Medical research and reproductive medicine in an ethical context: a critical commentary on the paper dealing with uterine lavage published by Munné et al.

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Abstract

A recent study published in Human Reproduction claimed that uterine lavage offers a non-surgical, minimally invasive strategy for the recovery of human embryos from fertile women who do not want or need IVF for medical reasons but who desire preimplantation genetic testing (PGT) for embryos. To prove this hypothesis, the researchers recruited dozens of young Mexican women. The prospective oocyte donors underwent ovarian stimulation to induce the production of multiple mature oocytes. Subsequently, these women were inseminated by donor semen. A few days later, the developing embryos were collected by uterine lavage (uterine flushing) and subjected to genetic testing for aneuploidies (PGT-A). Oocyte donors with persistently elevated hCG levels, indicating the implantation of one or more embryos after uterine lavage, had to undergo uterine curettage and/or treatment with methotrexate. A critical opinion paper discussing the aforementioned study was published by De Santis and colleagues and has raised critical issues that are largely technical in nature. However, this opinion paper neglects—from our point of view—critical issues of the Mexican study regarding ethical principles and moral standards in human research. These aspects are summarized below.

Keywords Uterine lavage · Oocyte donors · PGT-A · Ethics · Publication standards

Introduction

The rapid pace of development in assisted reproductive techniques (ART) prompts the question whether all studies in this

field performed in the name of science are ethically and morally acceptable, especially with regard to the *CRISPR-based human genome editing* experiments by He Jiankui. In January 2020, Human Reproduction published a study with the aim of comparing the chromosomal constitution of in vivo derived embryos with PGT-A findings of in vitro derived embryos [1]. The study protocol implied the production of human embryos in vivo, by intra-uterine insemination of participating women with non-partner sperm. Subsequently, the embryos were retrieved by uterine lavage for PGT-A analysis.

The publication of the study by Munné and colleagues was accompanied by a critical commentary by the Associate Editor of Human Reproduction, in particular with regard to the four medical-ethical principles of *autonomy, justice, beneficence* and *non-maleficence* [2] and by a justification statement “Ethics beyond Ethics” for publication by the Editorial Board despite several concerns [3].

We would like to point out that in our view, the study of Munné et al. still raises questions with regard to several key issues. The recently published opinion paper by De Santis and colleagues critically scrutinized whether uterine lavage of

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embryos (for PGT) is really required. Whereas De Santis et al. primarily discussed the shortcomings of technical aspects and concluded that the work of Munné and colleagues cannot be considered relevant in ART because of its technical limitations [4], we think that the moral and ethical impact of this study are of much broader extent (as explained in detail below).

Informed consent and psychological aspects

The study of Munné et al. (2020) reported for 11 of the 81 women an unwanted implantation which had to be interrupted with methotrexate and/or curettage [1]. First, there is no mention of a psychological consultation or guidance offered to the participants in the context of this intervention. While the psychological experience and response to pregnancy termination remains an area of interest and study, studies suggest that the psychological impact of pregnancy termination varies across women and is influenced by social, cultural, religious and legal context [5]. It is therefore highly questionable whether the termination of a pregnancy for mere scientific reasons has no or only minor effect on these women. Greater emphasis must be also placed in this context on the deeply rooted faith in a country where the overwhelming majority of citizens self-identify as Catholic and where abortion is seen as stigmata [6]. Additionally, the question remains whether the patients were followed up for their mental condition after the intervention.

Mexico is a federal republic comprising 31 states plus Mexico City. The legal criteria for pregnancy termination vary by the individual states. In fact, in the majority of Mexican states, the criteria for the induced abortion is very restrictive and, to the extent permitted by law, only allowed under very strict conditions [7]. The fertility clinic conducting the study is located in Nayarit and the majority of the participating women are residents of Puerto Vallarta (state of Jalisco). As far as we know, the only legally permissible reasons for pregnancy termination in both states are the preservation of women's health or the termination of pregnancies resulting from a crime against freedom and sexual self-determination [8, 9]. Therefore, the described curettage or methotrexate treatments do not seem to meet the legal situation in these states.

Second, Munné and colleagues stated that “subjects gave their informed written consent that in the event of persistently high hCG levels after uterine lavage they may be treated with uterine curettage and/or the administration of methotrexate” [1]. This raises the question of whether the informed consent document actually used the term “abortion” and whether the women were fully aware that the terms “uterine curettage and/or administration of methotrexate” did in fact refer to abortion techniques. Have the study participants been appropriately informed about their rights to refuse the abortion treatment?

Although not directly linked to this recent study, an almost 40-year-old interview in the US magazine “*People*” from Sue Ellen Jares with John E. Buster is striking. John E. Buster is the founder of Previvo Genetics Inc., (the sole sponsor) and co-author of the study Munné et al. (2020) as well as Nadal et al. (2019)—a publication discussed below [1, 10, 11]. The reason for this interview was the transfer of in vivo fertilized embryos from donor women into the wombs of two infertile recipients. In response to the question as to what kind of agreement is made between donor and recipient, Buster stated that “the donor agrees that if she should become pregnant with a retained egg (one that inadvertently was not flushed out) she would have a menstrual extraction or abortion” [10]. While patients have the right to choose or refuse any medical interventions, it is indubitable that the validity of these choices depends on the comprehensible information the study participants have been given about the interventions and on their capacity to make informed choices.

Furthermore, there is no mention of any informed consent obtained from the sperm donors regarding the use of their samples in the study Munné et al. To remove any lingering doubts on this matter, the informed consent should be made accessible by the authors or the journal *Human Reproduction* to a broad public.

Consequences of outsourcing clinical trials that must be classified as ethically questionable

Although the study of Munné and colleagues was performed in Mexico, 11 co-authors were either European or US residents. In recent times, there has been an increasing trend towards outsourcing clinical trials (CTs) to low- and middle-income countries. Possible reasons might be the inability to recruit enough research participants in high-income countries and sometimes also lower regulatory hurdles in low- and middle-income countries [12]. The outsourcing of CTs is sometimes associated with exporting practices that are not acceptable in the sponsor's country—a practice termed “Ethics Dumping” which was used for the first time in 2014 within the 7th Framework Programme Funder Reports of the European Commission.

To avoid misunderstandings, the practice of outsourcing is not morally wrong per se and does not imply that all study outsourcing to Latin America should be considered as ethics dumping. However, we should not hide the fact that ethics dumping in Mexican clinical trials is fairly common, thus posing a problem that cannot be ignored [13]. In addition, numerous studies highlight the use of some questionable practices in the informed consent processes for research projects conducted in Mexico [14]. Therefore, the question arises as to why this study in particular was outsourced.

Given the global controversial and highly emotional discussion on human embryo research, it is surprising that this study has passed all ethical valuation and approval processes. In several countries where the use of embryos for research purposes is permitted, research can only be carried out by the respective authorities (i.e. Human Fertilisation and Embryo Authority (HFEA) in the UK)—within certain conditions. These include, for example, the objective to increase knowledge about serious diseases or the causes of miscarriage. In the USA, using federal funds for the creation of human embryos for research purposes or using embryos for research purposes resulting in the destruction of human embryos is prohibited by the Dickey-Wicker Amendment [15]. And—what is important—in many countries, research is performed on surplus embryos resulting from IVF or abortion (i.e. Spain or France)—an approach that may be considered to be within the ethically tenable scope. From an ethical point of view, it can make a difference whether the embryos used are already available in laboratories and would otherwise be discarded or if they are created for research purposes only. It remains unclear whether the embryos of the Munné study were created for research purposes. This is at least what is indicated by a recently published opinion paper by Guido Pennings [16]. In fact, in the case of Mexico, the Federal Constitution does neither define a human embryo nor does it expressly defend human life from the moment of conception or fertilization [15], thus allowing in theory the creation of embryos *in vivo* for research purposes only. However, in contrast to the aforementioned legal situation, the fertility clinic where the study was performed is located within the state of Nayarit. Nayarit's constitution does, however, protect human life from the time of fertilization onwards. Quote included in the amendment [ADICIONADA N. E. REUBICADA ANTES FRACCIÓN XI] of December 16, 2010: “Every human being's right to life shall be recognized, protected and guaranteed from the moment of natural conception or artificial fertilization and it shall be considered born for all legal purposes until their natural death” [17].

Financial compensation

Financial compensation raises ethical concerns, which mainly include undue inducement, disproportionate burden on the poor as well as commodification [18]. In the study of Munné and colleagues, subjects received a considerable reimbursement of 1400\$ for their participation, an amount equivalent to a 71-working-day wage in Mexico [19]. Given the considerable financial compensation, the question arises as to the voluntary nature of decision-making. The Council for International Organizations of Medical Sciences (CIOMS) stated that monetary or in-kind compensation for research participants must not be so large as to persuade them to volunteer

against their better judgement or deeply held beliefs (“undue inducement”) [20]. In fact, other guidelines, such as the Belmont report as well as the principles of GCP, pointed out the danger of compromised capacity for free consent of individuals who are economically disadvantaged (WHO, 2002; National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, 1979).

According to the United Nations Economic Commission for Latin America and the Caribbean (ECLAC) report, the poverty rate within Latin America has not only stagnated but has slightly increased between 2011 and 2012, albeit with regional differences. While a decrease in poverty was observed in some States, such as Chihuahua, a sharp increase (between 2010 and 2012) could be witnessed, especially in Nayarit and Jalisco [21]. The poverty headcount ratio (% population living below the national poverty lines) in Mexico was reported at 41.9% in 2018 [22]. The situation is even worse in Puerto Vallarta, where ~10% of homes do not have potable water; 8% are not connected to a sewer system and 4% do not have electricity [19]. From our understanding, the outsourcing of such an ethically problematic study to an emerging region combined with a high reimbursement represents a clear infringement of ethical standards.

Monetary aspects and conflict of interest

In an interview, Laurie Zoloth, the Margaret E. Burton, Professor of Religion and Ethics at the University of the Chicago Divinity School, used quite drastic words when she said that researchers used a woman's body as a Petri dish [23]. However, it is questionable whether this will be a singular event. The two publications combined (Nadal et al., 2019 and Munné et al. 2020) do at least suggest that a further long-term objective might be to generate a kind of cheap oocyte donation program to replace “cost-intensive” IVF by insemination and subsequent uterine lavage or, at the very least, sell the lavage system. This assumption is even supported by the investigators themselves when stating in the description accompanying the study registration that the recovered embryos will be cryopreserved for future use or donated for future use [24] and by a statement that can be found on the Previvo website: “There are several options for those seeking treatment – from one of the least expensive methods, intra-uterine insemination (IUI), to one of the most expensive technologies, *in vitro* fertilization (IVF)”. In addition, it is said that Previvo Uterine Lavage fits within the continuum of ART and offers patients a potential cost-effective option [25]. To conclude, creating embryos with donor semen by insemination of oocyte donors at the Punta Mita Hospital would mean, at any rate, that the embryos were conceived in view to be donated, since the creation of embryos for the sole purpose of scientific research is expressly prohibited by local law [15].

Around the world, pharmaceutical companies conduct CTs. Meanwhile, the pharmaceutical industry is widely recognized to be the main driver when it comes to conducting studies involving humans. In 1994, 63% of CTs were conducted in academic settings, 10 years later; this figure dropped to only 26% [26]. This in itself is neither good nor bad but is quite simply owed to the fact that pharmaceutical companies have far greater financial resources available and are often more efficient than academic research. But not only research itself, but also the review processes of CTs are being performed with increasing frequency by for-profit organizations. This is true not only for the performance of the studies but the review process as well. In 2005, WIRB, which was also involved in reviewing the Mexican study, was responsible for the review of more than half of all submissions of new drug candidates to the FDA [27].

However, it is also widely recognized that the commercialization of medical research may sometimes create serious conflicts of interest [28]. This also applies to the review process. In case of a negative decision, the for-profit IRB runs the risk of losing the customer. So, if a company is the sole sponsor of a study, the founder and board chairman of this company has first-rate contacts to the financial community, and most investigators/authors have a financial relationship with the sponsor and, last but not least, the ethical approval is obtained by a commercial IRB. Does this provide a good basis for guaranteeing the scientific and financial independence of medical research?

Study discrepancies and publication ethics

As mentioned before, four of the co-authors of the Munné study published a paper in the journal “Medical Devices: Evidence and Research” [11]. This manuscript obviously shows the results presented in Munné et al. (2020), however without the PGT-A data. Both studies refer to the same registered study of [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03426007) (Identifier: NCT03426007), and both publications included 134 COS cycles with subsequent uterine lavage from 81 subjects with successful embryo collection in 42% of the cycles (56/134 cycles). There is a clear discrepancy between, on the one hand, the Munné et al. (2020) study and, on the other, a further statement by the authors: The Munné study states that the study volunteers were recruited from the hospital’s oocyte donor list and inseminated with fresh anonymous donor sperm ($n = 28$) and cryopreserved donor sperm ($n = 106$), whereas in a further statement, the authors claimed that “out of the total of 134 lavages, 11/134 (8.2%) were infertile couples attempting to conceive for more than 1 year” and that: “male partners of these women were of good general health and had normal semen parameters” [1]. There are some additional

discrepancies between both papers and the registered study which are summarized in the supplementary Table S1.

It is unclear why Munné et al. (2020) do not once make reference to Nadal et al. (2019). Both papers do not only include the same cohort of patients (see Table 1 each of the two papers), similar images showing the lavage system (Fig. 1, each of both publications), catheter positioning (Figs. 2 and 3, respectively). The results of embryo recovery after uterine lavage are identical, too [1, 11]. Do the additionally included PGT-A data in the Munné paper justify the publication of the results in a high-ranking ESHRE journal? The publication of previous data might fail to conform to the ethics of scientific publishing, i.e., the policies and procedures of Human Reproduction lay down that “The submission of a paper implies that it reports on unpublished work and that it is not currently under consideration for publication elsewhere. If previously published tables, illustrations or text are to be included, then this should be clearly indicated in the manuscript and the copyright holder’s permission must be obtained” [29].

In addition, with a view to the registration of clinical trials, the journal policies state that “Human Reproduction supports the International Committee of Medical Journal Editors (ICMJE) in calling for the registration of all randomized controlled trials (RCTs) at their inception, before the first patient is enrolled in the study” [29]. However, according to the trial, the first patient was included in August or September 2017, while the study was registered in February 2018 (see supplementary Table S1).

Benefit-risk assessment

It is beyond doubt that a favourable benefit-risk ratio should not be transgressed. It is also true, however, that it is anything but easy to produce an objective definition of benefit or risk. Therefore, this task is the responsibility of the referring review board. It is thus considered mandatory to weigh the risks against the benefits of the Munné study while taking into account both the interests of patients and society.

First of all, a hormonal substitution protocol to induce the growth of multiple mature follicles in the ovaries followed by insemination is always associated with the risk of multiple pregnancies. This might not play a role in the early stage of pregnancy—apart from the risk of late OHSS, which is more likely to be severe in multiple pregnancies [30]. However, if a subject becomes pregnant in spite of lavage and subsequently refuses to undergo an abortion, these risks (including the patient’s death) could manifest themselves.

Secondly, in regard to the clinical relevance, the scientific insights postulated by Munné and colleagues that in vivo and in vitro euploidy rates were comparable are not at all surprising. Although the editorial of Lambalk et al. (2020) postulates the scientific merits of the Mexican study as being significant,

they do not reveal any reasons for their suggestions [3]. All the theories which suppose that using higher FSH doses for stimulation may induce meiotic errors and subsequent aneuploidies are currently not only of an unconfirmed nature, but have rather been refuted by recent publications [31]. Also with regard to mitotic errors—resulting in chromosomal mosaicism—it becomes apparent that mitotic errors are not the exception but the norm in early embryogenesis [32, 33]. Additionally, all theories that mitotic errors might be linked to advanced age or culture conditions during IVF seem more reminiscent of hampering “rescue attempts” for the PGT-A technique which is brilliant in theory but does not work in practice. This has been documented by several publications, disclosing all shortcomings of PGT-A [34, 35]. In fact, there is not one meta-analysis seeing evidence of any beneficial effect of PGT-A [36]. Even the last larger RCT on PGT-A published (also first-authored by Santiago Munné) revealed that PGT-A did not improve overall pregnancy outcomes in women even when excluding mosaic embryos for transfer and choosing embryo transfer as a denominator instead of intention to treat [37]. Referring to the long-standing discussion whether the trophoctoderm (TE) represents the chromosomal constitution of the inner cell mass (ICM) of an embryo, a recent animal study from the group of Zernicka-Goetz indicates that aneuploidy cells undergo different fates. While the ICM aneuploidy cells underwent apoptosis, the counterparts within the TE underwent cell cycle arrest [38]. Worthy of note in this respect is the outstanding paper of Gleicher and colleagues, showing that a 6-cell biopsy is mathematically unable to predict the true chromosomal constitution of an embryo at blastocyst stage [39]. Viewed in this light, the PGT-A results of the Mexican study are in fact of a limited value. Therefore, we strongly doubt that the scientific results gained are for the greater good of society.

Eventually, there are two further issues arising from the papers of Nadal et al. (2019) and Munné et al. (2020). These issues are based on our assumption that the two publications are aimed at generating a low cost oocyte donation program. It has to be mentioned that the average costs of egg donation is quite high (~€25,000 whilst in Mexico, the cost for treatment with egg donation is still around ~€4000) [40]. It is entirely reasonable to believe that the fulfilment of a woman's desire for children must not be the exclusive privilege of richer patients. On the other hand, this must not be done at the expense of third parties.

According to the Munné study, pregnancy occurred in 13.6% of all patients despite uterine lavage. Not at least, in regard to the high incidences, not only the psychological situation of the donors should be considered. The risks of physical side effects (severe) associated with uterine curettage and methotrexate administration have to be taken into account, ranging ranges from Asherman syndrome and subsequent infertility after improper curettage to severe vaginal bleeding

and failed abortion with embryo malformations. We should therefore categorically exclude such a precarious technique from the range of procedures available for assisted reproduction.

According to some publications, certain aspects of in vitro culture of embryos such as prolonged culture, type and composition of culture medium are assumed to have adverse effects on the IVF-children's health [41, 42]. Therefore, one argument in favour of uterine lavage could be the avoidance of in vitro embryo culture. However, the evidence for claimed correlations between IVF and health risks affecting the offspring is weak. Moreover, it remains unclear whether certain elevated risks—if they exist at all—are either correlated to IVF culture or to certain aspects of infertility. The latter was substantiated by recent register studies [43, 44]. Additionally, we must point out that, according to the details provided by the study of Munné and colleagues, cleavage-stage embryos were kept in culture in order to develop into blastocysts. In fact, 24 out of 96 blastocysts have been obtained by additional embryo cultivation. This has already been pointed out in a previous opinion paper [4]. It is also important to note that uterine lavage does not mitigate the risks associated with ovarian stimulation.

At least, it is also worthwhile mentioning that the uterine lavage system is obviously not FDA approved since it is designed for investigational use only [25]. This is particularly important for the assessment of potential health risks to patients.

Wider-reaching implications of the Munné study on human research and reproductive medicine

To estimate the potential impact the Munné paper may have on reproductive medicine, it is crucial to take a look from a different perspective, namely that of stem cell (SC) research. SC research is rapidly growing in Mexico, and so was the number of SC therapies during the last years. In 2015, the first human embryonic stem cell (ESC) line derived from cells of Mexican origin was created using embryos discarded by a fertility clinic. While SC therapies are booming, there is a lack of relevant legislation and regulation in Mexico [45].

So, it comes with no surprise that the world's first 3-parent-IVF child by spindle transfer was conceived in Mexico. The absence of both specific regulations with respect to the use of assisted reproductive techniques and a competent authority at Federal level encouraged this approach that is highly experimental to say the least. However, as a consequence, Mexico initiated attempts to regulate assisted reproduction, including sperm banks, egg donation and surrogacy in a very restrictive manner—and this is in turn having detrimental effects on SC research [46].

The consequences of the uterine lavage study and similar “excesses” could be fatal for reproductive medicine, not only in Mexico, but also at an international level. Since the emergence of ART in 1979, reproductive medicine was pilloried, leading to increased calls for stronger and more restrictive laws. Such experiments will inevitably lead to more repressive legal regulations in the field of ART—doing a disservice to infertile couples seeking medical help.

Another critical point associated with the experimental application of uterine lavage is the risk of blurring of the boundaries between oocyte donation and surrogacy. A woman stimulated and inseminated with donor semen, and whose embryos are then recovered by uterine lavage in order to transfer them into the womb of the egg recipient is *per se* not an oocyte donor anymore. Whatever one’s views about oocyte donation and surrogacy, there is, of course, a difference with respect to the physiological and psychological burden placed on the women.

Conclusions

As practitioners in the field of IVF, we believe that this study as well as its publication should receive the utmost critical attention and give rise to a fundamental discussion on the ethical dimensions of clinical research in the field of human reproduction. Oron mentioned the four medical-ethical principles of medical ethics [2]. This runs together codes of clinical ethics (Hippocratic Oath) and research ethics (Declaration of Helsinki and Nuremberg Code) [47, 48]. The latter one is a set of 10 principles devised to protect human beings from unethical research (see below). These principles were compiled as a direct consequence of the darkest hour in the history of mankind when physicians performed atrocious experiments on prisoners during World War II. In the “Doctors’ Trial”, 23 physicians were indicted for crimes against humanity [49]. It should be remembered that several gynaecologists, including Carl Clauberg, were involved in these Nazi crimes, performing insemination and sterilization experiments on concentration camp prisoners [50]. Although the Nuremberg Code is not legally binding in any country, it is one of the most important documents on the ethics of clinical research and has markedly influenced the principles of Good Clinical Practice [51], the Declaration of Helsinki [47], the Belmont Report [52] (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979), the International Ethical Guidelines for Health-related Research Involving Humans by the CIOMS [20] and many others. There is no option for research beyond this “ethical firewall against inhumanity” if you do not want to deny these fundamental principles.

These principles are:

1. Voluntary consent is essential.
2. The results of any experiment must be for the greater good of society.
3. Human experiments should be based on previous animal experimentation.
4. Experiments should be conducted by avoiding physical/mental suffering and injury.
5. No experiments should be conducted if it is believed to cause death/disability.
6. The risks should never exceed the benefits.
7. Adequate facilities should be used to protect subjects.
8. Experiments should be conducted only by qualified scientists.
9. Subjects should be able to end their participation at any time.
10. The scientist in charge must be prepared to terminate the experiment when injury, disability or death is likely to occur.

In our view, at least three of the ten principles of the Nuremberg code could be infringed by the study. First, the greater good of this study is highly disputable, as the risks obviously outweigh the benefit.

Secondly, the scientific merits are not obvious and it is unclear whether the study results are of greater good of society.

Third, it is questionable whether the study is in compliance with voluntary participation as discussed above. This aspect is undoubtedly linked with a proper patient consent and whether participants could choose to discontinue participation in the study and opt against pregnancy termination. As an additional point, we believe, although the authors emphasized the shortcomings of animal experiments, that many aspects could and should have been investigated in animal models to gain more insight before performing tests on human embryos. There are currently almost no data on chromosomal mosaicism in the primate or bovine model systems neither from *in vitro* generated embryos nor from natural conceptions. From our point of view, these findings could give valid information whether or not chromosomal mosaicism is a natural phenomenon.

There is no doubt that human research is an integral part of science and some research questions can only be answered by human studies. Nevertheless, these studies must be performed under strict ethical rules and clear legal regulations. Thereby, it should not be possible for scientists as well as for pharmaceutical companies to “select the appropriate legal landscape” for their specific research interests. We, as scientists, embryologists and medical doctors have an ethical and clinical responsibility with respect to our work, today more than ever.

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