EDITORIAL

Context-based infertility care

Over the last few months we have reflected in these pages on a number of challenging issues that need to be addressed if clinical research in our field is to continue to impact on day-to-day infertility care (*Macklon et al., 2019*; *Fauser and Macklon, 2019*). As articulated by others (*Horwitz et al 2017*; *Kent et al. 2018*), we have argued that limiting clinical practice to only those interventions that have been shown to be 'effective' for a group of patients included in randomized controlled trials (RCTs) threatens to prevent rather than encourage the development of a clinically useful evidence-based medicine (EBM) for individual patients.

In our third and last contribution to this series of editorials, we consider the concept of 'context-based medicine' in the management of infertility. This term acknowledges the notion that clinical decision-making is not solely a question of applying clinical guidelines based on RCTs developed in well-defined groups of patients, but also requires the interpretation of the available pertinent evidence in light of the demographic, ethnic, diagnostic, personal and regulatory context in which the individual is being treated.

NO 'EVIDENCE' WITHOUT CONTEXT

EBM, considered by most to have its origins at McMaster University in Canada in the 1980s (*Smith and Rennie, 2014*), has transformed the quality and safety of medical care. It has served to reduce outlying and possibly harmful variations in practice based on 'personal experience' and the waste of resources represented by ineffective therapies. EBM is also considered to have provided a clear structure on which to base teaching, training and the development of guidelines, and has encouraged a professional meritocratic revolution by providing the tools required to enable the less experienced to challenge the practice of their seniors, and lay commentators to challenge certain medical practices. In other words, it has 'democratized' knowledge (*The Dutch Council for Public Health and Society, 2017*).

However, as we have stated previously, insisting that individual medical care should be directed solely by the outcomes of RCTs,risks leaving patients and doctors unsupported in clinical decision-making. Such an approach risks slowing down rather than accelerating the generation of useful evidence on which to base care (*Macklon et al., 2019*). Our call to reconsider the practical value of RCTs against other means of generating research evidence for addressing certain clinical needs has been challenged by some stakeholders in the EBM industry who have stated their reluctance to accept any criticism of the RCT approach (*Wilkinson et al., 2019*). However, a useful discussion is underway, and most would now agree that the majority of RCTs currently used to arbitrate on clinical effectiveness have significant shortcomings (*Wilkinson et al., 2019*). Moreover, it is notable that even the pioneers of RCT methodology acknowledged that EBM almost always represents a simplification of clinical reality.

Hence, distinct differences in context should be considered when assessing the association between patients and response to any medical intervention. In general, the term 'context' is defined as 'the circumstances or setting in which an event takes place'. What this might mean in the context of infertility care will be discussed below (see also FIGURE 1)

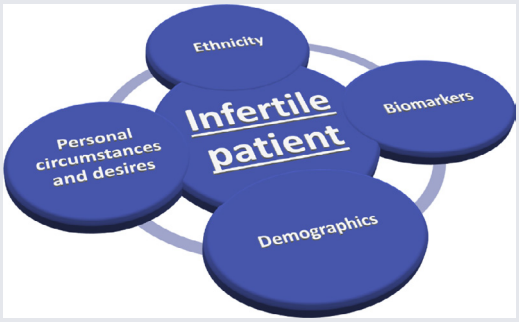

FIGURE 1 Key contextual considerations required in individual clinical decision-making

DEMOGRAPHIC CONTEXT

The simplification of clinical reality inherent to most RCTs becomes readily evident when reading the Methods section of almost any such trial. Here, a list of inclusion and exclusion criteria for acceptance of individuals into the study will usually be provided. Most RCTs will restrict inclusion to 'ideal subjects' in order to increase the chance that any therapeutic effect assigned to the novel intervention being tested is indeed revealed. By definition however, such a requirement also limits the generalisability of any conclusions drawn beyond the specific patient profile selected. In order to address this, alternative research strategies have been developed to assess demographic or other differences at initial screening which can subsequently be linked to individual differences in response to any given intervention (so called prospective, cohort, follow-up studies and subsequent multi-variate prediction analysis).

In the context of RCTs, variability in response that may be attributed to demographic factors can provide the basis for post hoc subgroup analysis, which is commonly performed only when the primary study outcome is negative (for example *Munne et al.,*

2019). This conventional type of subgroup analysis is clearly subject to bias, but represents a first step towards individualised care and may be helpful in applying study findings to specific patients by detecting 'relative effect modification'. However, it has been emphasised that this approach does not directly address the problem created by the fact that patients belong to multiple different subgroups, each of which may yield its own association with outcome (Kent et al., 2018). Moreover, subgroup analysis, even when defined before the study is carried out does not ameliorate the under-representation of 'real-life patients' in clinical trials. The significance of this issue was illustrated by a recent analysis of the proportion of patients attending a clinic who met the inclusion criteria for trials that were guiding clinical practice of ovarian stimulation for IVF. Only 37% did so, and those that did demonstrated a statistically significantly different ovarian response to treatment compared with those who did not meet the criteria (Hershkop et al., 2017). This phenomenon underlies the often-observed discrepancy between efficacy (does a drug work under ideal circumstances) and effectiveness (where the same intervention is tested in a much more heterogeneous patient population more representative of the patients we see in our everyday practice).

ETHNIC AND BIOMARKER CONTEXT

Within our own field, it has become clear that common conditions such as polycystic ovary syndrome (PCOS) can present very differently in women of Asian origin compared with Europeans (Guo et al., 2012). Moreover, response to ovarian stimulation for IVF can differ markedly according to ethnic background (Palep-Singh et al 2007). At an individual level, factors such as body weight, age and ovarian reserve markers such as anti-Mullerian hormone are central to determining treatment strategies or medication dosing (Fauser, 2017). In recent years the impact and increasing complexity of the matrix of individual factors that can determine response to an intervention has become clearer. It is becoming apparent that designing an intervention that adapts to the individual 'personalomics' profile (created by merging the genomic sequence with RNA, protein, metabolic, and auto-antibody profiles) and that of the target pathology (such as a tumour) can transform its efficacy (Gil et al., 2019). An additional dimension that adds further complexity to this is how these profiles might change with time. In one study of what was described as an individual's 'narcissome', one person's personalomics were assessed 20 times over a 14-month period (Dennis, 2012). Using this intense longitudinal diagnostic strategy, new disease susceptibilities and changes in response to therapy could be revealed.

The potential of pharmacogenomics to introduce a new era in IVF treatment has recently been summarized (Kalinderi et al., 2019). Much remains to be explored further, but it is to be expected that additional genomic information generated from large data sets will give rise to much improved individualized infertility care. The emergence of these and other sophisticated biomarkers will further aid in personalizing prognosis, which increasingly underlies clinical decision-making (Macklon and Fauser, 2004).

PERSONAL CIRCUMSTANCES

The notion of context defined by personal circumstances has at its roots the fact that requests for medical care do not come from a disease but from an individual who also brings their own values, desires and expectations regarding a given medical condition. These will in turn be defined by many elements including sexuality, relationship status, age, profession (for instance, doctors themselves more often refrain from intense cancer treatment), personal financial resources and religious adherence. An obvious example of how the latter may lead to 'non-evidence-based practice' is when for religious reasons, only embryos that will be transferred may be created.

The current debate on add-ons in IVF provides a salutary example of how personal values and concerns which might be described as the fear of regretting not having tried possibly useful therapies can drive the demand for them, even when an evidence base for their safety and efficacy is lacking. The impact on decision-making of patients bringing their own 'online research' into the consultation room is well known to clinicians. While this can be described as patient empowerment in shared decision-making, the well-known associated risks of exploitation by unscrupulous healthcare professionals represent the other side of this coin.

Despite these risks, there is a growing consensus that high-quality clinical decision-making requires equal input from the patient. 'Personalised' patient care is therefore not just about adapting protocols to individual medical and biological profiles but is care 'that is tailored to the individual need for aid, the characteristics and preferences of the patient, and their personal context' (The Dutch Council for Public Health and Society, 2017).

Patients themselves should play an important role in defining outcomes of medical intervention most relevant to them. Needless to say, the preferred outcome may vary considerably from one patient to the other. This approach represents an important trend in many recent developments in healthcare, such as value-based healthcare ('a healthcare delivery model in which providers are paid based on patient health outcomes'), shared decision-making (which 'depends on building a good relationship in the clinical encounter so that information is shared and patients are supported to deliberate and express their preferences and views during the process'), and patient-reported outcome measures (PROMs), defined as 'measurement instruments that patients complete to provide information on aspects of their health status that are relevant to their quality of life').

The financial context in which a patient is managed presents particular dilemmas to clinicians and patients when the 'best course' of treatment is deemed too costly. Despite the near-ubiquitous problem this presents, the majority of clinical studies and guidelines are published without reference to the costs of the intervention tested, either to the healthcare system or to the patient. It is, however, self-evident that enthusiasm for a particular treatment will depend on the financial implications of its application for the stakeholder concerned. Access to possibly effective

treatments can be excessively restricted when healthcare is provided through state funding or insurance, while clinical policies, such as elective single embryo transfer to reduce multiple pregnancy risk, may be harder to implement when the cost of additional treatments is not borne by the patient themselves. Cost-effectiveness studies can address this by providing financial context to clinical trial findings. However, most are limited in validity to the environment of the original trial (*Le et al., 2018*; *Bordewijk et al., 2019*). Sensitivity analyses that test the validity of conclusions according to varying assumptions, including those relating to economic context, can in part address this (*Hirshfeld-Cytron et al., 2012*).

REGULATORY CONTEXT

Finally, clinicians and patients must ensure that decision-making takes place within the legal boundaries set by the national regulatory framework in which they operate. Assisted reproductive technology (ART) is subject to a wide range of regulations that vary greatly between countries. On occasion, complying with these regulations requires deviation from 'best practice' as defined by research-based international consensus and guidelines. For instance, in Germany the number of embryos that can be created is limited to three and the freezing of embryos is banned unless there are compelling medical reasons for doing so. Moreover, egg and embryo donation, and surrogacy, remain illegal (*Wilson, 2017*).

Several studies have assessed the impact of regulatory variation on access to ART and its application in practice. In a study of data generated by the International Committee Monitoring Assisted Reproductive Technologies (ICMART), significant variations were reported in eligibility of single woman and lesbians to treatment, the requirement of a medical indication and the degree of public coverage of treatment costs (*Berg Brigham et al., 2013*). These findings explain the rise of cross-border reproductive care which can circumvent legal restrictions related to age, sexual orientation and civil status, and provide access to treatments such as anonymous gamete donation (*Shenfield et al., 2010*). Such an extensive variation in ART legislation derived from factors such as social structure, political and ethical issues and religious beliefs complicate both the creation of international standard regulations and the implementation of internationally derived clinical guidelines (*Gianoroli et al., 2016*).

IMPLICATIONS

High-quality care requires the linking of many sources of knowledge. Core sources will include judicious use of biomarkers, published observational studies along with meta- analysis of RCTs and evidence-based guidelines. However, it is clear that to be effective and relevant to each individual patient, this knowledge needs to be interpreted and applied after considering the interplay of EBM with the complex matrix of contextual factors discussed above. There is increasing interest in how this 'heterogeneity of treatment effects' (*Kent et al., 2018*) might be addressed when designing studies. Understanding the underlying distribution of risk for patients in RCTs can help inform anticipated subgroup sets based on factors known to vary impactfully in the context of reproductive medicine practice (such as age, amongst many others). An alternative approach is to develop prediction models of initial patient characteristics and treatment outcome, derived from well-designed, prospective studies collecting data that model treatment effects directly and thus increase 'benefit discrimination' for particular patient groups (*Imani et al., 2002*). However, while the application of prognostic modelling increasingly underlies clinical decision-making in infertility treatment (*Macklon and Fauser, 2004*), there are risks inherent in this approach, including the potential for statistical overfitting, and false discovery (*Kent et al., 2018*).

Another alternative strategy that has been proposed enjoys the descriptive term 'medicine-based evidence'. This concept acknowledges the 'multidimensional longitudinal profile' of the patient whose clinical care is being managed (*Horwitz et al., 2017*). In order to provide comparative evidence from a wider patient population, this requires careful, prospective, descriptive data collection at patient level and meticulous archiving for observational analysis. While subject to criticism on methodological grounds, it is interesting to note that improvements made to the design and analysis of prospective cohort studies are such that the average results of RCTs and of observational studies of the same treatment often produce similar results (*Benson and Hartz, 2000*).

As we have alluded to previously (*Macklon et al., 2019*), advances in bioinformatics now make it possible to access and analyse the collected experience of thousands of clinicians caring for many of thousands of patients. The application of large-scale genomic data to clinical practice is already being felt and is likely to be transformative in the relatively near future. The heterogeneity of practice patterns that will be represented, rather than being a weakness of this approach, is an advantage that can address the impact of contextual variables such as those discussed above. However, if this approach is to attract the necessary resources, a re-evaluation of the contribution that non-RCT studies can make will be required. We would argue that while clearly representing a major investment of time and money, this may represent a more valuable use of research resources than those consumed by RCTs of limited clinical pertinence.

In summary, it is clear that in order to practice 'context-based' infertility treatment, doctors must apply knowledge from a range of sources to their individual patients rather than relying solely on evidence from groups of patients generated from RCTs. This does not imply a rejection of the principles of EBM, but it does challenge the view held by some that gaps in the clinically useful evidence base can simply be filled by investing more resources in larger RCTs to the exclusion of other methodologies (*Wilkinson et al, 2019*). Moreover, it illustrates the need for all stakeholders, including methodologists and clinicians, to work together to understand how this evidence should be interpreted and applied in the context of optimized individualized care for patients seeking treatment to overcome infertility.

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