Observation shows, intervention teaches – Claude Bernard

J.L.H. (Hans) Evers
Editor-in-Chief

On several occasions I have commended at this place attempts by brave investigators to go against the grain and critically appraise new procedures in the IVF clinic, such as Preimplantation Genetic Screening (PGS) by Sebastiaan Mastenbroek and friends, and ‘scratching’ the endometrium by Tracy Yeung’s group. It didn’t bring me much fan mail. Recently I applauded Armstrong et al. (2015a) for shining their critical light on time-lapse monitoring of embryo development. In a so-called ‘Editor’s Highlight’ at the ESHRE website I reminded the readers that Reproductive Medicine is notorious for introducing unproven new screening tools, diagnostic tests, treatments and laboratory procedures into the clinic: ‘Based on a few small observational studies clinical implementation takes place rapidly and on a massive scale. The next thing you hear is that ‘it is no longer ethically appropriate to start a clinical trial now, since that would deprive the patient of an extra chance of a pregnancy’, or—even worse—’she is going for IVF anyhow, so why not prescribe her alpha-pipalonic-sulphate and allow her to increase her chances?’ And once everyone is doing it, it will be difficult to step back and do the proper trial: ‘Why would a patient take part in such a trial if she stands a 50% chance of not receiving the new drug?’ A fallacy (Evers, 2015).

In this issue of the journal we publish a very readable contribution to the discussion in a Letter-to-the-Editor by Basile et al. (2015) reflecting on the Armstrong paper. It addresses exactly this: ‘The main issue in bringing innovation to the IVF lab probably lies in making a compromise between conducting high quality clinical studies in order to gain evidence on one side, and not denying patients the access to innovations in a rapidly evolving medical field on the other side.’ Well said, but is it that simple? Can clinicians compromise? Or do we perhaps also have an obligation as experts to protect our patients (‘first do no harm’)? To protect them from the potential risks, also financially, of as yet unproven clinical treatments and laboratory procedures.

In their rebuttal, Armstrong et al. (2015b) reiterate that in their expert opinion there is still insufficient evidence for the introduction of time-lapse systems into our labs. They take a cautious stance: ‘(...) we remain convinced that randomized controlled trials must take place followed by studies which assess risk/benefit ratios and cost-effectiveness, prior to the widespread implementation of the technology. (...) Whilst we support innovations that seek to improve outcomes for couples undergoing ART, we must look to evidence-based medicine to adequately assess the safety and effectiveness (including cost-effectiveness) of these technologies.’

It was David Sackett, the godfather of Evidence-Based Medicine, who didn’t tire to repeat—over and over again—that Evidence-Based Medicine is the integration of (patho)physiological mechanisms and the outcome of top-quality clinical research. He stressed how both are important, biological plausibility and top-quality research. It doesn’t require a Randomized Clinical Trial to prove that IVF can benefit a woman without Fallopian tubes. Or that uterus transplantation can allow a woman with congenital absence of the uterus to give birth. However, ground-breaking developments like these are rare. The odds of success of most newly proposed assisted reproduction techniques are modest at best; they require huge trials to ‘reach significance’. And if you need a huge trial to make your point it cannot be a giant step forward. But Obstetrics & Gynaecology has a moral debt. We are the medical specialty that introduced diethylstilboestrol (DES) for recurrent abortion; heparin, aspirin, patellar leucocyte transfusion, intravenous immunoglobulin and prednisone for repeated implantation failure; antenatal fetal heart rate monitoring for checking the fetal condition; thalidomide as a mild sleeping pill for pregnant women; ICSI for unexplained infertility. All without sufficiently robust evidence of effect and/or the absence of harm. We now have the chance to do better with time-lapse monitoring. But also with PGS 2.0, blastocyst transfer, DHEA for rejuvenating old eggs, and ‘scratching’ the endometrium. Let’s seize the opportunity. Couples with infertility belong to a vulnerable group, they will do anything for a pregnancy, they should not be exploited (Nap and Evers, 2007).

References