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Education, education, education – now more than ever?

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Introduction

A whole generation of young scientists and medical doctors enthusiastically entered the field of assisted reproduction and infertility treatment after the birth of the first *in vitro* fertilized (IVF) child Louise Brown in 1978. A new paradigm for treating infertility opened and created unprecedented room for research and development. Indeed, the first years of the IVF era was characterised by a huge research effort understanding follicular development including ovarian stimulation and developing robust methods in the laboratory. Thus, many young clinicians and scientists found a significant career opportunity in the field. Their efforts and successes resulted in a logarithmic increase in activity. The SART register in USA have reported that the US had around 25 clinics performing a few thousands cycles annually in 1985, which today has risen to a little less than 400 clinics doing more than 200,000 cycles (SART, 2015). It is estimated that currently over 5 million IVF children have been born worldwide contributing significantly to the next generation (Fauser et al, 2013). Several of the clinicians and scientists who entered the field in the 1980'ties have been leading figures in IVF treatments but now 30-40 years later they have or are about to retire. This implies that the profession faces a massive transgenerational transition. This in itself calls for a strong educational effort of the new and coming generations, but a number of other factors also highlight the need for continued and expanded education in the field of reproduction.

The IVF era: Standardizing treatments

Whereas initially the emphasis was on basic research and development of the IVF technology, focus has during the past decades generally switched to optimising treatment outcome including standardisation and consolidating of procedures used clinically (De Ios Santos et al., 2016). This has resulted in improved reproductive outcome and more efficacious treatment modalities. The introduction of standardised operation procedures has stabilised results for most fertility clinics and currently many clinics perform with stable pregnancy rates. However, overall success rates have only shown modest increases in the last decade suggesting that continued increase in successful treatments is unlikely to derive from new and

different stimulation protocols and further standardisation of protocols and laboratory procedures. The above notwithstanding, success rates are still modest. According to recent ESHRE and ASRM reports a delivery rate of ~35 percent per cycle depending on patient selection (Calhaz-Jorge et al., 2017; SART, 2015). There is a growing understanding that a continued and expanded research effort is mandatory to continue an improvement of treatment outcome.

Since the field started in early 1980'ties, the business model for infertility treatment has dramatically changed from being mainly a public-sector activity to more private sector involvement; in 2016 almost 60% of all IVF and ICSI treatment in Denmark was performed in private clinics despite public funding for patients below the age of 40 years (Sundhedsdatastyrelsen, 2016). This has necessarily resulted in an increased focus on efficient clinical services and less focus on development of new techniques and improved understanding of the underlying physiological processes (Spencer et al., 2016). However, an improved understanding of the physiological and molecular requirements for successful follicular development, oocyte maturation and sperm selection is widely acknowledged, but currently there is a limited effort to secure knowledge transfer to the young generations and for continued education.

In this context it is interesting to notice that a wave of consolidation among fertility centres has taken place in recent years in which many private fertility clinics are sold to larger consortiums usually comprising several clinics in several different countries (Sydney Morning Herald, 2008; 2013; 2015). These consortia often establish a central research and development unit to serve all member clinics. In the US, investors are transforming an industry that has long been dominated by standalone clinics so much so that in the USA the top five largest fertility chains now account for more than 16% of the marked share (SART, 2015). However, as yet it is not clear to what extend these units will contribute substantially to the basic science development required to advance new procedures with significant clinical impact. In addition, a lot of smaller private fertility clinics contribute only to a minor extent to the education of new clinicians and scientists, which with the increased development in the private sector potentially exacerbates the educational gap.

Despite innovations in assisted reproductive technology (ART) such as intracytoplasmic sperm injection (ICSI), preimplantation genetic diagnostic (PGD), and stem cell research the massive task of effectively treating women at an advanced age is still unresolved. With the substantial postponement of childbearing seen particularly in the European countries (Mills et al, 2011) and the increase in infertile couples seeking help to have a child (Kupka et al., 2016; SART, 2015), the field of reproductive sciences is facing an unprecedented challenge in developing new techniques to individualize and advance treatments for infertility. Many of the potential new treatments that are to be developed will require a multidisciplinary approach with several areas of expertise involved – often skills which do not normally participate in the reproductive medicine arena. Examples of such new areas include *in vitro* follicle activation with activation of specific intracellular signalling pathways (Kawamura et al., 2013), culture of human preantral follicles on suitable scaffolds (Yin et al., 2016a; Laronda et al., 2017; McLaughlin et al., 2018), *in vitro* maturation of immature human oocytes (Yin et al., 2016b), generation of artificial gametes from stem cells (Hikabe et al., 2016), understanding *in vitro* meiosis, understanding and improving sperm quality (Barratt *et al.,* 2017) etc. In order to facilitate an effective and orderly translational transition into the clinic a substantial educational effort in broad areas of reproduction will be required.

The missing links to a new generation of reproductive scientists

Other medical professions may inspire our field on how to potentially improve and advance the educational effort. For instance, in the area of neuropathology PhD students are required to follow 10 obligatory courses and to pass an EU-course offered by the European Confederation of Neuropathological Societies (Euro-CNS) in order to obtain their degree. Moreover, Euro-CNS has established several specialized scientific and clinical programs to their European members on both junior and senior level to facilitate the exchange of scientific information between members and to help clinicians and researchers to stay up to date with the latest advances within their field. Further, the Federation of European Neuroscience Societies

(FENS) representing 42 European countries conducts courses and meetings to promote excellence in neuroscience research (EAN, 2018).

Another initiative recently launched is the UK based Medical Research Foundation national PhD training programme in anti-microbial resistance research. This innovative national programme will train 150 new researchers to explore ways to tackle anti-microbial resistance, one of the greatest emerging threats to human health and will provide a strong educational and networking platform, which will strengthen the UK's research capacity overall during education. Importantly, an alumni platform for continued interaction after PhD graduation is also included (University of Bristol, 2018).

These programmes are obviously expensive undertakings but perhaps international societies such as ESHRE and ASRM could lead similar initiatives in our field and explore the options for a much more detailed and comprehensive educational effort.

On a practical level the professions attitude towards participation in congresses and educational activities should be re-evaluated. Often young researchers are required to submit an abstract to a conference in order to be supported financially. Most conferences understand this policy and accept most -- if not all – abstracts. Unfortunately, this does not always result in a high-quality peer-reviewed paper and may serve only as an entrance ticket for participation (Lensen *et al*., 2017). Such a policy does not encourage senior researchers to act as reviewers and may in the long term reduce the quality of the reviewing process. Further, the abstract reviewing process is often not clear to neither those who submit an abstract and even to those who evaluate abstracts. This strategy does not support a strong and thorough research involvement from young clinicians and scientists and is in some aspects counterproductive to stimulate new substantiated ground-breaking research.

Moreover, in the early years of the IVF era the pharma industry had minimal restrictions on supporting participation in scientific conferences and symposia. Many young scientists and clinicians at that time benefitted and received a significant training and education due to support from the pharma industry, which to a large extent has disappeared today.

Additional challenges include the legal and regulatory structure for training in the field. For example, the recognition of clinical embryology, which is now developing into an area of its own right with highly skilled competences. This is not recognised in several countries, either educationally or legally and makes it less likely that highly skilled persons will persuade a career in the field of reproduction (Kovačič et al., 2015).

These changes, amongst others, have led to a gap in the education of young scientists and clinicians. There is a profound educational need to improve basic skills of the next generation to be able to take infertility and treatment to the next level, improve clinical practise and widen the use of ART and make it more accessible to larger population groups.

Multi-disciplinary educational platforms are needed

Although this educational challenge is widely recognised, it is interesting to appraise how we are currently addressing it. . Large professional organisations like ESHRE and ASRM indeed undertake a lot of educational activities including for example a one-and-a-half-day special interest group workshop that often dive into a narrow area and provide an update on the current knowledge. Other arenas are well catered for. For example, training of embryologists and nurses where there are a plethora of courses and an examination system. However, in general these programmes are mainly centred on clinical activities and provide to a lesser extent a broader knowledge base from which basic science-oriented research can benefit. A fundamental question is how we best train our new MD/PhD students?

The ReproUnion network is an EU- and local funded multi-disciplinary collaboration between 14 public fertility clinics and several basic science-oriented laboratories in the Capital Region of Copenhagen in Denmark and the Skaane Region in Sweden. To date it has educated 25 PhD-students. This network has provided 4 different PhD-courses centred on basic science in reproductive biology, ART procedures, male fertility and epidemiological studies with reproductive medicine. ReproUnion support the ReproYoung association – a network of young researchers working in the field of reproduction and infertility. ReproYoung has facilitated inter-laboratory collaborations, and hosted several International ReproYoung

conferences, where all participants are required to present their work and have feed-back from other young colleagues and senior researchers. These activities, together with monthly education seminars, where the PhD-students present their work combined with senior lectures, provides a new type of educational platform with a knowledge base that is able to sustain a larger collaborative effort within the area of reproductive medicine. Another inter-sectorial and multidisciplinary network has recently been established - 'GrowSperm' which aims to train and coach young scientists in the field of male reproduction, and comprises several public and private EU partners.

However, the educational skills of hands-on laboratory training, where students learn specific procedures by actually doing them are still missing in the educational programme of ReproUnion. In the US they have overcome this hurdle with the Frontiers in Reproduction (FIR) course. FIR is a very successful and world-renowned programme in reproductive biology held annually since 1998 at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. The 6-week summer course represent a unique high-quality training experience comprising daily laboratory exercises, informal seminars, one-on-one tutorials, and lectures in the morning and evening by highly experienced faculty in the field. The FIR course is designed for scientists-in-training who seek to improve their knowledge and experimental skills in order to pursue a career in reproductive sciences, and a 10-year follow-up survey performed on former attendees has recently confirmed the overall significant positive impact that the course has had on the training and upward career trajectory of the participants (Ascoli et al., 2016). Moreover, the success of the course highlights the excellent networking opportunities and research collaborations within and between attendees and faculty which cannot easily be duplicated by any online e-learning system. The efficacy and impact of physical interactions and personal communication should not be underestimated, and the inspirational and passion-driven lessons from pioneers in the field are fundamental to these learning experiences.

The FIR course serves as a good example of what can be accomplished with this type of training platform and is an approach that needs to be complemented and expanded with a potential European counterpart to significantly impact the advances in the reproductive sciences.

Currently there is enormous interest in new educational methods and how best to educate future generations of scientists and clinicians (Bosch et al., 2017). In reproductive biology we also need to take a fresh look at our current programs and evaluate if they are fit for the education of a new generation of PhD/MD in the field.

Conclusion

For half a century medical professionals have been trained and educated to standardize and streamline ART, but current treatment has reached a plateau in success rates and costs. We are facing a new era in which research and development is absolutely fundamental to advance reproductive sciences. A new generation of reproductive scientists needs to be educated in a more structured, broader and purposeful way than current platforms are providing. Multi-disciplinary educational platforms are required to advance the research and provide a more fully equipped educational package for young researchers in the field. Today's trends in society calls for 'thinkers' – not merely technicians/clinicians – and we need to take responsibility for the next generation in more than one way.

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Conflict of interest

C.Y.A is the editor-in-chief of the Reproduction section of Frontiers in Endocrinology and has received lecturing and consulting fees from Merck, Ferring, Merck-Serono and IBSA.

C.L.R.B is the editor-in-chief of Molecular Human Reproduction and Chair of the World Health Organisation Expert Synthesis Group on Diagnosis of Male infertility (2012-2017). C.L.R.B. has received lecturing fees from Merck and Ferring.

S.G.K. is chairman of ReproYoung and has received lecturing fees from Merck and IBSA.

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