44]. PGD and PTT are examples of excellent, safe and effective treatments which have saved and transformed many lives. The technology is advanced and relatively expensive but the benefits are enormous and the safety and efficacy are completely proven.

Endometrial 'scratching' (endometrial injury)

Endometrial 'scratching' was first introduced in 2003 as a proposed way of enhancing the receptivity of the endometrium to the implanting embryo. It has since been shown to have no beneficial effect and it has no biological basis [45]. Despite this the 'scratch' is still widely offered in fertility clinics, often with a disproportionate fee attached to it, and patients are trusting clinics that this might help in their treatment. The HFEA state that there is conflicting evidence regarding endometrial scratching and further research is needed.

Assisted hatching

Assisted hatching is the cutting or opening of the zona pellucida using acid, laser or other tools, on the basis that the procedure may help hatching of the embryo and thus enhance implantation [46]. More recently a meta-analysis of laser assisted hatching came to the conclusion that large scale, prospective, randomized controlled trials are needed to determine of assisted hatching is a clinically relevant [47]. The HFEA states that there is no evidence that assisted hatching is either effective or safe and the National Institute for Clinical Excellence (NICE) states: "Assisted hatching is not recommended because it has not been shown to improve pregnancy rates." Despite these opinions, and the highly conflicted medical literature, many clinics promote assisted hatching to their patients as a possible treatment modality and charge an 'add on' fee for the service.

Embryo glue

'Embryo glue' is a medium, used at embryo transfer, containing hyaluronan which is proposed to enhance the process of implantation [48]. The medical literature is conflicting on the use of embryo glue and the HFEA states that further research is required to confirm safety and efficacy. Embryo glue is often offered to patients who have had a previous failed IVF cycle despite the evidence that it will not help such patients [49].

Elective freeze all cycles

Elective freeze all cycles involve the creation of a batch of fresh embryos for a patient and then freezing all of these embryos for the future frozen embryo transfer at a later date [50]. Such an approach may be useful in those patients at risk of ovarian hyper-stimulation syndrome (OHSS) but not for those patients who are either normal or poor responders to ovarian stimulation. The HFEA state that

there is conflicting evidence for elective freeze-all cycles and further research is needed. If this 'add on' is offered to patients who do not need it then it will incur further cost on their treatment and the risk of embryo damage during the freezing process.

Reproductive immunology

Some IVF practitioners believe that manipulation of the female patients' immune system may result in an increase in fertility by reducing the activity of Natural Killer (NK) cells. The evidence in support of this concept is conflicting and many consider that reproductive immunology intervention should only be part of clinical research [51]. Such interventions include the administration of prednisolone [52], intravenous immunoglobulin (IVIg) [53], Tumour Necrosis Factor Alpha (TNF) antagonists [54], partner lymphocyte immunization [55] and Intralipid infusions [56]. Most recently a systematic review of immune therapies in the treatment of infertility raises the point of a need for better immunological diagnosis and the follow-up of infants born following immunological interventions [57]. The HFEA state that there is no evidence that reproductive immunology interventions are either safe or effective and all of the interventions carry risks. The cost of these reproductive immunology interventions is high and represents a significant income source in some IVF clinics.

Acupuncture

The proposition that acupuncture might assist in the treatment of fertility patients has resulted in the use of the technology for many years despite any clear rationale or benefit of use [58]. Acupuncture may have side benefits such as promoting relaxation and general well-being but it should not be used if the context is to enhance live birth rates.

DISCUSSION

Basic IVF, as developed by Edwards and Steptoe, is clearly a safe procedure providing the option of a family to millions of people which would not otherwise be possible. The discussion which we wish to initiate is related to 'add ons' to basic IVF which are often untested for efficacy and safety and in many cases do not have support of relevant Regulatory Authorities. There are many drivers to the use of 'add ons' in IVF including clinics who wish to optimise their income, manufacturers who only see profit and do not worry about patients and most surprisingly patients themselves. Fertility patients are very vulnerable and will do anything to meet their desire for a family. They put their trust in fertility clinics and if a clinic recommends an 'add on', regardless of cost, safety or efficacy, the patients will accept the advice and pay for the 'add on'. Patients also see and contribute to online discussions, which are totally unregulated, and opinions and advice from this source drive them to ask for 'add ons' to 'increase' their chances of success [59]. This is a unique and unacceptable type of medical practice similar to some dentists who may offer inappropriate treatment [60] simply for profit. It is also more convenient for IVF specialists to directly hop on questionable IVF technologies and blame such things as natural killer cells for an implantation failure. This is instead of telling patients that life-style interventions might better optimise their egg, sperm, endometrium and overall body health, leading to improved outcome and without the need for expensive, unproven and more harmful interventions. This is especially in those cases with the diagnosis of subfertility or unexplained infertility.

The clarity of information available to patients is also a serious concern in the context of 'add ons'. Regulatory authorities have very clear advice on 'add ons' but despite this, patients still request 'add ons' which are untested for efficacy and safety and clinics encourage these requests and ensure that they have all of the 'add ons' available. A good example is time lapse monitoring of embryonic development which almost all patients request. Many clinics offer time-lapse to every patient as if it is scientifically proven technology, which it is not. Those clinics without time lapse equipment often lose patients to other clinics who do offer time lapse. This simple example results in patients paying for an unnecessary procedure and even changing clinics to get the 'add on'. Manufacturers are selling their equipment to clinics with enormous profits. This cycle of patient demand and manufacturer greed supports the continued use of pointless, ineffective 'add ons'.

We propose that fertility patients are being seriously (and possibly unlawfully) misled by fertility clinics and the clinics and manufacturers benefit from this malpractice.

Regulators, such as the HFEA in the UK, have clear opinions and information on the safety and efficacy IVF 'add ons' but they do not enforce these restrictions in clinics. They sometimes express reservations and concerns with individual clinics but do not enforce these opinions with the backing of the law. We suggest that regulators must be more pro-active to protect patients from untested and unproven 'add ons' and to provide the protection that patients need. Regulators must send a very clear message to clinics that are generating significant income by promoting untested and unproven 'add ons'.

Many fertility practitioners will point to 'evidence' which shows that their 'add ons' are safe and effective. The patients are unable to critically appraise such information and in some cases the evidence might even be biased or worse still fake [61]. Fake, manipulated or totally fabricated scientific data seems to be becoming an increasing trend [62] and fertility practitioners must bear this in mind when making clinical decisions.

It is our view that the only 'add-on' in the list we provided above which should be used in routine clinical practice is pre-implantation genetic diagnosis (PGD). This procedure is offered to patients who carry genes for specific diseases and very often they have no fertility problems. It is therefore arguable that PGD is not a fertility treatment and as such should not be part of the current debate on IVF 'add ons' as we described above. We consider the rest of the 'add-ons' described, including ICSI with no clinical indication, to be unsafe and should not be used in clinical practice.

The level of counseling in IVF is poor because, unless counseling is mandatory, most fertility patients do not take advantage of counseling [63]. We propose that all patients considering 'add ons' should undergo mandatory counseling to ensure that they receive unbiased advice on the safety and efficacy of the 'add on' being considered.

Some authors will propose that 'multi-centre' clinical trials must be carried out in order to properly assess IVF 'add ons' [64]. The inherent problem with this approach in ART is that clinics use different stimulation protocols, they have different timing of ovulation induction, and they are situated in different climate regions and elevations (air pressure could impact culture media as do different "room temperatures" or air particles). They all use different culture media and the timing of such things as fertilization with IVF or ICSI differ. This means that drawing any meaningful conclusions from such studies is either difficult or meaningless.

We propose that there must be a standardization of conditions in fertility clinical trials so that the data collected will be comparable and relevant. We have to include enough patients in every single study to get the statistical power needed to make firm conclusions.

As suggested in the introduction starting from scratch might be wishful thinking and not manageable at all. Take the example of IMSI. The lead author of this paper co-authored [27] on embryo quality depending on the size and numbers of vacuoles seen in spermatozoa and this was done as follows: sperm, which were individually selected by normal magnification for ICSI were examined at high magnification before injection into the oocytes. Retrospectively, it was observed that those sperm with certain types and numbers of vacuoles influenced embryo development to the blastocyst stage. These findings raised many questions: Will it be possible to prospectively and deliberately inject sperm with various vacuoles into oocytes? Who would dare or risk to do so? Which ethical committee would give green light for such a study on large scale?

This is one of many examples we could list and is provided as a thought-provoking concept which nourishes new discussions on what is practical to achieve in the future and what we have to accept as 'given' with all publications available on IVF.

CONCLUSION

In summary we propose that the current and growing number of 'add ons' is unacceptable and poses a significant risk to the safety of patients. It is driven by patient pressure, corporate greed and the need of clinics to optimize their income. It is critical that regulatory authorities intervene in this 'vicious circle' to protect patients and that going forward with any new 'add on' must be supported by clear evidence of safety and efficacy before it is introduced. This might be impossible or very hard to accomplish but the safety of fertility patients must remain our prime objective.

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