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Commentary

Critical appraisal of the Vienna consensus: performance indicators for assisted reproductive technology laboratories

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A B S T R A C T

The Vienna consensus, based on the recommendations of an expert panel, has identified 19 performance indicators for assisted reproductive technology (ART) laboratories. Two levels of reference values are established for these performance indicators: competence and benchmark. For over 10 years, the Spanish embryology association (ASEBIR) has participated in the definition and design of ART performance indicators, seeking to establish specific guidelines for ART laboratories to enhance quality, safety and patient welfare. Four years ago, ASEBIR took part in an initiative by AENOR, the Spanish Association for Standardization and Certification, to develop a national standard in this field (UNE 17900:2013 System of quality management for assisted reproduction laboratories), extending the former requirements, based on ISO 9001, to include performance indicators. Considering the experience acquired, we discuss various aspects of the Vienna consensus and consider certain discrepancies in performance indicators between the consensus and UNE 179007:2013, and analyse the definitions, methodology and reference values used.

Introduction

The assisted reproductive technology (ART) laboratory is of crucial importance in fulfilling the reproductive wishes of infertile couples and of women without a male partner, in preventing the transmission of infectious or hereditary diseases and in the cryopreservation of gametes and embryos. Like any other clinical laboratory, it must meet its users' needs while providing quality, safety and efficiency. Performance indicators are recommended as a means of monitoring

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and improving performance in clinical laboratories (in accordance with ISO 15189-2012). For performance indicators to be effective, it is essential to have a clear and precise definition of each one, and to establish realistic performance targets (reference value or performance specifications). Following a recent consensus workshop held in Vienna (ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine, 2017), the recommendations of an expert panel of participants, on a total of 19 performance indicators for ART laboratories, have been published. The reference values for these performance indicators address two levels, competence and benchmark, in line with an earlier consensus on cryopreservation (Alpha Scientists in Reproductive Medicine, 2012).

In 2013, AENOR, the Spanish Association for Standardization and Certification, published a national standard (UNE 179007, 2013 System of quality management for assisted reproduction laboratories) defining specific requirements for human ART laboratories, with the aim of enhancing quality, safety and patient welfare. Participants in this project included members of the Spanish Association of Embryology (ASEBIR), the Spanish Fertility Society, the Spanish Society of Clinical Biochemistry and Molecular Pathology and the Spanish Andrology Society, as well as public and private human IVF clinics, AENOR, professional associations and the public-sector health administration (UNE179007, 2013, 2013; Ortiz et al., 2014).

The new standard for human ART laboratories, UNE 179007:2013, strengthens the ISO 9001 requirements in the following areas: training, e.g., the head of the embryology laboratory must have a biomedical science degree, a PhD or Master's degree and at least 5 years' relevant experience; professional tasks, such as stipulating the responsibilities of the head of the embryology, andrology and cryopreservation laboratory; minimum human and infrastructure resources and necessary environmental conditions, such as cleaning and disinfection, personnel clothing, air conditioning, air recycling and filters, positive pressure; control of laboratory equipment, e.g., calibration and validation, control type, frequency, parameter, measurement range and acceptance criteria; traceability (in relation to the embryologist responsible and the culture media, material and equipment used); product preservation, e.g. contingency and transport protocol, product data saved in two separate supports; and laboratory indicators (definition, method, periodicity). Special Interest Group in Quality of ASEBIR published indicators for these requirements in 2007 (de los Santos et al., 2007), and quality specifications for these performance indicators have been adapted and updated annually since 2009 (Mantilla et al., 2015). Since the publication of UNE179007:2013, ASEBIR has published annual quality specifications for ART laboratory performance indicators for three levels of quality (minimum, desirable and optimum) based on the state of the art.

Since the publication of the new quality management system, to adapt ISO 9001 for use in human ART laboratories, over 20 Spanish laboratories have been certified, which has enabled them to improve their monitoring and measuring procedures via the standardization of laboratory processes. This national experience provides the basis for our discussion of various aspects of the Vienna consensus document on performance indicators in ART laboratories.

Establishing quality specifications

The question of how to define reference performance indicator values for a clinical laboratory has been subject to much debate. For many years, the benchmark was the Stockholm hierarchy of performance goals (Kenny et al., 1999), five criteria based on clinical outcomes, physician's opinion or biological variation, professional recommendations, external quality assessment results and current performance (state of the art). In the context of an ART laboratory, the following criteria have been applied as quality specifications for performance indicators of the analytical phase of determining semen parameters: biological variation (Álvarez et al., 2003), state of the art (Castilla et al., 2005) and physician's opinion (Aguilar et al., 2008).

In 2015, seeking to remove some inconsistencies from the Stockholm hierarchy, a new proposal was made in this respect (Sandberg et al., 2015), according to which one of the following models should be selected: model 1, based on the effect of analytical performance on clinical outcomes; model 2, based on components of biological variation of the parameter analysed; or model 3, based on the state of the art. These criteria have been used by ASEBIR to establish quality specifications for ART laboratory performance indicators for the past 10 years. Therefore, the criterion of expert recommendations has been deleted, in the assumption that the expert making such recommendations will be aware of the state of the art (Jones et al., 2017). Following this update of the Stockholm hierarchy, in our opinion the criteria used by the Vienna consensus workshop are less appropriate than methods based on the state of the art.

It is no easy matter to establish quality specifications for ART laboratory performance indicators. Extrapolating useful models to obtain quality specifications with which to diagnose or monitor laboratory processes, to achieve viable gametes and embryos, is always a complicated procedure. In fact, the only criterion that can be applied straightforwardly is that of state of the art. When this criterion is used in analytical testing, data are obtained from an external quality assurance programme (EQAP) in which several clinical laboratories analyse the same sample. Although in ART laboratories, EQAP are used to assess embryo quality (Martínez-Granados et al., 2017a, 2017b; Ruiz de Assín et al., 2009), cytotoxicity (Castilla et al., 2010) and semen analysis (Alvarez et al., 2005), these programmes cannot be used to establish Vienna Consensus quality specifications for performance indicators.

On the other hand, as Vienna consensus recommends, what can be done is to examine the results reported by each laboratory to the national ART register, to determine the state of the art for certain performance indicators. Nevertheless, any comparison of data from different laboratories will always be difficult because performance indicator differences between ART clinics may be explained (at least in part) in terms of two basic types of variation: common cause variation, owing to data quality, e.g. different definitions of a single performance indicator, differences in patient characteristics (or case mix) or simply the effect of chance (particularly in the case of small numbers of patients); or special cause or systematic variation, caused by real quality differences between laboratories (Lee and McGreevey, 2002).

The ASEBIR quality specifications for ART laboratory performance indicators are based on data obtained from the official ART register compiled by the Spanish Ministry of Health and Spanish Fertility Society, which are used to derive quality specifications based on the state of the art. To minimize the effects of poor-quality data, participation is compulsory. This database is standardized and centralized, and over 15% of the participating centres are audited by an independent contract research organization. The participating centres in the official ART registry are randomly selected for auditing. These audits are carried out by external companies specialized in clinical trials and

data management. Such audits are costly, and so they are limited to 15% of the participating centres. The data are compiled centre by centre, and therefore it is not possible to minimize the effects of differences arising from mixed cases. Most of the variables that affect ART results. i.e., age, comorbidity, duration of infertility, and ovarian stimulation protocol applied, can be discarded when egg donor cycles are considered. A performance indicators specification for ART techniques using own or donor eggs is published by ASEBIR. Spain was one of the leading countries in ART in Europe in 2013 (European IVF-monitoring Consortium et al., 2017). Although ART centres that carried out fewer than 30 cycles were excluded from our analysis, most of our performance indicator specifications are calculated from the results of about 100 ART centres to avoid performance differences caused by chance.

Following the model developed by Fraser (1999, 2001) for analytical specifications, three levels of performance indicators quality specifications, from UNE179007:2013, are defined by ASEBIR (minimum, desirable and optimum). Of the different criteria that have been proposed to define these three levels (Jones et al., 2012; Plebani, 2017), we opted for those recommended by four leading Spanish laboratory medicine societies (Buño et al., 2008). The three quality levels are defined as follows: minimum, the 5th percentile of distribution of values obtained by the Spanish ART centre, i.e. 95% of Spanish laboratories perform better; desirable: the 25th percentile of this distribution, i.e. 75% of Spanish laboratories perform better; optimal: the 75th percentile, only 25% of laboratories perform better. As the confidence interval can be calculated for each percentile, ASEBIR reports the performance indicator quality specifications of UNE 179007:2013 with confidence intervals, and thus the evolution of this reference value over time can be evaluated (Mantilla et al., 2015).

As mentioned above, the Vienna consensus defines two reference values: competence and benchmarking. The gap between the two values is the 'desirable range'. By examining this range, the 'desirable' quality level of the ASEBIR specifications can be equated with the 'competence' value of the Vienna consensus. As observed by Jones et al. (2017), the rationale underlying the reference value affects the expected or required response to failure to meet the reference value. Thus, 'optimal' indicates no need for further improvement, 'desirable' indicates satisfactory performance and 'minimum' indicates considerable room for improvement.

Expert recommendations usually correspond to the performance commonly achieved by an expert (in general, working in laboratories that obtain very good results; therefore, they do not represent the real-life performance of most centres). According to our results, if the Vienna consensus 'competence' value was applied, over 50% of the centres in question would fail to achieve this level. In our view, it would be excessive to affirm that one-half of all laboratories do not reach a desirable level of performance. This situation might endanger the survival of many centres, especially if such a recommendation were incorporated into guidelines, codes of practice or government regulations.

A similar circumstance arises with performance indicators for cryopreservation, published by the Alpha consensus (Alpha Scientists in Reproductive Medicine, 2012), also based on expert opinion. It seems clear that the 'competence' values, at least, stipulated by the expert may not be realistic, and that their incorporation into quality systems would generate non-conformities in many laboratories. Accordingly, we believe the participant societies in the Vienna consensus publication should be aware of this problem and publish alternative reference values, termed 'minimum' (Fraser, 1999, 2001) or 'passable' (Jones et al., 2017). Hence, the three levels of quality specification should vary along a continuum, from a minimum value, which all reasonable laboratories would be expected to achieve; through a desirable specification, which should be obtained by most laboratories, but which would serve as a target for those falling short; to an aspirational or benchmark specification, one that might not be met by most laboratories until more advanced methods are developed.

We agree with the Vienna consensus recommendation that a national and international register should be created to compile data that can be used to determine performance indicator standard values, provided that the three quality levels described above are incorporated.

Defining performance indicators

As stated previously, a fundamental concern in comparing laboratory results is that of data quality. Therefore, the performance indicators to be compared must be clearly defined. The parameter 'failed fertilization rate' should reflect the proportion of attempts to fertilize an oocyte cohort with no evidence of fertilization. Cycles that are cancelled should not be included as fertilization attempts, because if they were, the performance indicators would not reflect the real performance of the laboratory in this respect. UNE 179007:2013, unlike the Vienna consensus (proportion of stimulated cycles with no evidence of fertilization), defines this indicator as the percentage of ovarian punctures performed that fail to achieve fertilization.

On the other hand, as the number of mature oocytes is unknown at the time of insemination by IVF, the only way to compare IVF and intracytoplasmic sperm injection fertilization rates scientifically and accurately is for the denominator to be the same both cases i.e., the number of cumulus–oocyte–complexes retrieved. This performance indicator more faithfully reflects the overall quality of cycle management (ovarian stimulation, oocyte handling and insemination) (Fleming S, personal communication).

Missing performance indicators: a lost opportunity

Under the Vienna consensus, indicators such as live birth rate or embryo utilization rate are rejected because reference values cannot be calculated, as these depend on factors that are unrelated to ART laboratory performance, such as uterine receptivity or the application of different policies for embryo transfer and cryopreservation in different centres. Similar indicators that are very useful to ensure that IVF laboratories are working well and within safety guidelines are those that monitor strategies for embryo transfer, such as multiple pregnancy rate (Germond et al., 2008) or number of embryos transferred per pregnancy (Abdalla et al., 2010). The exclusion of all these performance indicators from a minimum list of IVF laboratory performance indicators for use in monitoring IVF cycles would deny embryologists a significant role in the provision of safe, high-quality healthcare in response to patients' reproductive wishes. But, perhaps IVF laboratory professionals should participate in decisions about how many embryos to be transferred (Porter and Bhattacharya, 2005). If this is so, then consideration should be given to establishing policies on embryo transfer as part of the minimum laboratory performance required. UNE 179007:2013 includes both the embryo utilization rate and the number of embryos transferred per pregnancy, which

facilitates obtaining the three reference values mentioned above. It also includes the multiple pregnancy rate, but as this indicator is considered of crucial importance to patient safety, the only reference values reported are those of optimum and desirable. This is the only performance indicator for which this strategy is applied. The multiple pregnancy rate is so important to patient safety that any stakeholder involved in reproductive health care should include it in a minimum list of performance indicators.

In our opinion, this consensus meeting should be considered a lost opportunity, as no reference is made to the performance indicator of the extra-technique stages (pre- and post-technique) of the processes, especially the former. It is currently accepted, by many practitioners, that a large proportion of the errors observed in clinical laboratories occur in this stage (Plebani, 2010; Plebani et al., 2013, 2015). The ASEBIR Interest Group of Quality has just published a performance indicator list for the pre-technique stage of IVF laboratory work to facilitate the future development of an external quality assessment with which to establish quality specifications based on the state of the art. Logically, for certain indicators, such as simple identification, a policy of zero tolerance must be applied to cases of noncompliance. Identification of these indicators is based on previous research based on modal analysis of failures and effects (Intra et al., 2016; Molina et al., 2017; Rienzi et al., 2015).

In addition to the above, we believe that performance indicators for the ART laboratory should span all types of activities, apart from those discussed previously. ASEBIR is currently preparing performance indicators to monitor recommendations related to all areas of ART laboratory work, to support the establishment of protocols and consensus for institutions seeking to improve quality and patient safety. This initiative is in line with the proposal made by Brody (2010), which was first applied by The Good Stewardship Working Group (2011), and in the field of reproductive medicine by the American Society of Reproductive Medicine (2015), namely to consult the relevant scientific societies to draw up, for each case, a list of procedures or treatments that are often used excessively or inappropriately.

Conclusions

We welcome the recently published Vienna consensus on performance indicators, as they undoubtedly comprise a further step towards increasing the standardization and quality of ART laboratories. For the reasons set out above, however, ASEBIR maintains criteria that are not fully concordant with those recommended in the Vienna consensus. The specifications established by ASEBIR for the performance indicators of UNE 179007:2013 are, in our opinion, achievable and will ensure the provision of high-quality service, while not jeopardizing the viability of many laboratories that present good levels of performance.

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