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Citation:	EMJ Repro Health. 2026;12[1]:64-67. https://doi.org/10.33590/emjreprohealth/1N1T76AG
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Q1 With IVF success rates continuing to improve, where do you see the greatest remaining opportunities to optimise treatment outcomes for patients?

I'm not sure if IVF success rates have really improved, but what we can do is have a more targeted approach. We should do IVF in people who have a good chance of achieving success with it, then identify those who are highly unlikely to achieve success and try to channel them towards more appropriate treatment pathways. Typically, this goes towards donation or moving on in your procreation journey, so to speak.

I think, with that, you can make IVF more successful, but you will not treat as many patients who will not benefit from it. This requires that you have access to the full spectrum of methods, including all kinds of donations.

I would also argue that the sentiment in the field is more that IVF success rates have, in a way, levelled off. It's coming to a plateau. Germ cells are germ cells. Our patients get older and older. They are getting less reproductively fit in terms of BMI, concurrent disorders, potential accumulation of environmental toxins, negative health or lifestyle factors, and so on.

When we work with oocytes and sperm, we do not really interfere in any causal way with the setup of these germ cells. We have come to a plateau, or a limit, of what can be achieved.

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A lot of effort has gone into the selection of gametes and embryos. You can spend as much time selecting an embryo as you wish. You can observe an embryo through the microscope or through the means of AI, but the embryo does not get better because of that. I think we can all agree on this.

You can biopsy an embryo or perform tests on it; it will never get better from that. The embryo can only get worse from the biopsy, the freezing thereafter, even if only slightly, and because of false positive diagnoses on genetic findings. The end result of all of this is that we do not increase the number of women having a child through IVF, though success rates per treatment attempt can be inflated.

Q2 What emerging technologies or research directions do you think have the greatest potential to move reproductive medicine beyond the current limits of IVF?

So, if the question is what might move us beyond that plateau, then there are some new frontiers being explored.

One is the uterus. Many people are sceptical that much can be achieved on that frontier because the uterus is considered a rather simple organ. Decidualisation of the endometrium is a very ancient and reliable mechanism in humans, and there may not be much that we can theoretically improve.

The observation supporting that is that, in the oocyte donation setting, we see relatively stable success rates independent of uterine age. There was a presentation during the European Society of Human Reproduction and Embryology (ESHRE) Congress where they reported some decrease in live birth rate above 50 years of age in the recipient, independent of paternal age and other factors, so there is some uterine factor there. But many people argue that changing a uterine factor, such as endometrial receptivity, is not going to be the big game changer.

On another frontier, a technique that is often discussed is maternal spindle transfer. It brings together oocyte donation and a patient's own genetic material. The patient's nuclear genetic material is transferred into an enucleated donor oocyte at the right moment in meiosis. The oocyte is then reconstituted, and you essentially have a young oocyte with your own nucleus and human genetic material. Then the sperm is added.

The promise is that this could improve success rates in older women in a relevant way. There are, however, many safety concerns. You create 'three-parent children' because you're combining mitochondrial DNA from the donor oocyte with nuclear DNA from the mother and father. In essence, you create new genetic combinations.

This is already happening in clinical practice. However, in Germany, for example, it would be forbidden under penal law because it would be considered manipulation of the germline. But there are places where it is not regulated. In Greece, for example, the Institute of Life in Athens has permission to perform this and has published on it, including follow-up of pregnancies and children.

Many things are not yet fully understood about this technology, but, to me, this is an example of moving beyond conventional IVF.

Conventional IVF, as we see it today, has largely levelled off. We may still optimise culture media or incubator conditions, but those changes are unlikely to dramatically alter outcomes. What may make a difference are approaches that rejuvenate oocytes, repair age-related deficiencies, or create artificial gametes.

The oocyte remains the decisive contributor to fertility because it provides the machinery. I often show patients that the sperm is tiny compared with the oocyte. The sperm contributes mostly information and some small tools, but the oocyte provides the large machinery on top of information. When that machinery ages, fertility declines.

Q3 There has been a growing debate around treatment add-ons in reproductive medicine, with the current ESHRE Chair, Karen Sermon, describing preimplantation genetic testing for aneuploidy (PGT-A) as a "massively abused method." What is your view on the evidence supporting PGT-A and other add-ons, and when, if ever, do you offer these interventions to patients?

An embryo never gets better through testing. The promise that more women can achieve a live birth by applying the technology is likely false from the beginning.

People argued that it had secondary benefits. Particularly in the USA, they said that if you transfer only one embryo instead of two or three, you could reduce multiple pregnancies. The argument was that genetic testing would identify the best embryo and therefore support elective single embryo transfer. However, an RCT testing explicit single embryo transfer with or without PGT-A failed[1] to identify a real benefit, especially when factoring in the size of the embryo cohort available for transfer with or without genetic testing.[2]

The next argument was that the method is nearly 100% negative predictive when a uniform numeric aneuploidy is detected in an embryo biopsy, and I would agree with that. A woman who produces many supernumerary embryos could thus potentially avoid freezing and transferring embryos that will never result in a live birth. However, few women are in a situation to choose from a larger number of optimal blastocysts per one treatment cycle, so on a population level, the purported benefit will likely be negligible.

Regarding the overutilisation of technology in the context of IVF, Gleicher N et al.[3] have recently shown on the USA data that while more interventions are being added (PGT-A, freeze-all strategies, and so on), fewer fresh embryo transfers are occurring, and fewer babies are being born relative to the number of cycles started. This is why I am critical of being overly enthusiastic about some of these innovations.

Imagine a healthy 27-year-old woman with blocked tubes. She simply needs IVF. Instead, she may undergo excessive stimulation, freeze-all treatment pathways, additional interventions, and substantial expense that do not improve her chances of having a healthy baby sooner. If this continues for long enough, patients will increasingly question these practices. If there is no self-regulation, other forms of regulation are likely to follow.

To answer your question directly: do we apply PGT-A to our patients? Certainly not as a routine, I work in a centre that has licences to perform genetic testing. I participated in major studies, and my team could run the technology without any problem. Nevertheless, I would clearly discourage my average patient from doing it.

Which add-ons do you think are reasonable to discuss with patients?

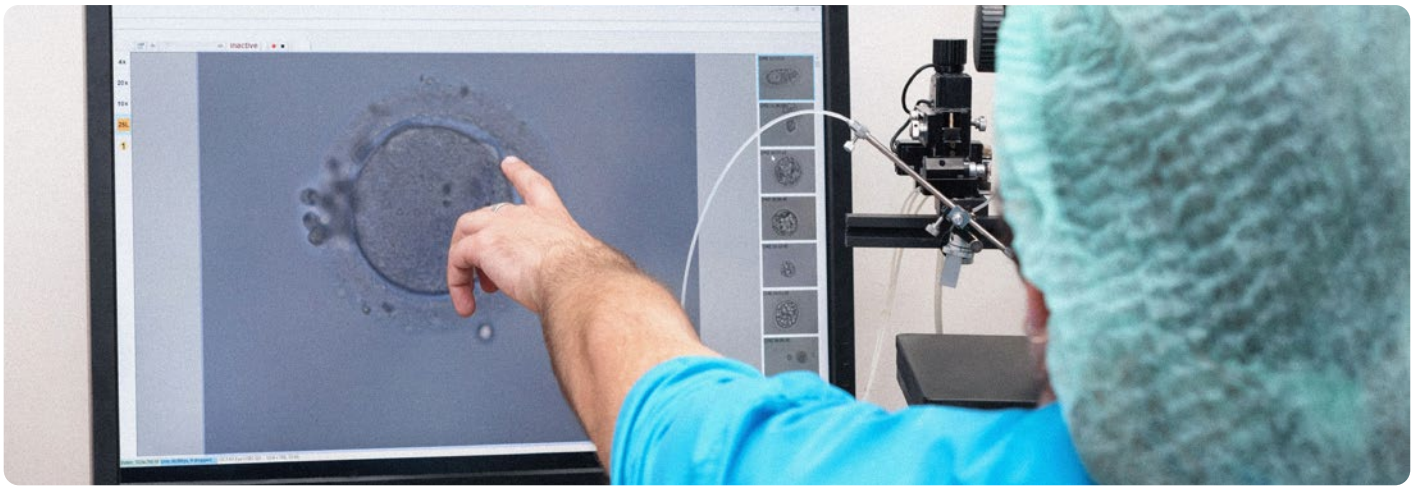
We have just published an RCT at this year's ESHRE on intra-ovarian platelet-rich plasma injections. The conclusion was that it does not appear to work. A similar result was presented by another group based on an RCT.

I'm not condemning add-ons in principle. Some interventions have a very low likelihood of harm and may reasonably be discussed with patients. For example, hyaluronic acid is relatively low-cost and unlikely to be harmful. If patients ask about it, I feel there is an obligation to explain that the evidence is limited, but that it is unlikely to cause damage.

We occasionally use sperm selection devices such as microfluidic systems, although I cannot say with confidence that they work.

We use karyotype testing in selected situations. We also apply CatSper testing (Truion GmbH, Münster, Germany) on sperm in idiopathic infertility cases. If positive, it can change the understanding of a couple's infertility.

In my practice, I tend to favour low-cost, low-risk interventions that have at least a theoretical possibility of benefit.



Q4 In areas such as recurrent pregnancy loss, some interventions, including intravenous Ig, continue to be used despite limited evidence. When, if ever, do you think these treatments are appropriate?

There was a recent Danish trial looking at intravenous Ig combined with corticosteroids. It is extremely difficult to run strong studies in this area. The signal from that study was somewhat encouraging. At least, corticosteroids were not associated with worse perinatal outcomes, which is the main worry in that context.

When a patient has had three pregnancy losses, all investigations are normal, and we genuinely do not know the cause, then there may be situations where I discuss trying something. This relationship must be built on trust and truth. I would explain that we do not know if it works, we think it is less harmful than previously feared, and, in the worst case, it is simply ineffective.

Medicine has advanced not only through systematic study but also through serendipity. Sometimes, clinicians try something and unexpectedly discover a useful effect. So, I am not opposed to case-by-case decision-making, provided it is honest and transparent.

Q5 AI and digital technologies are gaining momentum in reproductive medicine, while emerging approaches such as spindle transfer are beginning to move beyond the boundaries of conventional IVF. Which developments do you believe have the greatest potential to shape clinical practice over the coming years?

AI can help with better targeting of patients, better utilisation of resources, and better expectation management. I think its greatest value will be helping clinicians and patients understand more quickly which treatment pathway is appropriate. I am less convinced that AI-driven embryo selection will transform success rates because observing an embryo for longer with better technology still does not improve the embryo itself.

Looking beyond AI, I would point to the increasing discussion, particularly during ESHRE, around germline modification technologies, spindle transfer, artificial gametes, stem cell technology, and interventions aimed at rejuvenating oocytes. Those developments move beyond conventional IVF and represent genuinely new directions.

Q6 Looking ahead, what unanswered question in reproductive medicine would you most like to see addressed by future research?

There are many. One issue I find particularly interesting is the broader question of human reproductive fitness. I believe it is deteriorating, and I would like to understand the determinants of that decline. There are behavioural and psychological factors involved. Are people having less intercourse? Are there hormonal factors? How do these interact with trends in nutrition and lifestyle?

We are facing a real fertility crisis that many people do not fully understand. The problem is compounded because fertility decline behaves almost like an exponential process. Smaller generations produce even smaller generations. This is a much larger issue than IVF. IVF helps individuals fulfil personal wishes and family planning, but it sits within a much broader demographic picture. Understanding why reproductive fitness is declining is one of the great research frontiers.

I would argue that in 100 years, people may look back and be astonished by how reproduction worked in our era. Prenatal testing, for example, has already become routine. We now know information very early in pregnancy that previous generations could only discover at birth. If that trend continues, reproductive medicine may evolve into assisted procreation on a much larger scale than we can currently imagine. In the shorter term, however, I think germline modification and artificial gametes are among the most important frontiers.

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