Transparent collaboration between industry and academia can serve unmet patient need and contribute to reproductive public health

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ABSTRACT: The pharmaceutical and device industry has greatly contributed to diagnostic and therapeutic approaches in reproductive medicine in a very highly regulated environment, ensuring that development and manufacturing follow the highest standards. In spite of these achievements, collaboration between industry and physicians/academia is often presented in a negative context. However, today more than ever, partnership between industry and academia is needed to shorten the timeline between innovation and application, and to achieve faster access to better diagnostics, drugs and devices for the benefit of patients and society, based on complementary knowledge, skills and expertise. Such partnerships can include joined preclinical/clinical and post-marketing research and development, joint intellectual property, and joint revenue. In Europe, the transparency of this collaboration between pharmaceutical industry and medical doctors has been made possible by the Compliance and Disclosure Policy published by the European Federation of Pharmaceutical Industries and Associations (EFPIA), which represents the major pharmaceutical companies operating in Europe, and includes as members some but not all companies active in infertility and women’s health. Under the EFPIA Disclosure Code of conduct, companies need to disclose transfers of value including amounts, activity type and the names of the recipients. Health Care Professionals and Organizations. EFPIA member companies have also implemented very strict internal quality control processes and procedures in the design, statistical analysis, reporting, publication and communication of clinical research, according to Good Clinical Practice and other regulations, and are regularly inspected by competent authorities such as the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) for all trials used in marketing authorization applications. The risk of scientific bias exists not only in the pharmaceutical industry but also in the academic world. When academics believe in a hypothesis, they may build their case by emphasizing the arguments supporting their case, and either refute, refuse, oppose or ignore arguments that challenge their assumptions. A possible solution to reduce this bias is international consensus on study design, data collection, statistical analysis and reporting of outcomes, especially in the area of personalized reproductive medicine, e.g. to demonstrate superiority or non-inferiority of personalized ovarian stimulation using biomarkers. Equally important is that declarations of interest are reported transparently and completely in scientific abstracts and publications, and that ghost authorship is replaced by proactive and clear co-authorship for experts from industry where such co-authorship is required based on the prevailing ICMJE criteria. In that context, however, reviewers should stop believing that publications by industry authors only, or by mixed groups of co-authors from industry and academia, are more prone to bias than papers from academic groups only. Instead, the scientific quality of the work should be the only relevant criterion for acceptance of papers or abstracts, regardless of the environment where the work was done. In the end, neutrality does not exist and different beliefs and biases exist within and between healthcare professionals and organizations and pharmaceutical industries. The challenge is to be transparent about this reality at all times, and to behave in an informed, balanced and ethical way as medical and scientific experts, taking into account compliance and legal regulations of both industry and academic employers, in the best interest of patients and society.

Key words: pharmaceutical industry / company / device / academia / medical doctor / EFPIA / reproductive medicine / bias / transparency / compliance
Introduction

Today, relationships between industry and medical doctors are often viewed negatively. The Editorial Team of Human Reproduction deserves a lot of credit for bringing this topic, still taboo for many, to the Table of the public debate within the reproductive medicine and women’s health community. My contribution to this debate is based on my experience as a medical-scientific leader in both the pharmaceutical industry and academic reproductive medicine. As Vice-President and Head of Global Medical Affairs Fertility at Merck KGaA headquarters in Germany (ongoing role for 18 months, appointed in October 2015), my role is to provide medical and scientific leadership within the fertility therapeutic area. This is currently my main responsibility in terms of investment of time and effort. As a professor in reproductive medicine (ongoing role for more than 20 years, joint clinical and academic coordinator of Leuven University Fertility Centers for 20 years (1995–2015), initial academic appointment in 1996 at KU Leuven/University of Leuven, Belgium), my role is to do preclinical and clinical research and teach in the area of reproductive medicine and biology.

My move to industry has been very interesting and challenging. It was stimulated by more than 10 years experience as a key opinion leader in academia advising industry in preclinical development, clinical development (Phase II–IV trials), diagnostics, biomarkers, patient centered health and health economic studies. This move to a new role in global reproductive health was also positively influenced by my consultancy for 8 years as a senior consultant for the Department of Research in Human Reproduction at the World Health Organization (D’Hooghe, 2016). Indeed, the industry environment is fundamentally different from not only the clinical, medical and hospital world and the academic, research and teaching environment, but also from international professional organizations, such as ESHRE, ASRM, SRI, IFFS and WHO. Yet, all I have learned during 20 years in academic reproductive medicine has prepared me greatly for my current role in global reproductive health in the industry. Obviously, my current industry-related medical and scientific efforts are related to the differentiation and innovation of our portfolio of fertility drugs and technologies. While this focus may bring a certain limitation when compared to complete academic freedom (which is in practice often limited by availability of funds, people, expertise and time), it also increases focus and creates many opportunities to work together with healthcare professionals and researchers in reproductive medicine and biology, for the advancement of diagnostics, therapeutics and overall treatment approaches in reproductive medicine.

In this paper, I wish to share my view that there is major value in bringing industry and medical doctors and academia closer together, for the benefit of science, patients and society.

The essential role of industry in reproductive medicine today

Reproductive medicine is an area, unlike cancer or cardiovascular disease, with very low research funding from public resources in most countries worldwide, and with low reimbursement from national health services in most countries worldwide. In such a context, collaboration between academia and industry is not only a result of this situation but also an opportunity to join forces and to avoid duplicated work. Clinical scientists are usually interested in preclinical translational research projects and in clinical trials that may lead to improvements in diagnosis or treatment. A better understanding of each other’s role may actually allow more collaboration, which would be of benefit to all parties if done in a transparent and highly qualitative way.

Today, the practice of reproductive medicine would be unthinkable without the contribution of industry to development and manufacturing of both fertility drugs and technologies. Fertility drugs like gonadotrophins (FSH, LH and HCG) (Ludwig et al., 2002; Lunenfeld, 2002; Lehert et al., 2014; Peerstra et al., 2015; Ate and Seli, 2015; Humaidan et al., 2017) and GnRH agonists/antagonists (Al-Imany et al., 2016) are important for effective ovarian stimulation and ovulation triggering in order to obtain multiple mature and high quality oocytes in one cycle and to reduce time to live birth in patients. Indeed, there is clear evidence that the cumulative live birth rate per patient is correlated with the number of oocytes recovered after one ovarian stimulation cycle (Sunkara et al., 2011; Drakopoulos et al., 2016; Vaughan et al., 2017).

The choices for physicians to balance the importance of the number of oocytes versus the risk of ovarian hyperstimulation syndrome (OHSS) have been greatly expanded with flexible ways to determine not only the FSH starting dose, using a variety of blood or ultrasound biomarkers such as AMH, FSH and AFC and clinical markers such as female age, BMI and previously recovered number of oocytes, but also to adapt the gonadotrophin dose as needed with small dose changes of 12.5 IU, at any time during ovarian stimulation, to decrease the risks of either OHSS and poor ovarian response (La Marca and Sunkara, 2014; van Tilborg et al., 2016; Allegra et al., 2017). Oocytes can be successfully fertilized and embryos can be cultured in vitro up to the blastocyst stage using ever improving culture media and incubators (Youssef et al., 2015; Svontours et al., 2016). Luteal phase support with progesterone containing products has been well demonstrated to increase reproductive outcomes after both fresh and frozen embryo transfer cycles (Ván der Linden et al., 2015) and after ovarian induction for intruterine insemination (Green et al., 2017). At present, it is possible to manage emerging OHSS risks during ovarian stimulation by GnRH agonist triggering combined with either personalized luteal phase support using progesterone, estrogen and low dose HCG, or with a freeze all strategy (Engmann et al., 2016). Indeed, the success of vitrification of both oocytes and embryos, with close to 100% warming survival rates, has completely changed reproductive medicine for patients, with options for repeated ovarian stimulation/freeze all cycles in poor ovarian responders and in patients requiring multiple oocytes and embryos for relevant PGD or PGS (Debrock et al., 2015; Blockeel et al., 2016; Rienzi et al., 2017). A wealth of industry based technology now allows the assessment of ovaries, gametes, embryos, endometrium and early pregnancy: advanced ultrasound imaging in 2D or 3D with associated computer algorithms (Grozmann and Benacerraf, 2016), advanced molecular genetic assessment of oocytes and embryos (Dahdouh et al., 2015; Fragouli and Wells, 2015), and continuous embryo monitoring and assessment of embryos at the moment of embryo transfer (Adamson et al., 2016; Aparicio-Ruiz et al., 2016). Active research is aimed at better understanding and improving embryo implantation in the uterus after transfer (Garcia-Velasco et al., 2016). All these advancements which directly serve patients, are made available to physicians, embryologists and patients by industry in a very highly regulated environment, ensuring that the development and manufacturing of both drugs and devices follow the highest standards.
The value proposition for collaboration between industry and academia

Many of the developments listed above have been initiated and/or developed by scientists working in industry together with clinical scientists and academics, or vice-versa. Some of the latter have patented their discoveries, partnered with or created their own company, in order to make their invented products available to patients worldwide. Overall, this is a major success story, illustrating the essential value of collaboration between industry and academia. Indeed, industry values the opinion of key opinion leaders and medical and scientific experts, to understand the current state of the art, unmet needs, future trends, preclinical, clinical and post-marketing research, and development and innovation in reproductive medicine. Medical doctors and scientists contacted by industry for collaboration are usually among the best researchers with deep biomedical knowledge and extensive experience. It does not make sense to exclude them ‘by definition’ from contributions to expert groups, consensus projects, scientific meetings, or guideline development groups, as this would be an insult to their capacity of thinking independently. Instead, full and mandatory disclosure is needed. It is also important to realize that these experts are usually favorable referees and editorial board members for journals as well. The solution is not exclusion, but mandatory and controlled disclosure of financial payments and other remunerations.

Let us embrace the opportunity of collaboration: increasing partnership between industry and academia, can result in joined preclinical and clinical development, joint intellectual property (IP) and joint financial revenue. This is a positive perspective on how this collaboration can serve patients, science, society and business. In my view, after 22 years in academia, the future is more collaboration, not less (D’Hooghe, 2016). In the interest of not only both industry and academia, but more importantly also patients and society, the paradigm is evolving beyond internal company pipeline development to joint projects between industry and academia in preclinical, clinical and post-marketing research and development. This requires the mutual recognition of scientific excellence in both industry and academia, joint IP and joint revenue, and will shorten the pathway and time to get innovative products on the market, which is ultimately to the benefit of patients, health authorities and tax payers. In this context, industry also needs, now perhaps more than ever before, top clinical scientists with ample experience in research and patient care who are willing not only to advise, but also to make the transition to full-time or part-time employment in industry, thereby ensuring that industry has the experts needed for innovation and development, and is completely transparent about this to the external world.

Compliance policy and disclosure in collaboration between pharmaceutical industry and medical doctors: leading role of the EFPIA

At present, the European Federation of Pharmaceutical Industries and Associations (EFPIA) has a very clear compliance policy describing interactions between the pharmaceutical industry and medical doctors. The EFPIA, which represents the European pharmaceutical industry, is the EU voice of 1900 companies. These companies are engaged in research and development, aiming to bring patients new medicines that will improve global health and quality of life.

In the next paragraphs, the EFPIA compliance policy and disclosure code (http://transparency.efpia.eu/uploads/Modules/Documents/efpia_about_disclosure_code_updated-march-2016.pdf) is described in more detail.

Collaboration between industry and healthcare professionals (HCPs) and healthcare organizations (HCOs) benefits patients. This relationship has delivered many innovative medicines, with major impact on how diseases affect the lives of patients. The area of collaboration between industry and HCPs includes not only clinical research, but is also about sharing optimal clinical practice and exchanging information on how the patient care pathways may be affected and improved by new medicines. According to EFPIA, a fair compensation should be provided to HCPs because they provide valuable and legitimate expertise and services to industry. All hospitality granted to physicians has to be reasonable and strictly limited to the main purpose of an event. As a consequence, EFPIA members may not invite medical doctors on luxury cruises to expensive dinners in 3-star restaurants, or to other activities that might be seen as extravagant or renowned for entertainment.

In the context of increasing societal expectations on transparency, companies have started to greatly increase the transparency of this highly regulated and vital relationship. Indeed, since 30 June 2016, companies have been disclosing transfers of value made to HCPs, such as consultancy and advisory board membership, speaker fees and sponsorship to attend meetings. This transformational step in the relationship between industry and health professionals is a result of the EFPIA Disclosure Code.

The EFPIA Disclosure Code represents a code of conduct. Under this code, not only all EFPIA member companies but also companies that are members of EFPIA member associations are required to disclose transfers of value to HCPs and HCOs. This requirement includes the disclosure of names of HCPs and HCOs that have received payments or other transfers of value from industry. Disclosure, by the HCP or HCO, is needed for total amounts of value transferred and activity type. Activities may include a grant, a consultancy fee for speaking or advising, payment for travel, or registration fees for a medical education event. On 30 June 2016, the first disclosures were made public for value transfers made to HCPs or HCOs in 2015. A public platform is the place where this information has to be published. This platform can be a central platform (combining data from several companies in a country) or can be located on the website of the company. This EFPIA disclosure code was developed to protect the integrity of relationships between industry and HCPs or HCOs. It is an important step forward towards establishing greater transparency and trust between the European pharmaceutical industry, and the medical community and society.

The EFPIA Disclosure Code, formally adopted by the EFPIA General Assembly on 24 June 2013, applies to all EFPIA corporate member companies as well as member companies of member associations that are not directly members of EFPIA. The majority of pharmaceutical companies operating in Europe are EFPIA members. A list of EFPIA member companies and member associations (including the countries where they have activities) can be accessed at www.efpia.eu/about-us/membership. At present, among the companies manufacturing
Quality control in design, analysis, reporting, publication and communication of clinical research conducted by, or in collaboration with, the pharmaceutical industry

EFPIA member companies have also implemented very strict internal quality control processes and procedures in the design, analysis, reporting, publication and communication of clinical research according to the applicable regulations, such as Good Clinical Practice (GCP) and others. Compliance with these requirements is also regularly inspected by competent authorities such as the FDA or EMA for all trials used in marketing authorization applications.

Study design and analysis

In many companies, each research proposal is reviewed by different functions representing competencies in medical knowledge, clinical development, statistical expertise, pharmacovigilance, also taking into account overall compliance rules, regulatory matters and legal considerations. Only proposals that have been approved by all these functions can be developed into a final protocol and, in case of studies initiated by external clinical or scientific investigators, be eligible for funding. In clinical studies, statistical analysis needs to be predefined in a statistical analysis plan with clear primary and secondary efficacy outcomes and specific analysis of safety aspects. In my experience, company internal quality control processes are much stricter in Merck than in any university or hospital environment I had worked in previously.

Obviously, there are areas where more consensus is needed between industry and academia. For example, in the area of personalized reproductive medicine, it is important to have international agreement on the appropriate design for studies comparing the added clinical value of personalized ovarian stimulation using biomarkers. Traditionally, when comparing different drugs for ovarian stimulation in ART non-inferiority randomized controlled trials (RCTs), it has been standard practice to compare the primary outcome using the same starting dose for test drug and control drug for the first 4–6 days, followed by dose adaptation in line with the personal follicular response from each patient (Andersen et al., 2006; Devroey et al., 2012; Rettenbacher et al., 2015; Strowitzki et al., 2016; Humaidan et al., 2017). However, when comparing a fixed gonadotrophin starting dose with a personalized starting dose based on biomarkers, most (van Tilborg et al., 2016, Allegra et al., 2017) but not all (Andersen et al., 2017) investigators have compared the same brand of drug in both arms of the study. Obviously there is a major risk of bias that the groups differ not only with respect to the starting dose, but also with respect to drug brand, as has been highlighted recently (https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/12852-23086#comment-4479).

At the same time, we need to acknowledge that there is risk of scientific bias in both the pharmaceutical industry and in the academic world. When academics believe a hypothesis, they will build their case by emphasizing the arguments supporting their case, while refuting, refusing, opposing or ignoring arguments against their case. To reduce the risk of bias, there needs to be international consensus on the study design, analysis and reporting of outcomes (Wilkinson et al., 2016). This has been done in reproductive medicine for the reporting of infertility RCTs (Harbin Consensus Conference Workshop Group, 2014) but could be prioritized by leading global organizations like ESHRE, ASRM, IFFS, WHO, and is much needed in the area of personalized reproductive medicine. In order to make real progress here, it is important to invite senior medical and scientific experts from the pharmaceutical industry to participate in these consensus meetings, to benefit from their scientific input and experience in a transparent way, and to ensure that they apply the consensus in their own trials. Such a mature collaboration between a world leading scientific society and industry has been successfully achieved by the World Endometriosis Society with industry representatives contributing to and co-authoring reports of consensus meetings on management and research priorities for endometriosis (Johnson et al., 2013; Rogers et al., 2017).

In the design of RCTS addressing clinical outcomes of personalized ovarian stimulation, consensus is needed on the percentage relative improvement or the non-inferiority margin for which preferable reproductive outcome can be considered as added value, taking into account feasibility, cost and the perspective of stakeholders such as patients, physicians, industry and third party payers. A clear differentiation of primary outcomes and secondary outcomes and a prespecified statistical analysis plan and post-hoc analysis is also mandatory, as currently results from post-hoc analyses are often claimed as the ‘main results’.

In addition, consensus on safety outcomes for such trials is also needed, including not only general safety outcomes such as avoidance of OHSS or venous embolism but also specific reproductive safety outcomes such as preclinical miscarriages, ectopic pregnancies, clinical miscarriages. More specifically, it is important not only to differentiate and define preventive measures taken during ovarian stimulation to prevent excessive ovarian response (e.g. gonadotrophin dose adaptation during ovarian stimulation, type and dose of ovulation triggering, coating), but also to define and differentiate measures taken during oocyte retrieval to prevent OHSS (e.g. albumin administration, other medication, choice of luteal phase support). In this context, the consensus recently published on the consistent capture, classification and reporting of OHSS (Humaidan et al., 2016), based on a collaboration between investigators from academia, private clinical practice and industry, needs to be applied by all investigators planning future trials on ovarian stimulation in reproductive medicine.

Scientific reporting or publication and declaration of interest

One of the most important gatekeepers to ensure the quality of scientific reporting and publication, is the quality control of international peer review of papers in medical journals and of abstracts at
international meetings, and we all know that this process is complex, not perfect, and prone to its own bias. In this context, the quality of the work should be the only relevant criterion, regardless of where the work was done in academia, industry or mixed environments. Here, industry faces a prevailing mentality, among some reviewers or editors in medical journals, that research originating from industry is more likely to be biased. Here I plead for complete transparency, with publications where co-authors are selected only based upon ICMJE criteria, and where appropriate with joint co-authorships for experts employed by industry and consultants who have received ad hoc payments from industry. It could even be considered that the exact amounts of these consultancy fees are included in the declaration of interest forms required by most medical journals.

We need to recognize that, to the best of our knowledge, there is no systematic oversight or control to ensure the completeness of declarations of interest in publications, presentations, educational events, clinical guideline development groups, etc. Such oversight or control would probably not be easy, but could be prioritized by international organizations and journals in reproductive medicine. Once the declaration of interest is complete and correct, collaboration with industry should not be a reason to automatically refuse an individual’s participation in clinical guideline development groups, as long as there is sufficient agreement about the individual’s scientific rigor and objectivity. If an academic works together with industry, and is paid by industry, it does not mean that he/she cannot think independently. For most academics/scientists working with industry, personal scientific integrity is more important than the amount of consultancy fees. I, like many others, have consulted for industry for many years, and have enjoyed the focus, professionalism, and energy associated with my contract-based work in industry environments, without losing my academic independence. On the contrary, the new knowledge and insights based on this industry–academic collaboration has greatly inspired my academic and clinical work.

In the end, neutrality does not exist. We all have our beliefs and therefore our biases. The challenge is to be transparent about it at all times, and to behave in an informed, balanced and ethical way as medical and scientific experts, taking into account the compliance and legal regulations of both industry and academic employers, in the best interest of patients and society.

Discussion

The main content of my opinion expressed in this paper can be summarized as follows:

(1) Partnership between industry and academia is needed for faster development and access to better diagnostics, drugs and devices for the benefit of patients and society. Such partnerships are built on joint interests in improving diagnostic and therapeutic options for patients, and can be realized by joint preclinical, clinical and post-marketing research and development, joint intellectual property and joint revenue.

(2) In Europe, under the EFPIA Disclosure Code of conduct, EFPIA member companies need to disclose transfers of value including amounts, activity type and the names of the recipient HCPs and HCOs, and have very strict internal quality control processes and procedures for the design, statistical analysis, reporting, publication and communication of clinical research. If all companies, operating in reproductive medicine and women’s health in Europe, would be EFPIA members, there would be less confusion and more transparency and standardization regarding the mutual relationship between the pharmaceutical industry and HCPs and HCOs.

(3) Scientific bias exists not only in the pharmaceutical industry but also in the academic world. When academics believe in a hypothesis, they may emphasize the arguments supporting their case and refute, refuse, oppose or ignore arguments challenging their assumptions. A solution to such bias may be international consensus on study design, data collection, statistical analysis and reporting of outcomes, especially in the area of personalized reproductive medicine.

(4) Equally important is that declarations of interest are reported transparently and completely in scientific abstracts and publications, and that ghost authorship is replaced by proactive and clear co-authorship for experts from industry, particularly where such co-authorship is required based on the prevailing ICMJE criteria. In that context, however, reviewers should stop believing that publications by industry authors only, or by mixed groups of co-authors from industry and academia, are more prone to bias than papers from academic groups only. Instead, the scientific quality of the work should be the only relevant criterion for acceptance of papers or abstracts, regardless of where the work was done.

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Conflict of interest

I declare that are no conflicts of interest with respect to the content of this debate article and confirm that it has been written as my personal opinion, based on my joint experience in the pharmaceutical industry and academic medicine.

Author’s role

This article represents my personal opinion based on my joint experience in the pharmaceutical industry and academic medicine.

References

Adamson GD, Abusief ME, Palao L, Witmer J, Palao LM, Gvakharia M. Improved implantation rates of day 3 embryo transfers with the use of an automated time-lapse-enabled test to aid in embryo selection. Fertil Steril 2016;105:369–75.e6. doi: 10.1016/j.fertnstert.2015.10.030. Epub 2015 Nov 18.

Al-Inay HGY, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ, Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev 2016;4:CD001750. doi:10.1002/14651858.CD001750.pub4. Review.

Allegro A, Marino A, Volpes A, Coeffo F, Scaglione P, Gullo S, La Marca A. A randomized controlled trial investigating the use of a predictive nomogram for the selection of the FSH starting dose in IVF/ICSI cycles. Reprod Biomed Online. 2017;34:429–438. doi:10.1016/j.rbmo.2017.01.012. Epub 2017 Jan 23.

Andersen AN, Devroey P, Arce JC. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing
Aparicio-Ruiz B, Basile N, Pérez-Albalá S, Bronet F, Remohí J, Meseguer M. Automatic time-lapse instrument is superior to single-point morphology observation for selecting viable embryos: retrospective study in oocyte donation. Fertil Steril 2016;106:1379–1385.e10. doi:10.1016/j.fertnstert.2016.07.1117. Epub 2016 Aug 13.

Ata B, Seli E. Strategies for controlled ovarian stimulation in the setting of ovarian aging. Semin Reprod Med 2015;33:436–448. doi:10.1055/s-0035-1567818. Epub 2015 Nov 12. Review.

Blockeel C, Drakopoulos P, Santos-Ribeiro S, Polyzos NP, Tournaye H. A fresh look at the freeze-all protocol: a SWOT analysis. Hum Reprod 2016;31:491–497. doi:10.1093/humrep/dev339. Epub 2016 Jan 2. Review.

Dahdouh EM, Balayla J, García-Velasco JA. Comprehensive chromosome screening improves embryo selection: a meta-analysis. Fertil Steril 2015;104:1503–12. doi:10.1016/j.fertnstert.2015.08.038. Epub 2015 Sep 16. Review.

Debrock S, Peeraer K, Fernandez Gallardo E, De Neubourg D, Spiessens C, D’Hooghe TM. Vitrification of cleavage stage day 3 embryos results in higher live birth rates than conventional slow freezing: a RCT. Hum Reprod 2015;30:1820–1830. doi:10.1093/humrep/des134. Epub 2015 Jun 18.

Devroey P, Pellicer A, Nyboe Andersen A, Arce JC, Spiessens C, D’Hooghe TM. Recombinant FSH plus recombinant luteinizing hormone versus recombinant FSH alone for ovarian stimulation for IVF: a randomized controlled trial. Hum Reprod 2016;31:1055–1066. doi:10.1093/humrep/dew149. Epub 2016 Nov 29.

Garcia-Velasco JA, Acevedo B, Alvarez C, Alvarez M, Bellver J, Fontes J, Landeras J, Manau D, Martinez F, Munoz E, Fenning N, van der Poel S, Rienzi L, Racowsky C, Oocyte, embryo and blastocyst cryopreservation in ART: systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance. Hum Reprod Update 2017;23:139–155. doi:10.1093/humupd/dmw038.

Rogers PA, Adamson GD, Al-Jefout M, Becker CM, D’Hooghe TM, Dunselman GA, Fazleabas A, Giudice LC, Horne AW, Hull ML et al. WES/WERF Consortium for Research Priorities in Endometriosis. Research priorities for endometriosis. Reprod Sci 2017;24:202–226. doi:10.1177/1933719116654991. Epub 2016 Sep 27.

Stoufforis IA, Martins WP, Nashti CO, Viana IG, Navarro PA, Rainef Fennig N, van der Poel S, Rienzi L, Racowsky C. Blastocyst culture using single versus sequential media in clinical IVF: a systematic review and meta-analysis of randomized controlled trials. J Assist Reprod Genet 2016;33:1261–1272. Epub 2016 Aug 5. Review.
cycles in infertile women using assisted reproductive technology: a phase 3 open-label follow-up to Main Study. Reprod Biol Endocrinol 2016;14:31. doi:10.1186/s12958-016-0164-y.

Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. Hum Reprod 2011;26:1768–1774. doi:10.1093/humrep/der106. Epub 2011 May 10.

van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev 2015:CD009154. doi:10.1002/14651858.CD009154.pub3. Review.

van Tilborg TC, Broekmans FJ, Dölleman M, Eijkemans MJ, Mol BW, Laven JS, Torrance HL. Individualized follicle-stimulating hormone dosing and in vitro fertilization outcome in agonist downregulated cycles: a systematic review. Acta Obstet Gynecol Scand 2016;95:1333–1344. doi:10.1111/aogs.13032. Review.

Vaughan DA, Leung A, Resetkova N, Ruthazer R, Penzias AS, Sakkas D, Alper MM. How many oocytes are optimal to achieve multiple live births with one stimulation cycle? The one-and-done approach. Fertil Steril 2017;107:397–404.e3. doi:10.1016/j.fertnstert.2016.10.037. Epub 2016 Dec 1.

Wilkinson J, Roberts SA, Showell M, Brison DR, Vail A. No common denominator: a review of outcome measures in IVF RCTs. Hum Reprod 2016;31:2714–2722. Epub 2016 Sep 22.

Youssef MM, Mantikou E, van Wely M, Van der Veen F, Al-Inany HG, Repping S, Mastenbroek S. Culture media for human pre-implantation embryos in assisted reproductive technology cycles. Cochrane Database Syst Rev 2015:CD007876. doi:10.1002/14651858.CD007876.pub2. Review.