

EDITORIAL



Regulating ART: time for a re-think in the light of increasing efficacy, safety and efficiency

This Editorial is stimulated by an article in this issue of *RBMO* by *Humaidan and Haahr (2019)*, with the emotive title 'Bureaucratic overheating is a parasite hampering modern clinical research – a viewpoint from the belly of the beast'. The arguments made include the hypothesis that bureaucracies set up to protect existing 'very high' principles are giving a free hand to other nations to make the next wave of breakthroughs in reproductive medicine and assisted reproductive technology (ART). The nature of bureaucracies is often expansive and self-serving, increasing the power and control that they wield. This structure is created with the justification of ensuring the highest standards, including, in IVF, the best interests of any future children as well as the protection of patients themselves.

Last year the medico-scientific world celebrated the 40th birthday of Louise Joy Brown, the first person arising from IVF, a process which has now resulted in the birth of more than 8 million offspring worldwide. The story of the preliminary years leading to this IVF 'breakthrough' in 1978 reveals a history beginning in around 1935, with attempts by Gregory Pincus in the USA to generate IVF offspring in rabbits, eventually achieved by his associate MC Chang in 1959. Thereafter, another Pincus associate, Miriam Menkin, assisted eminent gynaecologist John Rock during the period 1938–1948 to generate human embryos from oocytes collected at the time of hysterectomy (*Rock and Menken, 1944*). Rock and Menkin described the generation of only 2 or 3 early-stage blastocysts from 144 attempts, leading them to conclude that the generation of extracorporeal human life was not possible (*Cohen, 2018*).

However, subsequent technological advances changed the situation. Developments included medical

ultrasound, gynaecologic laparoscopy, and pharmacologic preparations to stimulate ovarian folliculogenesis and to manage the associated luteal phase disorder. Embryologists were also advancing the quality of culture media to proceed beyond the 2-cell block and overcoming other limitations in generating mouse blastocysts by IVF, and thereafter for other animal species (*Alexandre, 2001*). From around 1960 to 1982 a number of 'founding pioneer' IVF teams emerged around the world, nine of which had delivered a live birth by Louise Brown's 4th birthday, and a few more by the end of 1982 (*Yovich and Craft, 2018*). These teams involved clinician/scientist/technologist combinations, precisely as established by the recognised 'Fathers of IVF', gynaecologist Patrick Steptoe and embryologist Robert Edwards, with technologist Jean Purdy. Each of the teams sought approval from their respective hospital board of administrators, some of which might also have a sub-committee dealing with ethical issues.

Following in the footsteps of the founding pioneers, IVF treatments spread rapidly around the world during the 1980's (*Cohen et al, 2005*). However, the technique was not necessarily recognised as an advanced endeavour by all scientists. Several professors in the social sciences, including feminists such as Robyn Rowland and Renate Klein (*Klein and Rowland, 1989*) and also Dita Bartels (*1987*) expressed the view that IVF researchers were taking advantage of vulnerable women, reducing them to 'living incubators'. Prominent paediatric scientist MG Wagner, publishing from World Health Organization offices in Geneva, decried IVF as a failed technology (*Wagner and Clair, 1989*), giving no better chance of pregnancy than a failed contraceptive device! His facetious remarks were published by *The Lancet* and included data from the USA

where relatively few live births had been reported from the numerous start-up IVF clinics around the country. This led to the only federal legislation concerning ART in the USA, namely the Fertility Clinic Success Rate and Certification Act 1992.

It was against this distorted historical background that journalistic colour was added to provide the public with the idea that IVF teams required 'control' lest they perpetrate adverse outcomes from their 'middle of the night' experiments. The press had already had a field-day when, following the birth of Louise Brown in the United Kingdom, they questioned why the USA had not achieved this historical 'first' and discovered the 1971 Del Zio story. In the 1950s and 1960s gynecologist Landrum Shettles published reports of his various experimental attempts at human IVF in the prestigious *American Journal of Obstetrics and Gynecology* (*Naftolin et al, 2018*). The Del Zio story revolves around highly respected gynecologist William J Sweeney at Cornell Medical School and its affiliate the New York Hospital and his patient Doris del Zio who was being treated for infertility. Following fertility surgeries which resulted in pregnancy loss and further infertility, Sweeney called in Shettles who was then Assistant Professor of Clinical Obstetrics and Gynecology at Columbia College of Physicians and Surgeons as well as visiting consultant at the Presbyterian Hospital. On September 12, 1973, at New York Hospital, Sweeney aspirated follicles from both ovaries at laparotomy and the test tubes containing the aspirates were handed to husband John Del Zio who drove across town to the Presbyterian Hospital and handed the tubes directly to Shettles who, in turn, gave John a specimen container for a semen sample. The 'combined samples' were placed in Shettles' incubator but the next day when Chairman of Columbia College

and Presbyterian Hospital, Raymond Van Wiele, heard about the process, it was stopped because formal ethics approval had not been sought; the incubated tube was subsequently placed in a freezer (and may still be there). The famous Del Zio trial ensued, with Columbia College and the Presbyterian Hospital having to compensate the Del Zio couple. This case undoubtedly played a part in the National Institutes of Health (NIH) recommending a voluntary moratorium on IVF research, which became the key factor in the delay in generating IVF births in the USA.

Against this historical background, some jurisdictions rushed into framing legislation, ostensibly to protect the public from undefined adverse practices; in Australia three states introduced specific legislative acts. In Victoria the Waller Committee was formed in 1982 to 'Consider the Social, Ethical and Legal Issues Arising from IVF' (Waller and Dill, 2018). This led to the Victorian Assisted Reproduction Act (VARTA) 2008, a bureaucracy which has expanded massively, now also covering donor issues, adoption, surrogacy arrangements and the families arising from such, with a corresponding huge growth in the number of registers. The Waller Committee was fully sensitive to Victoria's heritage, being strongly Catholic, a position clearly described in the Papal Decree issued in 1987 by the Congregation for the Doctrine of the Faith: *Instruction on Respect for Human Life in its origin and on the Dignity of procreation*. The latest iteration of VARTA (2016) demands that couples entering IVF facilities have a police clearance, to ensure their suitability for procreation. This bureaucratic excess is now reflected in legislation from two other states: the South Australian Assisted Reproduction Act 1988 and the Western Australian Reproductive Technology Act 1991; in all cases this has caused duplication of accreditation processes. In other states in Australia, the absence of legislation has not been associated with any untoward activity or outcomes, implying the legislations are redundant.

These bureaucracies impose onerous regulations restricting medical procedures for couples under the guise of statements such as 'the interests of the resulting child are paramount' and 'the health of the mother has to

be considered'. In fact, no medical practitioner requires such directives because their Hippocratic Oath (and professional regulation) ensures that these objectives are balanced in their very attempts to do their best to relieve anguish, pain and distress for all patients. IVF Medical Directors face tribunals for treating women of older years or for generating pregnancies in women with co-morbidities where other health practitioners may be critical. The laws provide opportunity for vexatious reporting and challenges. In Western Australia the bureaucracy entitled Reproductive Technology Council (RTC) has even questioned clinics on laboratory procedures, including having to justify a higher-than-average ICSI rate (Yovich et al, 2018). These bureaucracies also impose additional costs on IVF facilities, ultimately passed to the patient or taxpayer.

In 1988 the Ethics Committee of the American Fertility Society published a document in the USA countering the Papal Decree of 1987 (*Ethical considerations, 1988*). Whilst agreeing with the fundamental tenets regarding the rights of the human person, it disagreed with all the Papal conclusions and particularly those instructional calls asking nations to bring in legislation to make it a crime to engage in IVF, to research on embryos or on donor or surrogacy conception (Yovich and Grudzinskas, 1990). In the UK the Warnock Committee was convened in 1984 and led to the establishment there of the Human Fertilisation and Embryo Authority (HFEA). This organisation conducts registration and accreditation processes for all IVF facilities in the UK. While at times it is also perceived as extending its influence beyond its main remit, it is also recognised to have undertaken valuable work recently such as in informing patients of the limited data supporting IVF 'add-ons', with a traffic light system to highlight those treatments without sufficient evidence of efficacy and safety. That this is necessary reflects in part the competitive commercial environment around provision of IVF in the UK, as in many other countries, with a pressure to introduce novel developments before their validation by sufficient evidence – or indeed in the face of contrary evidence. The HFEA has also contributed very positively to the increased use of elective single embryo transfer in the UK. Recent

changes to the extensive documentation require patient consent for research, a change which seems laudable until one realises that this now undermines the value of analysis of anonymised data on the HFEA database by excluding the substantial proportion of couples who have not given this consent. One wonders about the quality of discussions around this consent, among the landslide of clinically important information given to patients about to start IVF. It is also very pertinent that the remit of the HFEA is based in primary legislation, most recently revised in 2008. This can obstruct change; for example, the legislation prohibits elective storage of oocytes for more than 10 years, generating conflict with the wishes of younger women to store their eggs at a more effective age than is often currently the case. How much it is the role of a regulatory body, rather than for example a national professional society, to drive changes in practice can also be questioned.

As to Continental Europe, we are aware of frustrations experienced by various clinicians and scientists who find difficulty in introducing the clinical application of new laboratory and clinical procedures as well as undertaking any novel research. In the absence of a common European Union regulatory authority, the responsibility for the approval of new treatment modalities is left to each individual country. For example, in Spain, the responsibility is shared between the central authority (the Ministry of Health) and the local ethics panels of each of the 17 autonomous regions. This system lacks transparency because the competencies of regulatory organs at both levels are poorly defined, hence concerns of favouritism and inconsistent decisions are often levelled.

Currently in the USA, regulation of ART exists at both federal and state levels, with the states having highly variable regulatory controls and the federal government acting via the minimalistic Fertility Clinic Success Rate and Certification Act 1992, which mandates only that all ART clinics report success rate data in a standardised manner (Frith and Blyth, 2014). In effect, ART is self-managed via guidelines provided by the American Society of Reproductive Medicine (ASRM) and its affiliated focus groups, the Society for Assisted Reproductive

Technology (SART) and the Society of Reproductive Biology and Technology (SRBT) which have developed codes of conduct for the various professionals involved (*Practice Committee, 2014*). Although the proponents of legislative control cite the freedoms within the USA as being the reason why control of multiple pregnancies in the USA lags behind other countries, our view is that those countries which have high single embryo transfer rates and low multiple pregnancies, such as Australia and New Zealand, have achieved this by self-regulation. The advantage of the USA system is a more rapid and greater uptake of services in the advanced reproductive areas of gamete (sperm and egg) and embryo donation as well as surrogacy services and child-balancing; the issues involved are regarded as essentially personal with decisions being made as part of the standard doctor-patient relationship.

In Canada, legislation was introduced relatively recently in 2004, with the only apparent initiating reason being to express a more European and British attitude, consistent with Canada's cultural history (*Hammond, 2015*). This means that gamete and embryo donation as well as surrogacy services must be conducted as altruistic, non-commercial procedures. However, such regulation has created a flood of patient movement to the USA where these procedures are conducted in a self-regulated commercial environment, without untoward outcomes. Other prohibitions, such as on cloning and DNA manipulations, are now also being seen as inhibitory to scientific development in Canada despite a well-established regulatory system of Ethics Committees which can control developments in these areas. There are calls now to review the legislation.

In Australia and New Zealand, there is a well-established self-regulatory system, the Reproductive Technology Accreditation Committee (RTAC), established in 1986 under the auspices of the Fertility Society of Australia (FSA; during the presidential tenure of JLY) and working under the advice of the National Health and Medical Research Council (NHMRC) which provides ethical guidelines, updated every decade after 'feeling the pulse' of the community. RTAC has established a code of practice drawn from advice by IVF Directors in Australia and New

Zealand, again working through the FSA. This system is highly respected by IVF facilities and the Federal Government which provides Medicare support to those patients attending IVF facilities suitably accredited by RTAC. This system generates the annual Australian and New Zealand Assisted Reproduction Database (ANZARD) data, the most recent showing that in 2016, the single embryo transfer rate was almost 90% and multiple pregnancies were <4%, being twins only; all achieved without any reduction in livebirth rates (*Fitzgerald et al, 2018*). These achievements occurred Australia-wide independently of any existing state legislation where three of the seven states (including the Northern Territory as a state) have no specific legislation and a fourth (New South Wales) only recently introduced minimally imposing legislation in 2010, essentially to assist surrogacy. New Zealand introduced legislation in 2004, but the single embryo transfer activity has ensued independently from its integration with the FSA.

We therefore endorse the article by Humaidan and Haahr. While their arguments relate to the bureaucracy associated with research, similar arguments apply to other aspects of medical practice in assisted reproduction. The 40-year track record of assisted reproduction indicates the time is right for review, with 'normalisation' in line with other aspects of medicine. Patients need protection from uncontrolled and ineffective interventions, particularly with the commercialisation of assisted reproduction across many areas of the world, and the recent furor over the inappropriate use of gene editing in human embryos (*O'Niell and Cohen, 2019*) shows that there remains a need for strong and clear regulation in our field. As practitioners we need to show, and continue to show, that we are willing and able to provide effective regulation ourselves, as without that, the regulators and legislators will step in. In this context RTAC and ANZARD, under the auspices of the FSA in Australia and New Zealand, sets the appropriate example.

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