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Reproductive immunology from the perspective of the clinician

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ABSTRACT

Investigators generate new and innovative ideas needed to advance knowledge, while physicians want proven treatments that provide the best care for their patients. Along with advances in reproductive immunology research, there have also been controversies such as immunologic treatments for recurrent pregnancy loss. Research deficiencies that are wasteful and misleading include: over-interpretation and extrapolation from animal studies to the human, inadequate sample sizes, lack of appropriate control groups, use of surrogate markers, associations presented as causation, un-blinded testing and treatments, unreproducible results, and non-standardized outcomes. The purpose of the EQUATOR Network (Enhancing the QUAlity Of health Research) is to improve the quality of research and its publication. These guidelines (CONSORT, STROBE, PRISMA, STARD, ARRIVE) have been accepted as mandatory by virtually all major medical journals, and all investigators should prospectively incorporate them into their study designs. From the perspective of a clinician-scientist and an editor, my premise is that the purpose of much basic science research and all clinical research is to improve the medical care of patients. Unproven and costly diagnostic tests and treatments for potential immunologic clinical problems can no longer be justified. The primary and most important outcome that should be reported for all pregnancy-related immunologic studies is the live birth rate of a healthy infant. Today's clinicians and patients expect unbiased research that leads to evidence-based recommendations for practical and effective treatments.

1. Background

I regard myself primarily as a clinician. However, I have also been involved in reproductive immunology research for over 40 years and was Chair of an academic Department of Obstetrics and Gynecology for 18 years. Starting out as a rural general practitioner and later as an obstetrician gynecologist and Editor-In-Chief of *Obstetrics & Gynecology,* I became acutely aware of what physicians want and need from research and the medical literature.

2. History

In my view, the modern era of reproductive immunology began within the field of transplantation. In 1953, Medewar, Brent and Billingham were able to induce immunologic tolerance in neonatal rats by injection of spleen cells from a donor animal so the recipient was no longer able to reject skin or allografts from the donor (Billingham et al., 1953). This remarkable finding immediately stimulated interest in the entire field of transplantation and extended into many other areas of reproductive immunology.

My own first exposure to research began as a resident in obstetrics and gynecology when many questions remained about immunologic rejection of allografts and whether some transplanted organs behaved differently (Scott et al., 1970, 1971). Since those days, transplantation of vital organs has progressed from impossible to routine and is now the treatment of choice for end-stage disease. Worldwide over a million solid organ transplants are now performed and lives saved each year. Successful pregnancies in transplant patients and the development of non-vital organ transplantation including uterine transplantation have also become clinical realities (Armenti et al., 2000; Holmgren and Scott, 2018; Brannstrom et al., 2015).

Medewar ultimately received the Nobel Prize in 1960 for his exceptional discovery. Billingham moved to the U.S. first as Chair of the Department of Genetics at the University of Pennsylvania and later as Chair of Cell Biology at the University of Texas (Southwestern) in Dallas. In 1964 he published a classic article in the New England Journal of Medicine on the importance of maternal fetal immunology in human pregnancy (Billingham, 1964). He specifically pointed out that investigating why the fetal-placental semi-allograft was not immunologically rejected was the key to important advances in transplantation and reproductive immunology.

Many were fascinated with this concept, and I became one of a

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group of young investigators he assembled in Dallas who carried out a variety of experimental reproductive immunology studies (Beer and Billingham, 1976; Beer et al., 1975; Scott et al., 1976). As more researchers were attracted to this new field and began studying basic immunologic mechanisms, societies of reproductive immunology were soon created in the U.S., Japan, Europe and internationally. The Journal of Reproductive Immunology was founded in 1979, and the American Journal of Reproductive Immunology was established in 1980.

The field expanded rapidly, and recurrent miscarriage was soon the focus of many immunologic studies. Recurrent pregnancy loss (RPL) became one of the most widely researched areas in medicine, and it was still the subject of almost 50% of the presentations at the 2018 ESRI meeting. This is most likely because RPL is a clinically important problem that is frustrating for both patients and their physicians. However, the chance of a successful pregnancy after three consecutive first trimester miscarriages with no treatment is in the range of 60–70% and is frequently overlooked. Since RPL patients are so discouraged and desperate for a baby, it is easy to attribute a live birth in the next pregnancy to whatever therapy had been used.

Based on a number of hypotheses, in 1985 paternal cell immunization was one of the first therapies suggested to prevent RPL (Mowbray et al., 1985). This led to the publication of multiple observational studies and small RCTs proposing a number of diagnostic tests and additional immunologic treatments which included third party donor cells, trophoblast, and intravenous immune globulin (IVIG) (Johnson et al., 1991; Christiansen et al., 1994, 1995). However, these treatments remained controversial. As more RCTS were published, multiple meta-analyses were performed with conflicting results, the most recent one often critical of the previous one (Fraser et al., 1993; Collins and Roberts, 1994; Scott, 1994; Coulam et al., 1994; Daya and Gunby, 1994; Clark et al., 2001; Scott, 2003; Liu et al., 2016; Cavalcante et al., 2017; Porter et al., 2006; Roepke et al., 2018; Wong et al., 2014). Difficulties encountered when pooling the data from these trials included heterogeneity of a variety of factors such as the definition of RPL, patient selection, cell preparations, immunization regimens, dosages, and routes of administration. In reality, this situation is common and illustrates the subjective nature of systematic reviews and meta-analyses which are dependent on which trials are included and how results are interpreted (Jeng et al., 1995). Nevertheless, no definitive and agreed upon answers were initially forthcoming regarding paternal cell immunization and other immunologic treatments.

Consequently, The RPL literature was confusing to patients and physicians as well-intentioned advocates for various hypotheses, diagnostic tests and immunomodulation resulted in passionate opinions sometimes overshadowing evidence and at times became rather contentious. During this time, immunologic tests and treatments for RPL were promoted for clinical use and prominently advertised. Lymphocyte immunization continued to be offered by a number of centers and was extensively marketed until banned in the U.S. in 2002 by the FDA for lack of evidence for efficacy and concerns about potential safety (Wong et al., 2014). The guidelines published by virtually all professional societies have now concluded that immunologic assays such as those for NK cells, lymphocyte immunization and IVIG are not effective in preventing RPL and should not be used (Royal College of Obstetricians and Gynaecologists Green-top Guideline No. 17, 2011; The Practice Committee of the American Society for Reproductive Medicine, 2012; Practice Committee of the American Society for Reproductive Medicine, 2018; The ESRI Guideline Group on RPL et al., 2018; Homer, 2018). Nevertheless, studies still appear in the literature, and clinics in some countries still offer these tests and treatments (Moffett and Shreeve, 2015; Gibbins and Porter, 2016).

This unfortunate chronicle of events is an example of research prematurely promoted and that was not beneficial to physicians and patients. It is likely that millions of health care dollars have been wasted over the years on unproven tests and treatments for RPL, and it is important to avoid this scenario in the future. Genetic causes of RPL are becoming better defined with the use of new techniques which detect a specific reason for most pregnancy losses and will lead to a more simplified and clinically useful approach (Popescu et al., 2018; Copp, 1995).

3. MODERN IMPROVEMENTS

What needs to be done to prevent events like this from happening again, and how can patients and physicians gain access to reliable and timely data? New and innovative basic research is vital for advances in reproductive immunology and should be supported. However, I believe that the primary purpose of original research articles published in medical journals is to improve patient care. Results should be evidence-based and valid, reproducible, clinically relevant and able to be compared with other treatments. (Gibbins and Porter, 2016) Ioannidis has argued that most published research does not fulfill these criteria (Ioannidis, 2005).

Clinicians have learned to be cautious about new findings and realize that they do not work as well in practice as reported in the literature. This skepticism is understandable because of well documented instances of publication bias, exclusion of certain patients from RCTs in order to obtain two homogenous comparable groups, industry influences with conflicts of interest of authors and trial sponsors, overhyped results, and less impressive outcomes in subsequent studies (Mulder et al., 2018).

Fortunately, a great deal of progress has been made in improving the quality of research studies over the past several decades. Weaknesses in study design and flaws in interpreting and reporting the results can and should be overcome. (Table 1)

The EQUATOR guidelines and checklists have already improved research and its reporting. These include CONSORT for randomized trials, STROBE for observational studies, PRISMA for systematic reviews, STARD for diagnostic studies and ARRIVE for animal preclinical studies (ANON, 2018a). The COMET Initiative promotes Core Outcome Sets which are agreed upon outcomes that should be included in each study of that disorder (ANON, 2018b; Scott, 2016). These are developed using robust methods involving multiple stakeholders including patients. Use of these approaches by investigators, guideline makers and medical journals help to eliminate controversies and waste, elevate the quality of research, permit comparison of studies, enhance systematic reviews and improve clarity for physicians and patients. Finally, clinical research studies should be reported in a form that is useful and understandable by physicians and patients. This means that they should include absolute values, attributable risks and number needed to treat (NNT) or harm (NNH) and not just odds or risk ratios with confidence intervals. (Nuovo et al., 2002; Tramer and Walder, 2005) Medical journals and their editors must take responsibility for upholding these standards (Armstrong and Naylor, 2019).

4. Future challenges and the Way Forward

The future of reproductive immunology looks bright. There have

Table 1
Common problems remaining in research studies.

Overreliance and extrapolation from animal studies
Questionable biologic plausibility
Sample size too small
Lack of an appropriate control group
Surrogate markers used
Unblinded and biased interpretation
Association implied as causation
Cherry picked results (data dredging, P-hacking)
Results not reproducible
Outcomes not clinically important

been many clinical successes that can serve as models for the future. Rh Immunization was once the most common cause of stillbirth. In the years between 1940 and 1970 the etiology and pathogenesis of the disease was discovered, effective diagnosis and fetal treatment was established, and the development of prophylactic Rh Immune Globulin has now essentially eliminated this devastating clinical disorder (Reali, 2007). The human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) epidemic in the 1980s and 90 s was catastrophic and caused an estimated 35 million deaths worldwide (AIDS, 2017). The development of antiretroviral medication can now slow the course of the disease and lead to a near-normal life expectancy (CDC, 2016).

Although the mechanisms that protect the fetal-placental unit from immunologic rejection by the mother have been remarkably resistant to scientific explanation, increasing sophistication and understanding the basic science of immunology makes me confident that this mystery will eventually be solved. When that occurs, it will fulfill Billingham's original concept to be able to induce tolerance in transplant recipients to lessen dependence on or eliminate the need for immunosuppressive drugs. (Kawai et al., 2008; Scandling et al., 2008; Alexander et al., 2008;Starzl 2008)

5. Conclusions

In 2019, physicians and patients expect proof of efficacy and safety for any reproductive immunology treatment. This can be accomplished by improving the quality of research and it's reporting with standardized and clinically important outcomes. This will lead to evidence-based objective guidelines that are clear-cut and clinically useful.

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