Human Reproduction Open, pp. 1–9, 2020
doi:10.1093/hropen/hoaa040

human reproduction open

OPINION

IVF, from the past to the future: the inheritance of the Capri Workshop Group

The Annual Capri Workshop Group*,†

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Submitted on March 18, 2020; resubmitted on July 7, 2020; editorial decision on July 14, 2020

ABSTRACT: Today IVF use is booming all over the world and has even started to play a role in demographic analyses. Prognosis-adjusted estimates suggest that up to two-thirds of couples could achieve a live birth. However, the scenario is less exciting in reality. Discontinuation during the cycles is common, and age and ovarian response continue to be crucial in modulating this rate of success. A growing interest is now given to the risk of abuses and in particular to overtreatment and to prescriptions of useless, if not harmful, expensive additional treatments ('add-ons'). A more rational, evidence-based and wise approach is needed. From a scientific perspective, several obscure aspects remain and warrant future investigations. Of particular interest are the neglected role of sperm selection, the potential adult implications of early embryo life *in vitro* and the issue of sustainability.

Key words: IVF / ICSI / preimplantation genetic testing for aneuploidies / epigenetics / developmental origins of health and disease / IUI / sperm / drop-out

Introduction

The ESHRE Capri workshop group is a long-lasting initiative, started in 1986, that annually brought together a varying small group of researchers from all over the world to discuss topics in the field of human reproduction. The Capri workshops were permanently discontinued in 2019. For the last workshop, held in October 2019, it was decided to discuss the achievements and challenges of IVF, the most outstanding accomplishment of modern reproductive medicine that evolved in parallel with the Capri workshop meetings. This article does not aim at a complete review of all IVF-related issues, it is a brief overview of selected arguments deemed to be particularly interesting for the scientific community to take forward in the future of reproductive medicine.

After the birth of Louise Brown on 25 July 1978, Edwards and Steptoe, the two driving forces of her IVF conception, moved to Bourn Hall where, 2 years later, they started a new infertility clinic. Meanwhile, other groups also had initiated IVF programs. By 1982 roughly 300 IVF pregnancies had been reported and discussed by the group of interested pioneers: from one clinic in the UK, two in the USA and four in Australia. This same year, in California, USA, the first international meeting on IVF was organized (Crosignani and Rubin, 1983). The conference attracted worldwide interest, and the key question of ethics was introduced, using the parable of Eve's umbilicus, by R. V. Short, Professor of physiology at Monash University (Melbourne, Australia): 'If Eve was really created from Adam's rib she could not possibly have had an umbilicus, but all past painters chose to ignore this point at the risk of being branded as heretic'.

IVF as a business opportunity

Fertility clinics have subsequently flourished. In the past, they used to offer hope exclusively to heterosexual couples who experienced problems conceiving. In more recent years, single women, same-sex couples and women following a professional vocation (or not having found a suitable partner yet) have also become part of the captive audience. Somehow, infertility treatments have overcome the boundaries of mere health care to expand into addressing societal issues of reproduction in the absence of infertility.

The extraordinary achievements of this discipline have encouraged its global spread and attracted financial interests. Oocyte freezing in particular has turned fertility health care into a booming industry (The Economist, 8 August 2019: 'Investors are pouring money into companies that promise to help people conceive'). The desire for offspring is universal. In some countries, more than 1 in 20 children are born following IVF, and fees of €10 000 and more per cycle are no exception. Hence the financial world is understandably thrilled. There is a long list of private investments and an increase in private equity firms involved in the global IVF sector in the last couple of years. The global fertility market, valued at €15 billion in 2016, is predicted to reach €28 billion

†The list of The Annual Capri Workshop Group contributors is given in the Appendix.

per annum in 2023 (Yunis and North, 2019). However, these exciting numbers should not hide some important and yet unsolved limitations of IVF.

Contribution of IVF to European demography

Thanks to ESHRE (with the European IVF-monitoring Consortium, EIM), international data have been available since 1997, and their reliability has constantly improved. The number of participating countries has increased from 18 to 39 (De Geyter *et al.*, 2018). For IVF and ICSI, the number of treatment cycles has increased by 3.8 folds in this database, and the number of live births by 4.8.

In the 34 countries with data on births, the number of IVF births in 2014 was 170 163, and the number of births following IUI was estimated at 22 767, resulting in a total of 192 930. This figure can be compared to the total number of births in the 34 countries in 2014: 7 465 421, giving a proportion of 2.6% for IVF births. If we assume that the number of IVF births in the other five countries is negligible, the proportion would be 2.3%, a minimum estimate. In fact, this rate varies widely among European countries, depending on factors such as the availability of public health coverage, whether registers are mandatory and whether registers have full coverage and proper follow-up. In Denmark, this rate reaches 6.6%, suggesting that there is yet a deficiency in recording and/or an unmet need throughout Europe (De Geyter *et al.*, 2020).

For all European countries with data on IVF births, we calculated the natural increase without IVF births and compared the two figures. In countries with a large natural increase (UK, Kazakhstan and France), the contribution of IVF is negligible, and in countries with a large natural deficit (Russia, Germany and Italy), IVF is far from significantly reducing the deficit. Its contribution is significant in a few countries with a moderate increase, such as Spain. For Europe as a whole (40 countries, Russia excluded), the natural increase in 2014 was +108 404 (a rate of +0.02%). The number of IVF births for the 33 countries in the ESHRE database (Russia excluded) was 145 129. Thus, without IVF, the natural increase of the European population would have been negative: 108 404 − 145 129 = −36 725. However, the general contribution of IVF to national fertility is limited: less than 0.1 additional children if we take into account the fact that not all IVF births are additional births, because many couples using IVF are only subfertile and may conceive on their own in the long term (Leridon, 2017).

Indications for IVF

The indication for the first successful IVF leading to the birth of Louise Brown was bilateral tubal blockage (Steptoe and Edwards, 1978). The whole process was actually indicated to replace the role of the tubes, i.e. the retrieval of the cumulus oocyte complex, the transport of the spermatozoa, the fertilization process and the final transport of the developing embryo into the endometrial cavity. Thereafter, indications have expanded widely, in most cases in the absence of evidence and rationale. While endometriosis, pelvic inflammatory disease and severe male factor are substantiated indications for IVF (ESHRE Capri Workshop Group, 1994; ESHRE Capri Workshop Group, 1996), some other conditions are inappropriately taken for granted by most reproductive health specialists. The most controversial are unexplained infertility (Crosignani *et al.*, 1993), repeated miscarriage, age-related infertility and low ovarian reserve (ESHRE Capri Workshop Group, 2017; Annual Capri Workshop Group, 2019). The potential detrimental impact of the undue extension of the indications for IVF is generally under-estimated. Indication creep, i.e. the adoption of a technology shown to be effective in a clinical area to other patients group, may cause significant wastage of financial resources (Bryan *et al.*, 2014). Technology adoption in the absence of documented benefits is an important driver of cost growth (Bryan *et al.*, 2014). In this context, the application of IVF for unexplained infertility, repeated miscarriage, age-related infertility and low ovarian reserve is inevitably a main concern, in particular for the latter two situations where IVF is even less efficient *per se*. Well-designed studies are pressingly warranted to address this concern.

Cumulative live birth rate and prognostic factors

Fertility treatment is burdensome as, apart from the medical side effects, most infertile couples face emotional and financial strain (Klitzman, 2017). To shape couples' expectations, to allow self-empowerment and to prepare emotionally and financially, effective and transparent communication prior to embarking on their treatment journey is essential. Information on some fundamental aspects must be clearly provided to couples.

The cumulative live birth rate

The most suitable outcome measure is cumulative live birth rate (CLBR) per couple. This can be the CLBR per IVF treatment, including the fresh transfer and transfers after cryopreservation, or the CLBR per multiple IVF treatments. Both are calculated with a certain time window. Outcomes should not be reported per transfer (Griesinger, 2016). The couple must be aware that IVF is a journey that rewards perseverance. In a prospective study based on the UK Human Fertilization and Embryo Authority (HFEA) data, 156 947 UK women received 257 398 IVF ovarian stimulation cycles between 2003 and 2010. These women were followed up until June 2012. The CLBR continued to increase up to the ninth cycle, with a cumulative prognosis-adjusted live birth rate (LBR) of 65.3% by the sixth cycle (Smith *et al.*, 2015). This rate, however, is an over-estimation because of the high rates of couples who discontinue treatments. To note, dropouts may be viewed as the Achilles' tendon of IVF (Gameiro *et al.*, 2013). In addition, and most importantly, the proportion of low-prognosis couples who enter IVF programs is high: they cannot be neglected or omitted in the reports. Providing results of IVF programs should always take into consideration the main predictive factors of success such as age, ovarian response and number of previous cycles.

Role of the woman's age

Natural fertility as well as IVF success linearly decline with women's increasing age after 35 years (ESHRE Capri Workshop Group, 2017). A

large national cohort study of all women initiating fertility treatments in 2007–2010 depicted well the effect of age: a long-term prognosis for live birth of 64% was achieved in women below 35 years of age, of 49% between 35 and 39 years, and of 16% over 40 years (Malchau *et al.*, 2017). Apart from oocyte donation, no treatment has been proven to overcome the detrimental effects of aging on the capacity of embryos to implant. This is, to date, an insurmountable limitation of IVF.

Prognostic role of the number of aspirated oocytes

Up to recently, LBR per oocyte retrieval was believed to increase with the number of aspirated oocytes up to 15 and stabilize, or even decrease, thereafter (Sunkara *et al.*, 2011; Briggs *et al.*, 2015; Drakopoulos *et al.*, 2015). However, a recent large multicenter study in women under 40 years of age showed that the CLBR per retrieval increased with the number of oocytes even beyond 15, reaching 70% when more than 25 oocytes were retrieved (Polyzos *et al.*, 2018). Hence, ovarian stimulation may not have a detrimental effect on oocyte/embryo quality in good prognosis patients. A good response to hyper-stimulation is a good prognosis factor on its own. A Danish national cohort study including 30 486 women initiating ART treatment with their own oocytes showed that the number of aspirated oocytes in the first ART cycle was associated with an increasing CLBR in up to four subsequent cycles (Malchau *et al.*, 2019). In women without a live birth in the first complete cycle, the number of aspirated oocytes predicted the outcome in the second and third cycle (Malchau *et al.*, 2019).

On the other hand, there is no evidence that increasing the number of oocytes by enhancing the dose of gonadotrophins could be of benefit (Lensen *et al.*, 2018).

Poor prognosis couples

The CLBR in poor prognosis patients is even more important for valuable counseling. In a Dutch multicenter cohort study based on the OPTIMIST trial, including 551 low-prognosis women aged <44 years and treated with a fixed FSH dose of 150 IU/day in the first treatment cycle (Leijdekkers *et al.*, 2019), the CLBR of the low-prognosis women was satisfactory, being on average 56% over 18 months of IVF. In addition, the authors showed that the outcome in previous cycles can be used to estimate the prognosis during subsequent cycles. Providing an age-stratified prognosis for chances of live birth and risk of ovarian hyperstimulation syndrome, incorporating prior failed attempts and previous ovarian response, can aid couples in the decision of treatment (dis)continuation. However, even when prognostic factors are well known, *a priori* individual counseling remains challenging and imprecise.

In general, improving our capacity to predict outcomes in IVF is fundamental in order to prevent useless exposure of women to the risks of the procedure, as well as wastage of resources, that could be employed in a more efficient manner. To note, IVF is unlikely to be cost-beneficial when the LBR per cycle is below 4–10% (ESHRE Capri Workshop Group, 2015).

The still wobbly evidence base of IVF

Procedures in Reproductive Medicine are not always the result of rigorous scientific assessment.

Jack Wilkinson and co-authors stated: 'It is not at all clear that a 'right to try' philosophy, where treatments are sold to vulnerable people on a speculative basis, benefits anyone other than the people making the sale, and may well cause harm' (Wilkinson *et al.*, 2019).

This quote sketches the potential worrisome drift of assisted reproduction. In some contexts, vulnerable patients (who are prepared to do anything to conceive) are burdened by (and charged for) often-costly treatments that lack scientific evidence. The internet- and social media-promoted 'alternative truth' does not help in this respect (Table I). The UK HFEA in 2019 critically appraised a number of so-called 'add-on' treatments and concluded that most lacked a solid scientific base for their efficacy and safety (Table II). Therefore, the HFEA advises clinicians to inform their patients about this lack of evidence and to start clinical trials of the effectiveness and safety of these 'add-ons' (HFEA, 2020). Overcoming this challenge is fundamental in guiding the development of assisted reproduction, and much has already been done. Over the last few years, there have been growing outstanding contributions in the high-quality scientific literature aimed at disentangling the effective from the non-effective interventions that have entered into clinical practice (Chen *et al.*, 2016; El-Toukhy *et al.*, 2016; Smit *et al.*, 2016; Wang *et al.*, 2017; Farquhar *et al.*, 2018; Shi *et al.*, 2018; Smith *et al.*, 2018; Vuong *et al.*, 2018; Lensen *et al.*, 2019; Miller *et al.*, 2019; Wei *et al.*, 2019).

The case of 'endometrial scratching' is a good example. Granot *et al.* (2000), much to their own surprise, noted that 11 of 12 IVF patients (92%) achieved a pregnancy when the IVF procedure was performed in the cycle after they had taken an endometrial biopsy. In a second observational follow-up study the same group of investigators (Barash *et al.*, 2003), found an LBR per embryo transfer that was more than 2 folds higher in the experimental group (49%) than in the (non-randomized) controls (23%). Many studies followed, some confirming the benefit of endometrial scratching, some failing to confirm it. In the meantime, endometrial scratching entered clinical practice (Lensen *et al.*, 2016). Most early studies were positive, and hence

Table I From the internet: 'Here are 10 science-backed ways to boost sperm count and increase fertility in men'.

- Take D-aspartic acid supplements
- Exercise regularly
- Get enough vitamin C
- Relax and minimize stress
- Get enough vitamin D
- Try tribulus terrestris
- Take fenugreek supplements
- Get enough zinc
- Consider Ashwagandha
- Eat maca root

https://www.healthline.com/nutrition/boost-male-fertility-sperm-count; Healthline, accessed 3 July 2019.

Table II The UK Human Fertilization and Embryo Authority critical evaluation of the so-called 'add-ons' to standard IVF treatment* and artificial egg activation.

Add-ons
- assisted hatching,
- intrauterine culture,
- reproductive immunology tests and treatment,
- IMSI (intracytoplasmic morphologic sperm injection),
- PICSI (physiological intracytoplasmic sperm injection),
- PGT-A (preimplantation genetic testing for aneuploidies).

Artificial egg activation by
- calcium ionophore,
- elective freezing in all cycles,
- embryo glue,
- endometrial scratching,
- time-lapse imaging.

*HFEA, 2020.

when the first systematic reviews were published they confirmed the positive effect of endometrial sampling. Subsequent, higher quality systematic reviews suggested the effect of scratching to be much more modest, if any at all (Van Hoogenhuijze *et al.*, 2019). After 19 years, a well-designed and sufficiently powered randomized controlled trial (RCT) was published that showed, in 1364 women, an identical LBR (26.1% and 26.1%) in both arms of the study, with and without scratching (Lensen *et al.*, 2019).

Early, small RCTs suffered from selective publication bias. By the same token, early systematic reviews were biased too, since they summarize and synthesize biased previous studies. We need less—but better—clinical research. We need fewer—but better—systematic reviews (ESHRE Capri Workshop Group, 2018).

The debated role of preimplantation genetic testing for aneuploidies

Within the debate on the pros and cons of 'add-ons' in IVF, preimplantation genetic testing for aneuploidies (PGT-A) merits an independent and deepening discussion. In fact, genetic analysis of human preimplantation embryos before transfer to the uterus was reported in the late 1980s, thus in the early phase of IVF (Handyside *et al.*, 1989). This soon was suggested to be used, not to prevent genetic risks but to increase the success rate of IVF, a procedure then called preimplantation genetic screening, but now referred to as PGT-A. The use of PGT-A, after the first reported pregnancy in 1995 and other enthusiastic initial reports (Verlinsky *et al.*, 1995), found its way into routine practice despite the lack of robust evidence for its ability to increase LBR or other outcomes. Notwithstanding the detrimental impact on the chances of pregnancy reported in subsequent pivotal studies (Staessen *et al.*, 2004; Twisk *et al.*, 2006; Mastenbroek *et al.*, 2007), PGT-A continued to be used. These studies, however, led to a reconsideration of the shortcomings of the first generation of PGT-A methods, and to adjustments being made (Forman *et al.*, 2013; Rubio *et al.*, 2013; Scott *et al.*, 2013; Yang *et al.*, 2015; Griesinger, 2016; Rubio *et al.*, 2017).

Despite substantial efforts to improve PGT-A, the evidence remains disappointing. To date, no single study provides high-level evidence of improved effectiveness of IVF with PGT-A. It has been suggested that potential benefits of the procedure are being limited to older women and to secondary outcomes (less transfers and possible shorter time to pregnancy) but high-level evidence is lacking here as well (Munné *et al.*, 2019; Paulson, 2020; Pagliardini *et al.*, 2020). In addition, the rationale of PGT-A is also increasingly being doubted. To start with, the standard method for selecting embryos in IVF, namely morphological evaluation, seems quite capable of ranking embryos based on their implantation potential (van Loendersloot *et al.*, 2014). More importantly, doubt has again been cast on the accuracy of the technical analysis methods used (Popovic *et al.*, 2018; Lawrenz *et al.*, 2019). There is evidence that mosaicism, or the lack of understanding thereof, undermines the efficacy of PGT-A, since embryos labeled as mosaic and even aneuploid in PGT-A were demonstrated to implant and result in healthy live births, although perhaps with less efficiency as genuinely euploid embryos (Scott *et al.*, 2012; Greco *et al.*, 2015; Bolton *et al.*, 2016; Patrizio *et al.*, 2019). Overall, based on the recent 'Single Embryo TrAnsfeR of Euploid Embryo' (STAR) RCT, the rate of live births lost as a consequence of misdiagnosis or blastocyst injury associated with PGT-A could be up to 30–40% (Paulson, 2020; Pagliardini *et al.*, 2020).

Sperm (and semen): unexpected players in the conceptus

With the introduction of ICSI in the 1990s, ART provided broader coverage than had been possible with traditional IVF (Rubino *et al.*, 2016). Higher fertilization and pregnancy rates were immediately realized as technology became more and more refined for a wide range of male infertility conditions. The profound impact of ICSI on the ART field cannot be understated despite persistent concerns being raised regarding possible long-term effects of both genetic and epigenetic determinants on offspring health (Rubino *et al.*, 2016). In the course of refining ICSI as a core ART, methods evolved for sperm selection in order to obtain the most motile fraction of sperm after extensive washing and swim up processing. Only recently, more data has emerged to suggest that sperm carry important factors gained intrinsically during spermatogenesis or extrinsically during storage and ejaculation in the male reproductive tract (Rubino *et al.*, 2016). In fact, the role of spermatozoa within ART has been neglected for years, but the time may have come to reorientate our thoughts and our scientific efforts. For too long, the systematic and blinded use of ICSI has shifted our attention away from fundamental biological processes that can ultimately reveal new means to improve IVF success. In our opinion, this new awareness on the fundamental role of the spermatozoa may open new fruitful areas of research and, therefore, deserves to be emphasized here.

The fact that sperm carry more than a genome and centrosome has added more complexity to this process, especially since sperm factors

other than DNA in animal studies indicate their role in the later stages of embryonic development. Among these factors are various species of RNA molecules that are acquired by sperm either in the testis or while transiting through the epididymis (Sharma *et al.*, 2016; Burl *et al.*, 2018; Turner *et al.*, 2020). These RNAs are delivered to the oocyte at the time of fertilization, and appear to be directly involved with remodeling of the embryos maternal and paternal contributions to the newly formed zygote. Given that even normospermic ejaculates exhibit heterogeneity in sperm with respect to motility, degree of DNA fragmentation, and acrosome integrity, characterizing both the source and function of these sperm RNAs has become a future research priority in the area of sperm selection (Turner *et al.*, 2020).

Just downstream from fertilization itself is the process of syngamy during which integration of parental genomes is believed to occur. Mounting evidence now seems to suggest that the formation of a novel genetic entity, defined by merger of maternal and paternal nuclear DNA, appears to be far more dynamic and malleable than previously thought. Such core concepts derived from many years of research are being challenged on a regular basis as more sensitive and revealing technologies are brought to bear on the earliest stages of human development. A final example of our changing perception of fertilization relates to the blocks to polyspermy. High resolution live imaging studies have now confirmed a fast block to polyspermy in the human that must precede the biochemical block that had long been attributed to the exocytosis of cortical granules and their components (Mio *et al.*, 2012). Moreover, the modulation of egg activation and concurrent influence of egg secretions on sperm motility constitute a much more robust defense against polyspermy than previously imagined. Specifically, divalent zinc ions stored in the oocyte are released in regular burst ('sparks') from a distinct population of cortical granules mediating both the removal of sperm receptors from the zona pellucida as well as zona hardening to effectively limit supernumerary sperm access at the time of sperm entry (Kushnir *et al.*, 2017; Que *et al.*, 2017). These and other insights yet to be gleaned from ongoing investigations should be kept in mind as our current techniques in ART continue to be judged for efficacy and safety going forward.

Adult effects of early human embryo life *in vitro*

After the initial pioneering period, safety in IVF has received more and more attention. To date, researchers are called to focus more than ever on the health of newborns, both in the short and in the long term. Prevention of multiple pregnancy with widespread uptake of elective single embryo transfer has been a cornerstone of the second and wiser phase of IVF development (ESHRE Capri Workshop Group, 2000; McLernon *et al.*, 2010). But, still, huge efforts are required. Noteworthy, Louise Brown is only 42 years old now and the millions of IVF babies throughout the world are younger. Evidence on the risk of chronic conditions developing in the second half of human life is lacking.

In this regard, the embryo and fetus can respond to an environmental challenge and develop into different phenotypes through an altered epigenetic regulation of genes, a situation that can increase the risk of chronic conditions such as cardiovascular diseases later in life (Bateson *et al.*, 2014). In the last two decades, it has become more and more clear that insults during prenatal life are an important factor for the development of some diseases in adulthood. In a study using data of a large number of individuals born between 1930 and 1938 in the Ukraine of which 43 150 developed diabetes, Lumey *et al.* (2015) found a positive correlation between famine severity during prenatal development and the odds of type 2 diabetes in later life. Similarly, adults exposed during their intrauterine life to the Dutch famine in various phases of gestation (i.e. infants born between 7 January and 8 December 1945) had an over 50% excess rate of ischemic heart disease, more diabetes, a more atherogenic lipid profile, altered stress response and food preference (Roseboom *et al.*, 2006), accelerated brain aging (de Rooij *et al*, 2010) and shorter life span (van Abeelen *et al*, 2012) than the comparison group of infants born before 7 January 1945 and conceived after 8 December 1945.

Other stresses that affect the epigenetic regulation of genes, such as exposure to toxic agents and IVF, were shown in animal models to result in adult health consequences (Feuer and Rinaudo, 2012). Factors in IVF that could theoretically have an impact on adult life are controlled ovarian hyperstimulation, cryopreservation, and *in vitro* culture of oocytes and embryos: concerning the latter, it has been shown that the type of culture medium does affect birthweight of the newborns (Dumoulin *et al.*, 2010). The finding was confirmed by a multicenter, double-blind RCT comparing two culture media (Kleijkers *et al.*, 2016). The effect becomes manifest as early as the second trimester of pregnancy and persists during at least the first 9 years of life (Zandstra *et al.*, 2018).

New perspectives

In 2015, the United Nations (UN) launched a global campaign to ensure future sustainability for all. This initiative, aimed at addressing in a comprehensive manner the current global challenges, including those related to poverty, inequality, climate, environmental degradation, prosperity and peace and justice. It is planned to run for 15 years duration and is subdivided in 17 goals (sustainable development goals). Of utmost relevance is the concept that all these goals are interconnected and that all human beings and stakeholders should be primarily committed to these aims. Reproductive health in general, and infertility treatment in particular, do not represent an exception and have to be viewed as an integral part of this ambitious plan.

Recently, a commendable global initiative (priority setting partnership for infertility) was undertaken, aimed at identifying research uncertainties in four main areas of reproductive medicine, i.e. male infertility, female and unexplained infertility, medically assisted reproduction and ethics, access and organization of care (Duffy, 2019). In line with the modern UN commitment for sustainability, this effort was aimed at directing more efficiently the resources and energies to outcomes that matter to treating patients. Over 700 healthcare professionals and patients were brought together to disentangle the top 10 research priorities for the four areas using robust consensus development methods. Table III depicts those priorities as related to medically assisted reproduction. In addition, 11 out of the 30 priorities of the other three infertility-related areas are somehow related to IVF. Most of them are within the domains of ethics, access and organization of care, and thus in line with the UN commitment for sustainability.

Table III Top 10 research uncertainties in medically assisted reproduction.

	Item
1	What are the causes of implantation failure?
2	What is the optimal treatment for women who are poor responders undergoing IVF to increase LBRs?
3	What is the optimal method of sperm selection during IVF cycles?
4	In couples with unexplained infertility does IUI increase LBR when compared with other ARTs, including IVF?
5	In couples with unexplained infertility what is the optimal number of IUI cycles before moving to IVF?
6	What is the optimal method of embryo selection during IVF cycles?
7	What are the factors which affect cycle to cycle variability in the number and quality of oocytes produced during IVF cycles?
8	What is the optimal time interval between ovulation and IUI?
9	What is the emotional and psychological impact on children born using donor gametes?
10	What is the emotional and psychological impact of repeated fertility treatment failure?

LBR, live birth rate.

On the other hand, research is based on freedom. In spite of the above-mentioned commitment for rationality and sustainability, basic research in particular should go on freely to explore new avenues. There is currently particular enthusiasm for the possibility of gene editing of human gametes and embryos (Church, 2017), reactivation of folliculogenesis through ovarian cortex fragmentation (Suzuki *et al.*, 2015), mitochondria replacement (Kang *et al.*, 2016), folliculogenesis *in vitro* (Telfer, 2019), reconstitution of oocytes from stem cells *in vitro* (Hikabe *et al.*, 2016; Morohaku *et al.*, 2016) and ovarian rejuvenation (Labarta *et al.*, 2019). Of relevance here is that science should do everything possible to avoid false hopes and undue exposure of patients to risks. Researchers are called to resist financial pressures that can cause the premature and hazardous use of new technologies. Robust experimental evidence on effectiveness and safety are mandatory prior to fostering clinical application of any new technology (Wilkinson *et al.*, 2019).

Conclusion

The time for the Capri group workshops has drawn to a conclusion, after 33 years of activity, 56 workshops and 270 lectures. The initiative involved researchers from all over the world and from different generations. The meetings took place annually and consisted of grouping together top scientists for some days to discuss, in an open face manner, various topics in the field of reproduction. The ultimate aim was finding out shared views and providing inputs that could open new avenues of thinking and research. For the last meeting that took place in October 2019, and whose results are presented in this narrative review, a minority of the proud founders was still present. The time has come to pass the baton to the new generations and for the use of more modern and effective methodologies of consensus. As underlined in the present contribution, several new challenges are in front of us. They are complex but the scientific community has the intellectual armamentarium to take up the challenges and overcome them.

We would finally like to express an immense gratitude to all the researchers who participated in the Capri Workshops over the years.

Acknowledgements

The secretarial assistance of Mrs Simonetta Vassallo is gratefully acknowledged.

Authors' roles

All lecturers and chairmen contributed to the preparation of the final article.

Funding

Funding was provided by Institut Biochimique SA, Switzerland.

Conflict of interest

None.

Appendix

The annual Capri Workshop on infertility (7–8 October 2019) discussed the 'IVF: wider use and new challenges'. The lecturers included: David F. Albertini (Director Division of Laboratories, Center For Human Reproduction, New York, USA), PierGiorgio Crosignani (IRCCS Ca' Granda Foundation, Maggiore Policlinico Hospital, Milano, Italy), John Dumoulin (Department of Obstetrics and Gynaecology, IVF Laboratory, Maastricht University Medical Center, Maastricht, The Netherlands), Johannes L.H. Evers, (Maastricht University and Academisch ziekenhuis Maastricht, Dept. Obstetrics & Gynaecology, Maastricht, The Netherlands), Henri Leridon (INED (French Institute for Demographic Studies) and French Academy of Sciences, Paris, France), Sebastiaan Mastenbroek (Center for Reproductive Medicine, Amsterdam Reproduction and Development Research Institute, Amsterdam UMC, University of Amsterdam, the Netherlands), Rebecca Painter (Department of Obstetrics and Gynecology, Amsterdam UMC, location AMC, Amsterdam, the Netherlands; Amsterdam Reproduction and Development Research Institute, Amsterdam UMC, Amsterdam, the Netherlands), Anja Pinborg (Fertility Clinic, University Hospital Copenhagen, Rigshospitalet, Copenhagen, Denmark), Edgardo Somigliana (ART Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; Università degli Studi di Milano, Milan, Italy). The chairs included: David T. Baird (Centre for Reproductive Biology, University of Edinburgh, UK), Anna Glasier (Simpson Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK), Carlo La Vecchia (Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milano, Italy).

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