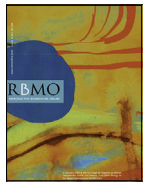
RBMO



COMMENTARY

Research and business – the yin and yang in modern medicine

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ABSTRACT

Yin and yang is a concept of dualism in Chinese philosophy, describing how opposite or contrary forces may be complementary, interconnected and interdependent, and how they may give rise to each other as they interrelate with one another. In line with this, modern clinical research and business can definitely be described as yin and yang. With the increasing need for funding, researchers at a very early stage during the development of a new concept may be forced or tempted to enter the business world. Furthermore, researchers are encouraged and supported by their own universities to collaborate with possible future business partners, not only to acquire funding, but also to explore potential patenting. This collaboration between the business world and research can definitely be very fruitful and provide benefit for both parties, patients and society as a whole, but it may also introduce the risk of premature materialization.

As previously described (*Masic et al., 2008*), 'Evidence based medicine (EBM) is the conscientious, explicit, judicious and reasonable use of modern, best evidence in making decisions about the care of individual patients.' However, one might ask how many interventions in daily clinical practice are based on low-quality evidence. Probably more than anticipated and, in reality, low quality of evidence should not refrain clinicians from using their common (biological) sense to make recommendations for a clinical intervention.

This is one of the key aspects of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical recommendation system, which is endorsed by renowned institutions worldwide such as the Cochrane Collaboration (*Alonso-Coello et al., 2016*; *Guyatt et al., 2008*). For example, due to the risk of infection, the majority of reproductive specialists would agree on administering prophylactic antibiotics prior to oocyte retrieval in patients suffering from severe endometriosis (*Pereira et al., 2016*). However, to the best of our knowledge, this intervention has never been investigated in randomized controlled trials (RCT), as the risk of severe infection may be too high compared with the relatively minor side effects of the intervention.

'Another aspect of clinical decision-making in GRADE is not only to balance quality of evidence in a benefits and risks assessment, but also to take into account costs and patients' preferences (*Guyatt et al., 2008*). In the example given above, the cost would be minimal, and patients would probably prefer to reduce the risk of infection at the expense of risking antibiotic side effects. Using this example, it can be emphasized that there are definitely exceptions where an intervention can be recommended despite low-quality evidence. However, this should be the exception not the rule, and even in the example mentioned above one could argue for a rigorous RCT given the increasing awareness of unnecessary antibiotic usage.

In the case of development of new interventions, we suggest that novel interventions and applications should be withheld from clinical usage until substantial benefits outweigh the risks – ideally with high-quality evidence to support it, as recommended by the GRADE system.

In this commentary, we wish to focus on the fact that the need for high-quality evidence as regards new interventions is hugely more important when commercial aspects are involved in research – and ultimately in clinical decision-making.

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KEY WORDS

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THE CHALLENGE

When a novel scientific invention becomes a business case, funding can be obtained to promote scientific development into a successful business model that will subsequently create jobs and value for society. This strategy is widely promoted by, for example, the EU Horizon 2020 programme, which defines impact as research excellence, but states that: 'Impact indicators represent what the successful outcome should be in terms of impact on the economy/society beyond those directly affected by the intervention' (https://www.ffg.at/sites/default/files/horizon2020indicators.pdf, accessed October 2019). This is an admirable goal, and researchers currently need to address these societal aims of impact in their funding application. The question, however, is whether research excellence could be compromised by this strategy. Maybe not in terms of innovation, but possibly through impatience – i.e. not awaiting further research in order to obtain better quality evidence, for instance in terms of GRADE, before recommending an intervention for clinical practice. Another concern is the need for scientific transparency, which may be hindered by business secrets related to patent applications and other aspects of commercialization.

The real problem arises if the novel intervention comes to clinical application prematurely – or, even worse, gets commercialized prematurely – with the objective of promoting the business case. Currently, business success does not necessarily rely on high-quality evidence. For example, small studies with a very low quality of evidence according to GRADE may appear successful. This could encourage a start-up business to expand further by attracting investors and research funds – now both business and science are thriving. However, when the new intervention comes to clinical application and becomes commercialized before good-quality evidence is present, the incentive to expand the initial research with more robust and costly studies to improve the quality of evidence may be less warranted. This situation is well known in sexually transmitted disease (STD) research, where point of care tests for *Chlamydia trachomatis* self-testing based on enzyme detection appeared on the market with CE marks – presumably the business is still thriving today after more than 25 years under different company names, regardless of poor-quality evidence (*Schachter, 2016*). Thus, Schacter commented on the typical marketing strategy for these *Chlamydia* tests (*Schachter, 2016*): 'It was not the typical approach of assessing test performance by multicentre trials, publishing results in peer-reviewed journals, and obtaining US Food and Drug Administration (FDA) clearance. Rather, they hired space at a major medical exposition, passed out materials describing their test, its performance and advantages. This gained exposure to the press, to some members of the STD community, and, most important, to potential distributors of their product. The press reports the information presented by the companies. The companies in turn issue press releases describing the favorable reception received at the expo and how much excitement their test had generated'. And considering the validation study, Schacter continues: 'There was no information as to the performance or design of the "home brew" PCR'.

It is important to emphasize that premature application to the general market may destroy not only the incentive for a company to investigate quality of evidence from the initial low-quality studies that appeared successful, but also the incentive for patients to enter trials initiated by third-party/independent researchers. In a low-risk intervention setting, resourceful patients may ask themselves: 'Instead of entering a trial with the perceived risk of being randomized to a standard treatment or placebo group, why not just go to the internet and pay for this intervention, which is already commercially available and appears successful.'

When the intervention consists of investigational medical drugs or well-known drugs seeking a new indication, legislation and regulators demand RCTs to investigate both safety and the quality of evidence for the intervention prior to clinical application. Importantly, this is not the case for new diagnostic tests, screening interventions and dietary supplements, although the GRADE approach still recommends the same standards before clinical application (*Schünemann et al., 2018*).

DO WE ENCOUNTER THIS CHALLENGE IN MODERN ASSISTED REPRODUCTIVE TECHNOLOGY?

A new and interesting area in assisted reproductive technology (ART) is the potential use of several emerging implantation/receptivity tests claiming to assess the fertility potential of an individual and to improve embryo transfer strategies in IVF by assessing the genital tract microbiota (https://www.varinos.com/english, https://receptivity.com/?lang=en and https://www.igenomix.com/provider-tests/endometrial-microbiome-metagenomic-analysis-emma, accessed September 2019). Some tests already have dedicated webpages, Twitter accounts and Facebook pages claiming their beneficial usage. Moreover, it is not unlikely that these new tests will be encountered in the industry booths at conferences.

Undoubtedly, the studies behind vaginal and endometrial microbiome testing are interesting and point towards an association between dysbiosis and poor pregnancy outcome. Unfortunately, however, studies are mostly observational and include only small numbers of patients (*Koedooder et al., 2019b*; *Kyono et al., 2018*; *Moreno et al., 2016*). Hence, the evidence for testing and the subsequent clinical decision-making is currently very limited. Interestingly, two tests are based on a next generation sequencing (NGS) method for analysing the endometrial microbiome (https://www.varinos.com/english and https://www.igenomix.com/provider-tests/endometrial-microbiome-metagenomic-analysis-emma). In NGS it is important to keep in mind the huge heterogeneity in the analytical pipelines, making reproducibility and thus interstudy comparison and clinical application problematic (*Berman et al., 2019*). The endometrial tests use relative abundances of bacteria, applying an arbitrary cut-off of over 90% to determine a *Lactobacillus*-dominant microbiome. This method can be criticized for not taking into account the total abundance of bacteria, which is especially important in biological samples with low biomasses, such as the endometrium, from which cervical contamination during sampling is difficult to avoid (*Berman et al., 2019*; *Haahr et al., 2019b*; *Vandeputte et al., 2017*). Moreover, a recent Japanese study investigating blastocyst transfers only

could not find any effect of *Lactobacillus*-dominant endometrial microbiota on the ongoing pregnancy rate (*Hashimoto and Kyono, 2019*): 38% (26/68) versus 45% (14/31) favouring the dysbiosis group.

Another test evaluates the vaginal microbiota as a predictor of IVF outcome (*Koedooder et al., 2019b*). This was recently debated for being non-transparent and not validated against standard methods of measuring vaginal dysbiosis (*Haahr et al., 2019a*). In the subsequent response, the authors stated that their molecular technique was CE/IVD marked (*Koedooder et al., 2019a*), which should ensure high-quality in-vitro diagnostics, but as discussed above in relation to chlamydia tests, the CE/IVD is not a good marker of quality. However, according to the most recent EU regulation, this is likely to change soon. The most recent regulation states that clinical evidence should be present to evaluate 'whether the test achieves the intended clinical benefit' before a CE/IVD mark can be granted (http://data.europa.eu/eli/reg/2017/746/oj, accessed October 2019). Until now, obviously, there seems to have been a discrepancy between how the CE/IVD and GRADE evaluate clinical evidence as regards certification/recommendations, and it can be argued that this leads to confusion for researchers, clinicians and the lay person.

From their webpages, some providers even go as far as to suggest postponing embryo transfer and performing one or several follow-up tests in subsequent menstrual cycles. As far as we know, this approach of 'wait and transfer once the microbiota is favourable' – which by necessity assumes a causal relationship – has never been investigated in a clinical trial. Moreover, an important issue is the fact that consensus on the 'optimal genital tract microbiota' as regards reproductive outcomes has not been reached. Furthermore, the optimal treatment of an abnormal/unfavourable microbiota is also presently unknown: antibiotics, antibiotics and lactobacilli, lactobacilli alone or something else? So, by offering the patient testing, she is posed a dilemma once the diagnosis is 'abnormal/unfavourable microbiota' because no clinical recommendations are available for this situation. In this case ART patients might go to the commercial market for probiotics, which advertises solutions for 'abnormal/unfavourable microbiota'. However, probiotics are not medical drugs and have limited product information available, and only a few probiotics have been investigated correctly in clinical trials. Even for those probiotics investigated in clinical trials, interstudy comparisons are hampered by heterogeneity (*van de Wijgert and Verwijs, 2019*).

All of the microbiota tests mentioned above resulted in scientific publications in important journals within this field. Nevertheless, the conflicts of interest declaration is misleading in several cases, stating 'nothing to disclose' in letters, reviews and even original articles that indirectly or sometimes directly promote the business case (*Kitaya et al., 2019*; *Koedooder et al., 2019a*; *Kyono et al., 2018*; *Moreno and Simon, 2018*; *Simon, 2018*). In our opinion this is an example of an omission that has at best been caused by forgetfulness. In a recent Editorial the importance of transparent disclosure statements was thoroughly discussed, with recommendations for optimal transparency (*Fauser and Macklon, 2019*).

In conclusion, research and business delicately go hand in hand, like yin and yang – and balance is definitely the key word. Research and development of new concepts/interventions should be handled in a way that ensures replicability by third parties to obtain a high quality of evidence for future clinical application. Premature launching of products does not benefit patients, society or the scientific community.

DECLARATION

TH has received honoraria for lectures from Ferring, IBSA, Besins and Merck. PH has received unrestricted research grants from MSD, Merck, and Ferring as well as honoraria for lectures from MSD, Merck, Gedeon-Richter, Theramex and IBSA. JSJ has received speaker's fee from Hologic, BD, SpeeDx and Cepheid and serves on the scientific advisory board of Roche Molecular Systems, Abbott Molecular and Cepheid. PH, TH and JSJ have all received an unrestricted research grant from Osel Inc. which produces LACTIN-V, a live biotherapeutic product with *Lactobacillus crispatus*. PH and TH are listed as inventors in an international patent application (PCT/UK2018/040882) involving 'Use of vaginal lactobacilli for improving the success rate of in vitro fertilization'.

REFERENCES

Alonso-Coello, P., Oxman, A.D., Moberg, J., Brignardello-Petersen, R., Akl, E.A., Davoli, M., Treweek, S., Mustafa, R.A., Vandvik, P.O., Meerpohl, J., Guyatt, G.H., Schunemann, H.J. **GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines.** BMJ 2016; 353: i2089

Berman, H.L., McLaren, M.R., Callahan, B.J. **Understanding and Interpreting Community Sequencing Measurements of the Vaginal Microbiome.** BJOG Int. J. Obstet. Gynaecol. 2019: 139–146 doi:10.1111/1471-0528.15978

Fauser, B.C.J.M., Macklon, N.S. **May the colleague who truly has no conflict of interest now please stand up!** Reprod. Biomed. Online 2019; 39: 541–544. doi:10.1016/j.rbmo.2019.09.001

Guyatt, G.H., Oxman, A.D., Kunz, R., Falck-Ytter, Y., Vist, G.E., Liberati, A., Schünemann, H.J. **GRADE Working Group. Going from evidence to recommendations.** BMJ 2008; 336: 1049–1051. doi:10.1136/bmj.39493.646875.AE

Haahr, Humaidan, P., Jensen, J.S. **Non-transparent and insufficient descriptions of non-validated microbiome methods and related reproductive outcome results should be interpreted with caution.** Hum. Reprod. Oxf. Engl. 2019. doi:10.1093/humrep/dez167

Haahr, Jensen, J.S., Humaidan, P. **Vaginal microbiota and IVF outcomes: poor diagnosis results in flawed conclusions.** Reprod. Biomed. Online 2019; 39: 178. doi:10.1016/j.rbmo.2019.04.006

Hashimoto, T., Kyono, K. **Does dysbiotic endometrium affect blastocyst implantation in IVF patients?** J. Assist. Reprod. Genet. 2019; 36: 2471–2479. doi:10.1007/s10815-019-01630-7

Kitaya, K., Nagai, Y., Arai, W., Sakuraba, Y., Ishikawa, T. **Characterization of Microbiota in Endometrial Fluid and Vaginal Secretions in Infertile Women with Repeated Implantation Failure.** Mediators Inflamm. 2019; 20194893437. doi:10.1155/2019/4893437

Koedooder, R., Schoenmakers, S., Budding, A.E., Laven, J.S.E. **Reply: Non-transparent and insufficient descriptions of non-validated microbiome methods and related reproductive outcome results should be interpreted with caution.** Hum. Reprod. Oxf. Engl. 2019: 2084–2086 doi:10.1093/humrep/dez168

Koedooder, R., Singer, M., Schoenmakers, S., Savelkoul, P.H.M., Morré, S.A., de Jonge, J.D., Poort, L., Cuypers, W.J.S.S., Beckers, N.G.M., Broekmans, F.J.M., Cohlen, B.J., den Hartog, J.E., Fleischer, K., Lambalk, C.B., Smeenk, J.M.J.S., Budding, A.E., Laven, J.S.E. **The vaginal microbiome as a predictor for outcome of in vitro fertilization with or without intracytoplasmic sperm injection: a prospective study.** Hum. Reprod. Oxf. Engl. 2019; 34: 1042–1054. doi:10.1093/humrep/dez065

Kyono, K., Hashimoto, T., Nagai, Y., Sakuraba, Y. **Analysis of endometrial microbiota by 16S ribosomal RNA gene sequencing among infertile patients: a single-center pilot study.** Reprod. Med. Biol. 2018; 17: 297–306. doi:10.1002/rmb2.12105

Masic, I., Miokovic, M., Muhamedagic, B. **Evidence based medicine - new approaches**

and challenges. Acta Inform. Medica AIM J. Soc. Med. Inform. Bosnia Herzeg. Cas. Drustva Za Med. Inform. BiH 2008; 16: 219–225. doi:10.5455/aim.2008.16.219-225

Moreno, I., Codoner, F.M., Vilella, F., Valbuena, D., Martinez-Blanch, J.F., Jimenez-Almazan, J., Alonso, R., Alama, P., Remohi, J., Pellicer, A., Ramon, D., Simon, C. **Evidence that the endometrial microbiota has an effect on implantation success or failure.** Am. J. Obstet. Gynecol. 2016. doi:10.1016/j.ajog.2016.09.075

Moreno, I., Simon, C. **Relevance of assessing the uterine microbiota in infertility.** Fertil. Steril. 2018; 110: 337–343. doi:10.1016/j.fertnstert.2018.04.041

Pereira, N., Hutchinson, A.P., Lekovich, J.P., Hobeika, E., Elias, R.T. **Antibiotic Prophylaxis for Gynecologic Procedures prior to and during the Utilization of Assisted Reproductive Technologies: A Systematic Review.** J. Pathog. 2016; 20164698314. doi:10.1155/2016/4698314

Schachter, J. **Point-of-care tests using enzyme detection to diagnose Chlamydia trachomatis infection do not work. But when they fail in clinical trials, they reappear under different names.** Sex. Transm. Infect. 2016; 92: 406–407. doi:10.1136/sextrans-2015-052508

Schünemann, H., Brozek, J., Guyatt, G., Oxman, A., 2018. GRADE Handbook [WWW Document]. URL http://gdt.guidelinedevelopment.org/app/handbook/handbook.html#h.m9385o5z3li7 (accessed 6.9.19).

Simon, C. **Introduction: Do microbes in the female reproductive function matter?** Fertil. Steril. 2018; 110: 325–326. doi:10.1016/j.fertnstert.2018.06.041

van de Wijgert, J.H.H.M., Verwijs, M.C. **Lactobacilli-containing vaginal probiotics to cure or prevent bacterial or fungal vaginal dysbiosis: a systematic review and recommendations for future trial designs.** BJOG Int. J. Obstet. Gynaecol. 2019. doi:10.1111/1471-0528.15870

Vandeputte, D., Kathagen, G., D'hoe, K., Vieira-Silva, S., Valles-Colomer, M., Sabino, J., Wang, J., Tito, R.Y., De Commer, L., Darzi, Y., Vermeire, S., Falony, G., Raes, J. **Quantitative microbiome profiling links gut community variation to microbial load.** Nature 2017; 551: 507–511. doi:10.1038/nature24460

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