RBMO

COMMENTARY

Learning from incidents in medically assisted reproduction: the Notify Library as a learning tool

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ABSTRACT

Biovigilance is the systematic monitoring of serious adverse reactions and events (SARE) that ensures the quality and safety of tissues and cells for human application in medically assisted reproduction (MAR). The Notify Library is an open access database launched by the World Health Organization and supported by the Italian National Transplant Centre (CNT) that has collected information on documented adverse occurrences in transplantation, transfusion and MAR. It is not a SARE register, but rather a collection of SARE types identified primarily by review of published articles and case reports from national or regional vigilance programmes. The Notify Library includes many well-documented records of adverse occurrences in MAR treatment, representing a useful tool for MAR operators in the evaluation of the risks associated with the clinical application of reproductive tissues and cells. It is updated with new records when a new type of incident is reported for the first time. All incident types described might have teaching value during the risk management carried out by a MAR centre. Sharing lessons learned from these incidents represents an important didactic opportunity that can help MAR centres to improve their processes and to achieve higher standards of quality and safety.

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INTRODUCTION

Medically assisted reproduction (MAR) refers to reproduction brought about through various strategies aimed at treating different forms of fertility impairment and infertility. These strategies include ovulation induction, ovarian stimulation, ovulation triggering, assisted reproductive technology (ART) procedures, and intrauterine, intracervical and intravaginal insemination with the semen of husband, partner or donor (*Zegers-Hochschild et al., 2017*).

Although MAR helps millions of people to achieve a pregnancy, it is associated with potential health risks for both the mother, e.g. risks associated with a multiple-birth pregnancy or from ovarian hyperstimulation syndrome (OHSS), and the infant, e.g. preterm birth and low birthweight (*Sunderam et al., 2019*). Moreover, fertility treatments are complex as each MAR cycle consists of several steps that, if incorrectly executed, could result in the loss of a chance of a viable pregnancy (*Farquhar and Marjoribanks, 2018*).

Gametes, embryos and gonadal tissues can be included under the term 'medical products of human origin' (MPHO) intended for clinical use. This term covers a wide range of substances of human origin, from cells and tissues to blood and organs, all donated by a human with the goal to benefit others, with shared exposure to risks through breaches of ethical, legal and safety standards, leading to a potential undesirable outcome (*Strong, 2018*).

Biovigilance is a set of surveillance procedures covering the entire process chain from the donation of organs, tissues and cells to the follow-up of recipients, living donors and offspring. It aims to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of MPHO and to prevent their occurrence or recurrence. Biovigilance in MAR involves vigilance in terms of tissues and cells, but also pharmacovigilance, e.g. OHSS, vigilance of medical devices, e.g. media, incubators, aspiration needles, and potential adverse outcomes on the donor, the recipient and the offspring (*European Directorate for the Quality of Medicines & HealthCare of the Council of Europe, 2019*).

European Union legislation requires member states to have in place a system for the reporting of serious adverse reactions and events (SARE) relating to the application of the aforementioned substances of human origin (European Union Directives 2004/23/EC and 2006/86/EC) (*European Commission, 2004*; *European Commission 2006*). In recognizing the need for the surveillance of such occurrences, in May 2010, the World Health Assembly, called the World Health Organization (WHO) to facilitate inter-alia member states' access to 'appropriate information on the donation, processing and transplantation of human cells, tissues and organs, as well as assisted reproductive technologies, including data on severe adverse events and reactions'. In 2011, in accordance with these resolutions, WHO, the Italian National Transplant Centre (CNT) and the EU-funded Project SOHO V&S (Vigilance and Surveillance of Substances of Human Origin, 2009–2012 - Grant Agreement 20091110) collaborated to organize a major global initiative that aimed at raising the profile of MPHO vigilance and surveillance called Notify Project (*Petrisli et al., 2021*).

NOTIFY LIBRARY

The Notify Library is the major output of the Notify project. It consists of an open access database of published didactic cases of adverse occurrences arising with the donation, processing or clinical application of MPHO. The Notify Library aims to be comprehensive, describing all adverse occurrence types that might have teaching value and assist in the estimation of risk (*Fehily et al., 2013*).

The work was initially conducted on a WIKI site where over 100 experts from across the WHO regions (regulators, clinicians, professional society representatives, scientists) gathered didactic information on documented types of adverse outcomes in transplantation and assisted reproduction (*Notify Group, 2011*). Subsequently, several international experts were asked to collaborate in editorial working groups to allow the uploading of the information to a new relational database hosted by the Notify Library website (https://www.notifylibrary.org). Between 2015 up to 31 December 2020, 84,125 users visited this website.

The Notify Library is not a vigilance reporting programme, but a continuously updated compendium of information identified primarily by review of published articles in the scientific literature as well as case reports from national or regional vigilance programmes defined as grey literature (*Strong, 2018*). In fact, regulatory or professional vigilance programme reports represent a unique source of cases with teaching value that are usually not published in the medical literature. To promote the inclusion and dissemination of the information described in these cases, a work package of the European Union co-funded Joint Action VISTART (*Vigilance and Inspection for the Safety of Transfusion Assisted Reproduction and Transplantation, 2015–2019, VISTART Joint Action, 2017*) focused on providing instructions to facilitate European member states' competent authorities in the selection and analysis of cases from their annual vigilance reports with didactic value for submission to the Notify Library.

In the Notify Library, each record describes a specific type of adverse occurrence in one type of MPHO and can be linked to one or multiple different references. The selection and review of references for inclusion is carried out by international experts who collaborate in five topic-specific editorial groups (infections, malignancy, process-related incidents, clinical complications and living donor reactions). Expert analysis focuses on how the adverse occurrence was recognized and how it was associated with the donation, processing or clinical application of the MPHO. The records are enhanced didactically with expert comments, highlighting key informative points arising from the cases. To facilitate a structured database search, all records have been classified according to a taxonomy of two main groups, the adverse occurrence types and the MPHO types, both further subdivided according to standardized definitions and terminology (*Whitaker et al., 2017*). Types of adverse occurrence include harm to a recipient, harm to a donor and harm to a fetus or offspring and risk of harm. In particular, the 'risk of harm' group is further categorized into five subgroups: donor disease without transmission, loss of a suitable MPHO, unsuitable MPHO released for clinical use - no harm, mix-up and other adverse occurrences. For MAR field, the Notify Library collects occurrences involving the partner donation and non-partner

donation as well, using the term 'donor' in both cases.

At present, the Notify Library contains 1718 records, 73 of which are related to reproductive tissues and cells and are linked to a total of 54 source references (*Petrisli et al., 2021*).

NOTIFY LIBRARY AND MEDICALLY ASSISTED REPRODUCTION

The Notify Library is of interest to all stakeholders in MAR. Many examples of serious adverse occurrences regarding reproductive cells and tissues have been reported. In the Notify Library, the occurrence of adverse effects related to MAR mainly concern the loss of a suitable MPHO (32/73), e.g. relating to inappropriate storage, packaging or shipment conditions, processing error, damage during procurement (TABLE 1). Moreover, the 'Reproductive Cells' section contains an overview of incidents involving spermatozoa, oocytes and embryos, and most cases described concern spermatozoa and embryos, 40% (29/73) and 36% (26/73), respectively (TABLE 1). Incidents associated with oocytes represent 21% (15/73) of the cases in the Notify Library.

The most important cases of risk of harm in MAR procedures involve the misidentification of a patient, gamete or embryo that could lead to dramatic consequences. High workload, lack of communication between team members, distraction, time pressure and complex procedures are the risk factors that could result in misidentification or a witnessing error, also called 'mix-up'. Although the frequency is low, mix-up cases have been described worldwide. In the section 'risk of harm' in the Notify Library, the section 'mix-up' is available for both embryos and gametes. Reported cases of gamete and embryo misidentifications are sourced from National Registries such as the TRIP annual report from the Netherlands.

In the Notify Library, cases of damage to gametes, embryos, and ovarian tissues caused by inappropriate freezing technique, failure of gas supply or equipment failure have been reported (*Agence de la biomédecine (ABM) 2009*; *TRIP Foundation (Transfusion Reactions In Patients) 2009*).

Other adverse events derive from preventable human actions, e.g. overlooking an embryo when carrying out assessments, dropping a dish, incorrect labelling, improper pipetting technique, unusually poor thawing, and inadvertent discard of sample.

The Notify Library has described many medical complications related to oocyte retrieval procedure, include OHSS, ovarian torsion, thromboembolism, bleeding and urinary tract injury (*ESHRE Working Group on Ultrasound in ART; D'Angelo et al., 2019*). In addition, viral or bacterial infections could potentially result in a reduction of the effectiveness, efficiency and, especially, the safety of MAR treatments. Infections can occur from vaginal puncture, with contamination from the vaginal bacteria into the intra-peritoneal space; from contamination in embryo culture medium; or through the introduction of contaminants into the uterine cavity during the procedure. Infections of women after insemination caused by pathogens present in ejaculated semen have also been demonstrated. The Notify Library includes some examples in this category.

Another adverse reaction in donor cycles could be the birth of a newborn who has inherited a genetic disease that was undisclosed or undetected in the gamete donor. Offspring affected by a genetic

TABLE 1 REPORTS IN THE NOTIFY LIBRARY OF MEDICALLY ASSISTED REPRODUCTION BY ADVERSE OCCURRENCE AND BY MPHO TYPE (AS OF END OCTOBER 2020)

	Spermatozoa	Oocyte	Embryo	Ovarian tissue	Combined	Total
Harm to a recipient						
Infections	5	1	3			9
Detrimental immunization	1	1				2
Harm to a fetus or offspring						
Genetic	11		2		1	14
Harm to a donor						
OHSS		2				2
Infections		2				2
Insertion of needle		1				1
Risk of harm						
Loss of highly matched or autologous MPHO	5	8	17	2		32
Unsuitable MPHO released for clinical use	4		1			5
Mix-up	3		3			6
Total	29	15	26	2	1	73

Source: Notify Library.

MPHO, medical products of human origin; OHSS, ovarian hyperstimulation syndrome.

disease after preimplantation genetic testing for aneuploidy represents another type of adverse reaction. The causes of misdiagnosis include human errors, such as mismatch of embryo diagnosis with the consequent transfer of the 'affected' embryo, instead of a healthy one.

STRENGTHS AND LIMITATIONS OF THE NOTIFY LIBRARY

The Notify Library does not only provide a register of adverse outcomes but describes all incident types that might have teaching value. It assists in the estimation of the risk, reporting also estimation frequency of each type of event, when available, the time of detection and the root cause of each case. For this reason, the major strength of the Notify Library is its usefulness as a tool when conducting risk management in the MAR field. This tool may increase awareness of risks and inform on the implementation of effective approaches necessary to decrease complication occurrence and errors in the MAR centres.

On the other hand, the Notify Library presents some limitations. First, although analytics data showed a steady increase in access to the Notify Library, it is challenging to establish a direct correlation between library visits and improved clinical practices and outcomes. Second, it relies on the free and voluntary contribution of biovigilance experts from around the world. The bibliography and information are not guaranteed to be complete or to be fully up to date at any moment. Moreover, it may seem difficult to add new insights to the Notify Library because most adverse reactions and events are known to those working in the MAR field. Cases, however, are considered having instructive value when they describe in detail unusual signs or symptoms in the recipient or donor, as well as uncommon or unexpected causes or errors, an unforeseen level of severity or new corrective actions taken. Also, cases, that did not cause harm but had a significant potential to do so, can represent informative records in the Notify Library. Therefore, clinical and laboratory professionals are encouraged to search and review its content, propose information that might still be missing and support this didactic initiative. In this context, to promote the use of the Notify Library, international and national congresses, scientific meetings and dedicated vigilance workshops have been organized, generating an increased number of library visits worldwide. For instance, the Human Fertilisation and Embryology Authority has encouraged clinic staff to access the Notify Library, promoting it at various conferences and annual meetings and via their in-house publications.

In conclusion, despite the improvements provided by the European Directives in terms of safety, unfortunately, some incidents in the MAR field have been detected and reported to regulatory or professional vigilance programmes. For this reason, MAR centres must implement risk analysis and risk minimization strategies, mostly through a proactive approach. In view of this, the Notify Library helps to identify what could go wrong in the process and in promoting learning from the experience of others. Indeed, it is wise to use mistakes to promote learning, but it is wiser and safer to learn from the mistakes of others.

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