Local privileges not universal rights: geographic variations in the science and clinical practice of reproductive medicine

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Abstract

Based on personal experience in the science and clinical practice of reproductive medicine in different settings, enormous variations are highlighted, demonstrating that freedom of research and clinical practice in reproductive medicine is a local privilege, not a universal right.

The unparalleled pace of new scientific discoveries was what attracted me to the field of reproductive medicine in the first place. The extraordinary sense of fulfillment in the clinical practice of reproductive medicine validates my choice of specialty every day. However, over the years in this field working in multiple US states and in Europe, I have also come to realize that geographic choices of practice location directly affect professional satisfaction. Legal, cultural, ethical, political, and economic differences result in major local variations in the science and clinical practice of reproductive medicine—quite possibly more than in any other field of medicine.

Research differences

As a Reproductive Endocrinology and Infertility (REI) fellow at the University of Southern California, I witnessed the opening of the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC by then Gov. Arnold Schwarzenegger. Donated embryos from our clinic were used to derive human embryonic stem cell (hESC) lines,

and I had an opportunity to participate in research elucidating mechanisms of reprogramming in induced pluripotent stem cells (iPSCs) [1, 2]. Stem cell research holds the promise of major breakthroughs in reproductive medicine, such as new treatment strategies for decreased ovarian reserve, Asherman's syndrome, and male factor infertility. However, in many US states, no public or private support for embryonic stem cell research exists, and patient counseling regarding the destiny of surplus embryos is fundamentally different. Federal funding of research involving human embryos has been a matter of contention ever since the discovery of in vitro fertilization (IVF). In 1996, then President Bill Clinton signed the first appropriations bill containing the Dickey-Wicker amendment, which has been added to National Institutes of Health (NIH) appropriations bills in subsequent years. The amendment prohibits the Department of Health and Human Services (whose funding includes funding for the NICHD) from using appropriated funds for “(1) the creation of a human embryo or embryos for research purposes or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risks of injury or death” [3]. Vast regional differences exist in non-federal funding of stem cell research. While states like California [4] and Wisconsin [5] are sites of active hESC research institutes using other sources of support, regenerative research is underfunded and therefore virtually non-existent in other US states.

As junior faculty at the University of Oklahoma Health Sciences Center (OUHSC), my research focus inevitably shifted towards multicenter clinical trial research. It was fascinating to be part of a clinical unit that quickly became one of the biggest recruiters for the Reproductive Medicine Network (RMN), funded through the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

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Fertility and Infertility Branch. Over the years, the RMN has produced major practice-changing advances in the field of reproductive medicine [6–10]. Remarkably, most of the landmark RMN studies elegantly circumnavigate research into assisted reproductive technologies (ART), despite the fact that it is undoubtedly a core topic of interest in reproductive medicine. This notable avoidance is another consequence of the federal funding barrier imposed by the Dickey-Wicker amendment.

Being part of a different research environment at OUHSC, I felt privileged to complete a Master's program in Clinical and Translational Science, participate in a faculty leadership program, and become an ASRM CREST scholar. If I felt old and mature enough to provide advice for aspiring trainees, my advice would be to strive to make the most of variable opportunities that each particular clinical and research setting holds, even if they seem invisible at first.

Local differences in clinical practice: non-ART

Ectopic pregnancies

Local discrepancies in clinical practice are just as apparent as those in scientific focus. On my operative case lists from residency in Boston (Brigham/MGH) and fellowship in Los Angeles (USC), the surgical treatment of ectopic pregnancy consisted of salpingectomy in over 90% of cases in Boston and salpingostomy in 100% of cases at USC. Massachusetts is a “mandated state” with IVF coverage for its residents, resulting in a lower threshold for removal of a diseased fallopian tube. Contrary to this, the question at weekly “Morbidity and Mortality” meetings at USC was no longer “why did you do a salpingostomy?” but “why on Earth did you do a salpingectomy?” Because the vast majority of patients at USC/LA County Hospital had no access to ART, the principles my mentors there taught me were those of their mentors: “You should work as hard as possible to conserve the lady's tube in her first ectopic, just as you would if this were her second ectopic in the only remaining tube.” [11]

The correlation between the surgical management of ectopic pregnancy and access to ART also exists internationally. During my early days of Obstetrics and Gynecology training in the UK, the standard of care recommended by the Royal College was that “in the presence of a healthy contralateral tube, salpingectomy should be performed in preference to salpingostomy” [12]. In the UK, restricted government funding for ART procedures is provided through the National Health Service (NHS) [13].

While the best surgical treatment method for ectopic pregnancies is a matter of debate, there is a global trend towards increasing use of medical management of confirmed ectopic pregnancies with Methotrexate. Purposeful expectant

management of ectopic pregnancies, commonly performed in some European countries such as the UK [14], is rarely attempted in the USA [15, 16].

Perhaps the largest confusion surrounds the management of non-viable pregnancies of unknown location (PUL), both regionally within the USA and globally. Survey data from the USA reveals that physicians are split between offering uterine curettage first versus presumptive methotrexate [17], while expectant management is frequently used in Europe for subgroups of patients [18, 19]. Results from an ongoing “Reproductive Medicine Network” multicenter randomized trial comparing the three management strategies will provide new data to guide clinicians in this context.

Treatment of hypothalamic anovulation

An example of a practice difference benefitting patients in Europe compared to the USA is the option to treat patients with hypothalamic anovulation using a GnRH pump. Hypothalamic anovulation may be congenital, such as in Kallmann syndrome, or more commonly acquired and referred to as functional hypothalamic amenorrhea (FHA) [20]. In FHA, a decrease in hypothalamic GnRH secretion is caused by a disturbance in hormones controlling energy intake and output [21]. Based on the landmark discovery that intermittent pulsatile, but not continuous administration of GnRH can reestablish sustained elevated gonadotropin concentrations [22], therapeutic substitution of GnRH for hypothalamic anovulation must also be cyclical. Pulsatile GnRH can be administered intravenously or subcutaneously. In the USA, this is currently only possible in a research setting, whereas a commercially available subcutaneous pump is available for treatment of both men and women in Europe [23, 24]. With normal pituitary function in treated patients (a prerequisite for this therapy), normal feedback mechanisms of the hypothalamic-pituitary-ovarian (HPO) axis are maintained, leading to the induction of monofollicular ovulation in most cases [25]. When exogenous gonadotropins are used, feedback mechanisms are no longer intact, and the risk of multiple folliculogenesis leading to multiple gestations is increased [26]. Differential drug regulations regarding pulsatile GnRH therapy have led to geographically discordant practices in this context.

Intrauterine insemination

Another transatlantic divide is the attitude towards intrauterine insemination (IUI) in the treatment of unexplained infertility. Based on somewhat dated, but solid clinical trial evidence, it was engrained in my North American-trained brain that IUI is a useful tool to increase pregnancy rates in the treatment of unexplained infertility [6]. As I learned in lectures and symposia, the prevailing European perspective is that “the

evidence on the effectiveness and safety of IUI and IVF has been evaluated in two Cochrane reviews which both suggested that there is insufficient evidence to conclude that IUI or IVF is effective compared to sexual intercourse in couples with unexplained subfertility.” [27] In one lecture discussing this “clinical dilemma,” Prof. van der Veen from the University of Amsterdam drew an analogy between current clinical practice and a medical treatment principle discussed in Céline’s novel “Voyage au bout de la nuit”: “Since most diseases resolve spontaneously after 5 days, the smart doctor starts to prescribe medication on day 3.”

In the UK, the National Institute for Health Care Excellence (NICE) advised in its most recent fertility guideline that IUI should no longer be offered in unexplained infertility, and recommends 2 years of sexual intercourse followed by IVF [28]. Interestingly, 96% of fertility clinics in the UK continued to offer IUI despite these recommendations according to 2015 survey data [29, 30].

A recent randomized, controlled trial from a third continent, conducted in two fertility clinics in New Zealand on 201 participants with unexplained infertility, may influence the ongoing debate: women randomly assigned to IUI had a higher cumulative livebirth rate than women assigned to expectant management (31 versus 9%; risk ratio [RR] 3.41, 95% CI 1.71–6.79; $p = 0.0003$) [31].

Local differences in clinical practice: ART

Perhaps the most striking difference in reproductive practice patterns concern the field of ART, secondary to cultural, legal, religious/ethical, economical, and healthcare-system related factors. Upon arrival in Switzerland, I was witness to the transition from the existing reproductive legislation to the new amended Swiss reproductive law on September 1, 2017. Until that point, the core of the strict regulation concerning ART was that “it is only allowed to develop as many fertilized human eggs outside the female body as can be immediately implanted.” (Paragraph 810.11 of Swiss law, “Bundesgesetz über die medizinisch unterstützte Fortpflanzung”, [32]).

Prohibited were the in vitro culture of more than three zygotes past the two-pronuclear stage in a fresh IVF cycle, resulting in an unpredictable “lottery” for couples: heartbreak resulted when no zygote developed to the blastocyst stage; clinical dilemmas arose when 2–3 good quality embryos became available, given that blastocyst cryopreservation was illegal. The legislation was a disservice to patients, with low pregnancy rates and a high risk of multiple gestation when pregnancy occurred [33]. Also prohibited were pre-implantation genetic diagnosis, egg and embryo donation, treatment of singles and same-sex couples, and surrogacy. Sperm donation was only allowed for married couples with male factor infertility. Given the unique principle of “direct

democracy” of the Swiss political system, which allows the electorate to directly propose and vote on amendments to the Federal Constitution, a referendum on the existing Swiss reproductive law was held in June 2016. After a hard-fought campaign, 62% of the 47% participating eligible Swiss citizens cast their vote to loosen reproductive regulation. After a lag time of 15 months for the new law to take effect, embryo/blastocyst cryopreservation and pre-implantation genetic testing are now legal according to the revised “Fortpflanzungsmedizingesetz” (Revised Section 810.11 of Swiss law, “Bundesgesetz über die medizinisch unterstützte Fortpflanzung”, [34]). Egg and embryo donation, as well as the treatment of singles and same-sex couples and surrogacy remain prohibited.

Variations also arise from tightly engrained local practice patterns and the interpretation of existing medical evidence. As a US-trained REI, I was curious to observe that many oocyte retrievals in Switzerland were done under local anesthesia and that a senior colleague mandated the universal use of a tenaculum for embryo transfers because “when one realizes that it is needed, it is already too late.”

Insurance reimbursement patterns also heavily affect clinical practice: in Switzerland, ART is not covered by insurance, whereas in Belgium, it is reimbursed linked to a rational embryo transfer strategy. As a result, Belgium has one of the highest elective single embryo transfer (eSET) rates in Europe [35], whereas insurance-related and already mentioned legal factors until 2017 have resulted in low eSET rates in Switzerland. Historically, there had been somewhat of a transatlantic divide in the uptake of eSET, with seemingly more proponents of an elective single embryo transfer strategy in Europe [36] than in the USA [37]. However, with improvements in laboratory technologies including vitrification, increased use of genetic testing of embryos, and raised awareness of the risks of multiple gestation, there is an increasing trend towards single embryo transfer in both Europe and the USA.

Local differences in the science and clinical practice of reproductive medicine combined with increasing globalization have created compelling trends. As an example, despite the fact that egg and embryo donation are illegal, the number of births to Swiss women in the 45–50 age group has increased from less than 100 per year in the 1990s to over 400 per year in the years 2014–2016, a 300% increase (source: Swiss National Department of Statistics/Bundesamt für Statistik, <https://www.bfs.admin.ch>, [38]). It is safe to assume that this dramatic increase is not due to a sudden explosion in spontaneous fertility in Swiss women over 45, but rather an example of reproductive tourism from a country where egg donation is prohibited, to countries where it is legal. Like people, reproductive tissues are increasingly mobile, and legal and ethical dilemmas will arise in the future, as variations in local regulations may clash with the increasing ability to ship frozen gametes and embryos anywhere.

From the perspective of physicians and scientists in reproductive medicine, local variations may lead to a “brain drain” phenomenon, with the migration of motivated workforce to areas with a favorable professional environment.

My personal experience certainly taught me that the cultural, legal, and scientific environment is very important when choosing where to practice. Along with a broader perspective on the practice of reproductive medicine, my path has afforded me with a whole new level of appreciation for privileges I used to take for granted.

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