OCATT TISSUE AND CELL VIGILANCE REGISTRY 2014 REPORT

Generalitat de Catalunya
Departament de Salut

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1 INTRODUCTION

Tissue and cell transplantation benefits thousands of recipients every year in Catalonia. However it is not free of risks. One of the risks that should be borne in mind is the possibility that a tissue or cell could transmit a disease to the recipient or the results of the transplant might not be as expected.

BACKGROUND

In 2004, Directive 2004/23/EC of the European Parliament and Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells was published. Article 11 of this directive establishes the procedure for the reports of adverse events and reactions in this field.

In 2006, the community regulation was transposed to domestic Spanish law with the publication of Royal Decree 1301/2006. In Catalonia, for the purposes of implementing the regulation, in 2008 a manual for the report of adverse events and reactions was produced and professionals were provided with registries to report any adverse events or reactions occurring from the tissue or cell donation to transplantation.

OBJECTIVE

The main objective of vigilance is to improve quality and safety in tissue and cell donation and transplantation by reporting incidents, sharing information, learning from errors, improving practices and implementing measures that can prevent possible adverse events and reactions. In addition, the vigilance system monitors reports and follows up on the corrective and preventative actions that are implemented.

The main objective of the Tissue and Cell Vigilance Report is to inform all tissue and cell professionals in Catalonia of the reports received during 2014. This year, the report is structured differently from previous years, as it aims to provide the data in a more comprehensible format to enable quantification of the risks detected in these procedures in our field.

- **Action 1:** we have added the number of distributed tissues and the centres where they were obtained, processed and transplanted.
- **Action 2:** we have added data on the reports in assisted human reproduction.

However, this year it will be extremely difficult to draw conclusions from the available data, as the liability of the tissue and/or cell could not be clarified in all reports and there are still a large number of professionals who do not take part.

At the OCATT Tissue and Cell Vigilance Registry, we would like to thank the professionals for their continuing efforts, as without their involvement this report would not have been possible. We would also like to encourage all professionals to continue reporting all the events they detect related to obtaining tissues and cells, work at the bank, transplantation and patient follow-up.

2 DEFINITIONS

- **Incident (non-severe adverse event):** any unfavourable, unexpected and unplanned event or circumstance related to obtaining, assessing, processing and distributing organs, tissues and cells and which could lead to disease transmission affecting their safety, quality or traceability. Incidents are non-severe adverse events.

- **Severe adverse event:** any unfavourable, unexpected and unplanned event or circumstance related to obtaining, assessing, processing and distributing organs, tissues and cells and which could lead to disease transmission, death or life-threatening situations for the patient, cause disability or trigger or lengthen hospitalisation or the disease.

- **Severe adverse reaction:** any unexpected response in the donor or recipient, including transmissible disease, associated with obtaining or applying tissues or cells in humans, which proves fatal or potentially fatal, causes disability, or triggers or lengthens hospitalisation or the disease.

- **Non-reproductive tissues and cells:** eye tissue (ET), sclera (S), amniotic membrane (AM), musculoskeletal tissue (MSK), tendon and cartilage (TC), cardiovascular tissue (CV), skin tissue (S), haematopoietic stem cells (BM/PB) and umbilical cord blood (UCB).

- **Health alert:** situation of a suspected severe health risk associated with tissues or cells that have been distributed to different countries.

- **Reproductive tissues and cells:** semen, oocytes, ovarian tissue, testicular tissue and embryos.

- **Assisted human reproduction (AHR):** the set of techniques used to give people with fertility problems the chance of having children.

3 TISSUE DISTRIBUTION ACTIVITY IN CATALONIA AND AUTHORISED CENTRES

Table 1 shows the tissue distribution activity in 2014. Over 10,000 non-reproductive tissues and cells were distributed, although data have been available for reproductive tissues since 2015.

Table 2 shows the number of centres authorised for the donation, processing and clinical use of non-reproductive tissues and cells.

Table 1. Non-reproductive tissue and cell distribution activity

Non-reproductive tissues and cells	Units distributed 2014
Eye tissue	1,135
Amniotic membrane	158
Sclera	155
Musculoskeletal tissue (including tendons and cartilage)	7,808
Cardiovascular tissue	210
Skin tissue	25
Haematopoietic stem cells	407
Umbilical cord blood	129
Total units distributed	**10,027**

Table 2. Authorised centres

Tissues and cells	Collection centres	Tissue bank	Transplantations
Eye tissue	24	2	51
Amniotic membrane	23	2	51
Sclera	24	2	51
Musculoskeletal tissue	23	1	78
Cardiovascular tissue	23	1	8
Skin tissue	23	1	2
Stem cells (BM/PB)	9	2	10
Umbilical cord blood	42	1	5

4 VIGILANCE REPORT

The vigilance report includes 101 reports received in 2014: 33 reports related to non-reproductive tissues, 67 to reproductive tissues and 1 health alert.

4.1 REPORTS RELATED TO NON-REPRODUCTIVE TISSUES

The 33 reports related to non-reproductive tissues were classified by degree of severity as:

- **12** incidents
- **13** severe adverse events
- **8** severe adverse reactions

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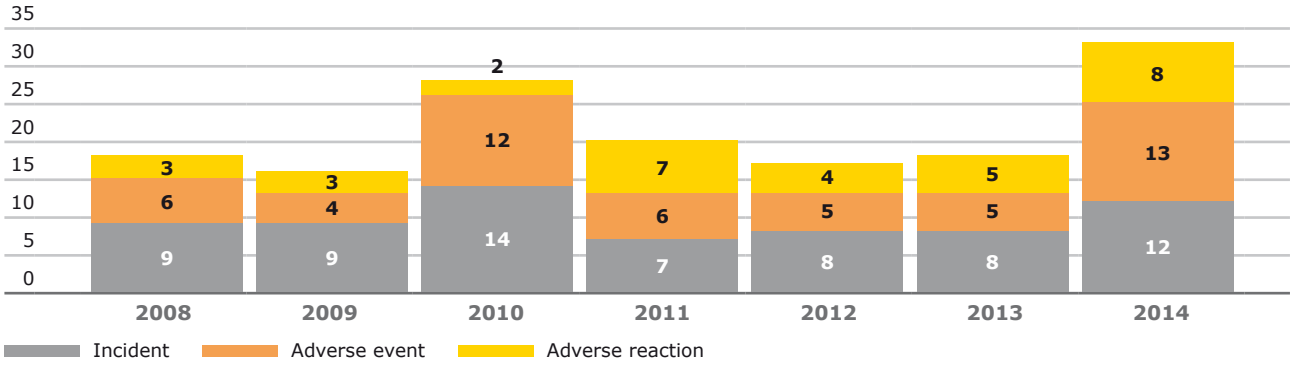
Reports classified as severe:
64 %

Compared to previous years, there were more reports of all types: incidents, severe adverse reactions and severe adverse events. However, this is still considered a period of low report, which should be assessed and analysed so that the necessary corrective measures can be adopted. Graph 1 shows changes in the number of different types of reports in recent years.

Graph 1. Yearly change in the number of reports received



4.1.1 INCIDENTS (NON-SEVERE ADVERSE EVENTS) RELATED TO NON-REPRODUCTIVE TISSUES

There were 12 reports classified as incidents, which mainly (11 cases) occurred with umbilical cord blood (UCB), with one case during transport of blood cells for research. They are classified here by type of incident:

Table 3. Incidents related to non-reproductive tissues

Type	Type of error	Number	Case summary
UCB	Typing	2	– Unit sent to another autonomous community. On reception, discrepancies in the HLA-C antigen were reported. The information was revised in the source bank and the error was confirmed. – The unit showed differences in the HLA antigen (source bank and receiving bank). Transplantation was possible after the discrepancies were checked.
UCB	Serology	2	– *Treponema pallidum*-positive antibodies in the mother and the UCB unit: rejected.
UCB	Culture	2	– Positive for *E. faecalis* and plasmacoagulase-positive *Staphylococcus*: gonnococcus-positive PCR in the donor was rejected and the unit was eliminated.
UCB	Quality	1	– During the assay for estimated proliferation in the patient, the unit showed low viability and poor recovery. Rejected.
UCB	Transport and traceability	3	– A dry shipper was sent to another country with a device marking the tilt of the transportation container. Presence of the device was not mentioned, but the gradient data were correct and the UCB was transplanted. – Labelling error for a unit processed at another bank; transplantation was permitted once the error was resolved. – Error in outer labelling of the unit; transplantation was permitted once required measures were taken.
Eye	Transport and traceability	1	– Eye balls (ET) from five donors, for research use, were lost in transport and appeared intact in the containers after three weeks.
UCB	Others	1	– Postpartum bleeding after donation, causing rejection of the unit obtained.

4.1.2. SEVERE ADVERSE EVENTS RELATED TO NON-REPRODUCTIVE TISSUES

There were 13 reports classified as severe adverse events affecting the following tissues, as shown in graph 2: 5 eye tissue, 2 haematopoietic stem cell, 2 umbilical cord blood, 2 musculoskeletal tissue and 2 cases involving multi-tissue donors.

The severe adverse events were found to occur mostly in eye tissue (ET), followed by haematopoietic stem cells (HSC), umbilical cord blood (UCB), musculoskeletal tissue (MSK) and finally those affecting multi-tissue donors.

The tissues that had no associated severe adverse event reports were: amniotic membrane (AM), sclera (S), cartilage (TC) and cardiovascular tissue (CV).

Graph 2. Types of tissue with severe adverse events in 2014

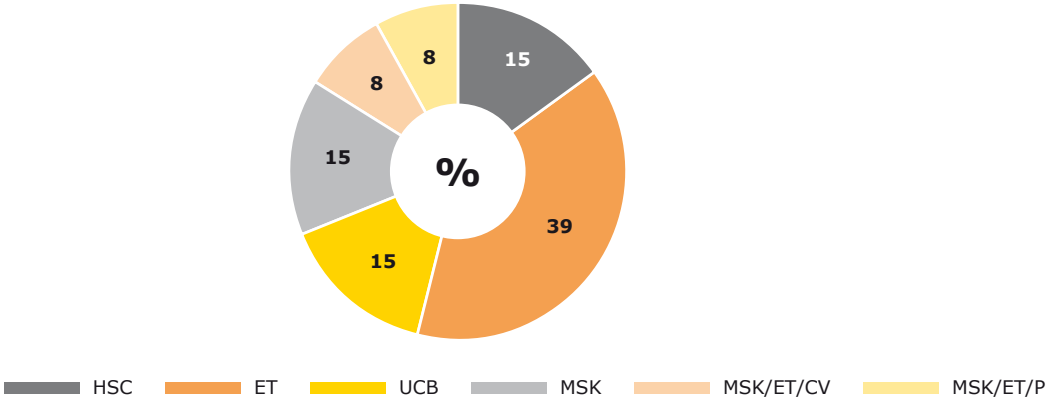


Table 4. Severe adverse events related to non-reproductive tissues

Type	Type of error	Number	Case summary
MSK/ET/CV	Serology	1	– Weak positive for HBV DNA in multiple organ and tissue donor (transplanted corneas). The immunological status of the organ and two cornea recipients was determined: none showed seroconversion. The remaining tissues from this donor were rejected.
ET	Culture	6	– Sclera culture positive for gram-negative bacteria *Acinetobacter Iwoffii* supernatant (after corneal transplantation). Contralateral cornea culture negative. The two recipients progressed favourably. – Sclera culture positive for *Aureobasidium pullulans* (after corneal transplantation), a germ with very low pathogenicity potential: considered contamination. The patient progressed satisfactorily. – Cultivated cornea transport medium positive, processed by the bank. In the transplantation centre, the culture was positive for a yeast (*Rhodotorula*). The cornea recipient progressed favourably. – Sclera culture positive for *Candida glabrata* (after corneal transplantation). The donor's BAS culture was positive for the same germ. The contralateral sclera culture was negative. **Recommendation:** isolate the extraction field of the corneal tissue. Transport medium positive for the gram-negative bacteria *Burkhoderia cepacia* in four cultivated corneas (from the same batch). The result came from the cornea transport liquid after transplantation. The recipients progressed favourably in all cases.
UCB	Culture	1	– Culture after transplantation of two umbilical cord blood units was positive for gram-positive bacilli. In one case, the recipient was already receiving antibiotic therapy and therapy was started in the second case.
PB/BM	Culture	1	– Microbiological control of the cryopreserved aliquot of HSC obtained by apheresis, already transplanted, was positive for coagulase-negative *Staphylococcus*. However, the microbiological control of the transplanted product was negative.

Type	Type of error	Number	Case summary
MSK	Quality	1	– Lack of osteoinductivity in three batches of DBM Putty, made by the supplier. Thirteen of the tissues had already been transplanted. The follow-up of the recipients was satisfactory in all cases, although the quality of the product was decreased due to lack of osteoinductivity. The results of the operations were satisfactory.
MSK	Quality	1	– A cranial vault was received for autologous use at the transplantation centre: it had not been processed and showed defects in labelling and identification. The tissue was considered unsuitable for transplantation until it had been processed and its suitability for transplantation confirmed. **Recommendation:** stress the importance of following the recommendations of the Musculoskeletal Tissue Advisory Committee with regard to sending cranial vaults to the tissue bank for processing before transplantation.
PB/BM	Others	1	– The patient's peripheral accesses for obtaining HSC for an autologous transplantation were insufficient. The procedure was delayed. **Recommendation:** review HSC donor acceptance protocols.
MSK/ET/P	Others	1	– In one multiple organ and tissue donor, the definitive hystological study showed the presence of changes compatible with viral lymphocytic meningoencephalitis when the organs and corneas had already been transplanted. The existence of lymphoproliferative disorders was ruled out. The recipients progressed favourably. Ongoing follow-up with no additional therapy was recommended. The remaining tissues were rejected.

4.1.3 SEVERE ADVERSE REACTIONS RELATED TO NON-REPRODUCTIVE TISSUE DONATION OR TRANSPLANTATION

Eight reports of adverse reactions in donors and recipients were received. Of these reactions, two were considered non-severe. See table 5:

Table 5. Non-severe adverse reactions: probable liability

Type	Type of reaction	Number	Case summary
Autologous PB	Infection	2	Two patients presented with fever during the apheresis process to obtain HSC and both cases were treated with antibiotics.

Of the six reports classified as severe adverse reactions, five (three from HSC donors and two patients who underwent apheresis for an autologous transplantation) affected HSC donors and one affected a heart valve recipient. They are described in the following table:

– **5** adverse reactions in HSC donors
– **1** adverse reaction in a valve tissue recipient

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Severe adverse reactions reported:
83 % of HSC donors

Table 6. Severe adverse reactions related to non-reproductive tissue donation or transplantation

Tissue or cell	Type of reaction	Number	Case summary
CV	Tissue loss	1	On the day of the transplantation, the bank could not find the valve in the nitrogen tank. The recipient underwent an alternative plasty that progressed correctly, but this is considered a severe adverse reaction as the type of surgery had to be changed (first indication was a heart valve).
Allogenic HSC	Related hypocalcaemia	1	During the apheresis process, generalised paraesthesia, dizziness and pains appeared. Recovery after adequate treatment.
Autologous HSC		1	During the apheresis process, paraesthesia, vomiting and epigastric pain appeared.
Allogenic HSC	Toxicity	1	Healthy donor who developed generalised pain and major headache during the apheresis process. She was treated in the emergency department and received pharmacological therapy.
Allogenic HSC	Others	1	Prolonged extravasation in the lymphapheresis process due to accidental disconnection of the collecting equipment (Hb from 13 to 10 mg/dL). The donor completely recovered after appropriate pharmacological treatment and a period of relative rest.
Autologous HSC	Others	1	Patient with history of severe cardiovascular problems developed HTN and precordial pain while donating peripheral blood, likely due to stress. The patient recovered fully.

4.2 REPORTS RELATED TO REPRODUCTIVE TISSUES

In 2014, for the second time, the OCATT received reports of adverse reactions and events from centres authorised to perform assisted human reproduction. In total, 67 reports were received, which were classified as: severe adverse events (6), adverse reactions (24) and others (37).

4.2.1 SEVERE ADVERSE EVENTS RELATED TO REPRODUCTIVE TISSUES

With regard to reproductive tissues, the severe adverse events are classified by type of tissue involved (semen, oocytes and embryos) and by the adverse event detected. There were a total of six reports of severe adverse events related to reproductive tissues. These are listed in table 7:

Table 7. Severe adverse events related to reproductive tissues

Type	Type of error	Number	Case summary
Oocytes	Incorrect identification	1	– When the straws were withdrawn from an oocyte donor for devitrification, one was identified with a different name. Although they were all in the same clearly identified visotube, not all the names were the same. They were all rejected and a search was made for cryopreserved oocytes from another donor.
Embryos	Incorrectly distributed tissue	1	– Only one embryo was transferred instead of the planned two, due to surgeon error in reading the protocol.
Oocytes	Accidental loss	1	– Loss of four oocytes due to a slip with a culture dish stained with mineral oil. Seven oocytes were recovered from the same dish and six embryos were then vitrified.
Embryos	Accidental loss	3	– Loss of 2 out of 11 embryos from a patient when the culture dish fell. The patient became pregnant after the transfer of two embryos. – The Pasteur pipette broke when vitrifying the last remaining embryo from a patient. Two embryos were transferred but without pregnancy. – Loss of 3 embryos from a patient out of the available 10, as the slide hit the microscope. Two embryos were transferred and the other one was cryopreserved. The patient became pregnant.

4.2.2 SEVERE ADVERSE REACTIONS RELATED TO REPRODUCTIVE TISSUE DONATION OR TRANSPLANTATION

A total of 24 reports of severe adverse reactions were received, as listed in table 8:

Table 8. Severe adverse reactions related to reproductive tissue donation or transplantation

Cells	Type of reaction	Number	Case summary
Oocytes	Ovarian hyperstimulation syndrome	15	Haemoperitoneum after follicular puncture which was resolved after laparoscopy and hospital admission.
Semen	Infection	2	Two semen donors with samples contaminated by *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. The samples were rejected in both cases.
Oocytes/ semen	Genetic alterations	7	Confirmed genetic transmissions that produced one miscarriage, three still births and three newborns with genetic alterations (congenital ichthyosis, Pierre Robin syndrome, and Gaucher disease).

4.2.3 OTHER

Initially, 37 reports were received as adverse reactions, but were then classified in the 'Other' section for different reasons:

- Seventeen reports were analysed and the genetic alterations in the newborn or foetus were found to be *de novo*. Therefore, the genetic alterations were not due to the tissue or cell (liability rejected).
- In 15 genetic alterations, which were reported and studied after AHR techniques, no relationship between the reproductive material and the genetic alteration could be found (insufficient data to establish liability). In these cases, there were five voluntary abortions.
- There were five ectopic pregnancies that required salpingectomy. They were reported, although the problems with the fertility treatment were not caused by the genetic material used.

According to the European Commission, a severe adverse reaction must be counted for each individual who has an adverse reaction after donation or application of human cells or tissues, where the 'severe' reaction could be related to the safety or quality of the donated or applied tissue or cells.

4.3 HEALTH ALERT

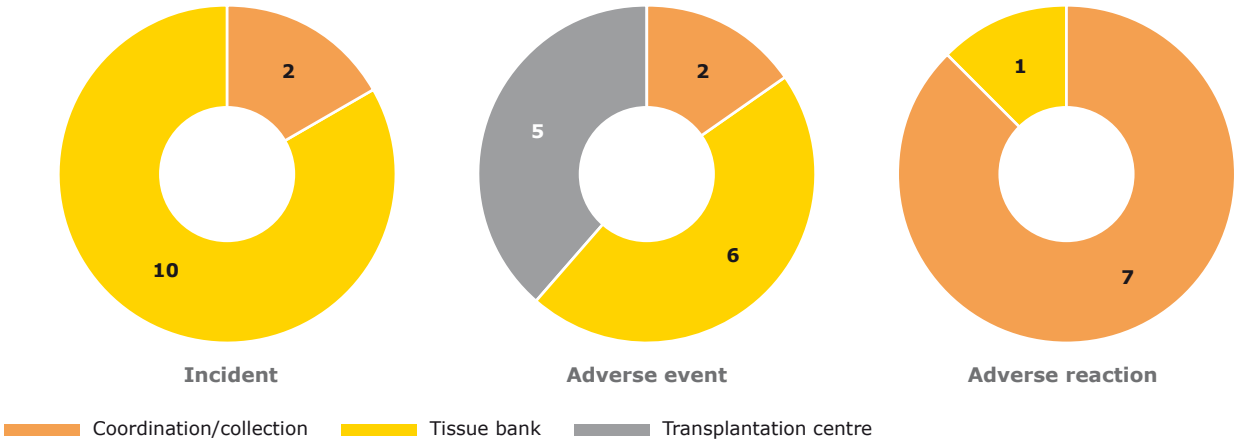
In 2014 there was only one health alert. This was due to the detection of problems related to the temperature control on some freezer models used for the gradual freezing of tissues and cells. The alert was sent by mail to all tissue and cell banks (including the centres who freeze reproductive cells), while there was no response from the centres who used some of the models affected by the alert.

5 WHO REPORTS AND WHERE THE REPORTS OCCUR

There were 33 reports related to non-reproductive tissues. Most of them were made by the tissue bank (17 out of 33, representing 52 % of reports); next were the transplantation coordinators (11 out of 33, representing 33 %) and finally, transplant surgeons (5 out 33, representing 15 %).

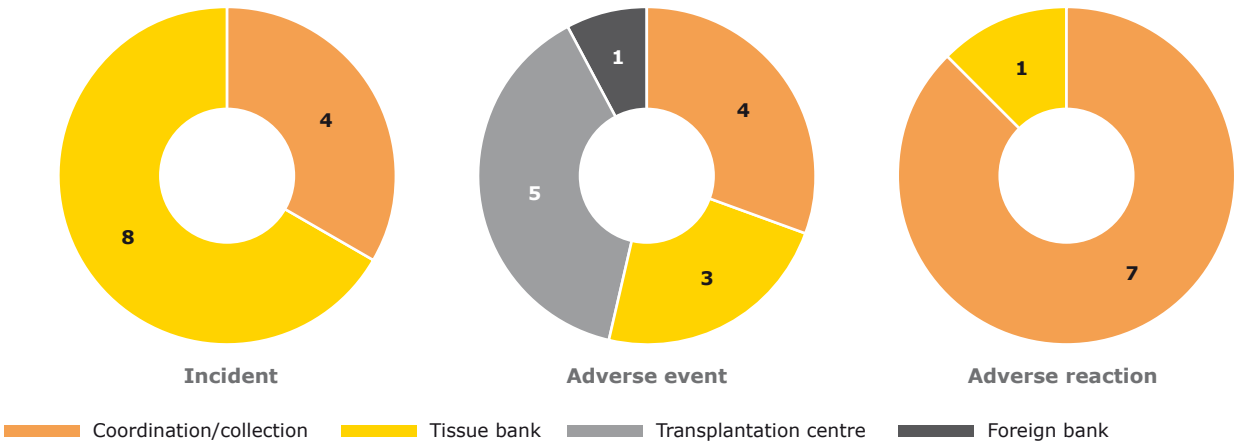
With regard to reproductive tissues, all reports came from an assisted human reproduction clinic authorised to obtain gametes and process and apply assisted human reproduction techniques. In all cases, the reports were made by the centre's physicians.

Graph 3. Level at which incidents, severe adverse events and severe adverse reactions were detected



Graph 4 shows the level of the donation and transplantation process at which the adverse event or reaction occurred. The graph shows that the level where the event occurs is not always the level that detects it. This fact is very important as it shows everyone involved in the process must be ready to send reports, even though the error occurs in another part of the process.

Graph 4. Level at which incidents, severe adverse events and severe adverse reactions occurred



6 THE VIGILANCE NETWORK: CENTRES AND MANAGERS

The network consists of all the centres in Catalonia authorised by the Ministry of Health Directorate-general for Professional Management and Health Regulation. The activities for which they can be authorised are: obtaining tissues and cells; processing, storage and distribution by the tissue banks; and transplantation of tissues and cells.

Each centre with Ministry of Health authorisation for donation, processing or transplantation of tissues, cells and assisted human reproduction must have a vigilance responsible. This responsible must be appointed by the centre director. His or her function is to report to the OCATT Vigilance Registry all incidents and adverse events and reactions that occur throughout the process, from donation to transplantation of tissues and cells. The manager must also gather the information required to conduct the investigation.

7 OCATT VIGILANCE REGISTRY

The OCATT Vigilance Registry was created and started working in June 2008. The reports sent to the registry are analysed in conjunction with the centres involved, who assess the importance of the events, the application of corrective measures and follow-up of cases, when required.

The report is made possible thanks to the collaboration of the centres and professionals who make the reports and their dedication in detecting cases and assessing their severity and liability, and possible impact of each report.

8 SUMMARY

– In 2014, over 10,000 tissues were distributed in Catalonia.

– A total of **101 reports** were received by the tissue and cell vigilance registry.

– The number of reports received in relation to non-reproductive tissues was notably higher than in previous years (from 18 to 33 reports). These were classified as: 12 incidents, 13 adverse events and 8 adverse reactions.

– Thus, of the reports received in relation to non-reproductive tissues, 64 % were classified as severe and affected all types of tissues except amniotic membrane, sclera and skin.

– The most frequent adverse event reported were related to culture, transportation, serology and quality of the tissue or cell.

– The severe adverse reactions in relation to non-reproductive tissues mostly occurred in the peripheral blood donation process.

– The number of reports related to reproductive tissues was 67.

- These were classified as: 6 severe adverse events, 24 severe adverse reactions and 37 others.

– The most frequent adverse events relating to reproductive tissues were: accidental loss of reproductive material (4), incorrect identification (1) and incorrect distribution (1).

– Of the 24 severe adverse reactions relating to reproductive tissues, most (15) were due to ovarian hyperstimulation syndrome, 7 due to confirmed transmission of genetic alterations and 2 due to infections.

– Most reports received in 2014 arrived from a tissue bank or an assisted human reproduction clinic.

– Although up, the number of reports remained low. Future actions should be considered to ensure the involvement of all professionals and the management of incidents to benefit recipients.

– It would be highly beneficial to set up a vigilance advisory committee for the different tissues and cells in order to share reports, research and learn from errors together and generate recommendations agreed on by the OCATT advisory committees with regard to the different types of tissue.

9 RECOMMENDATIONS AND ACTIONS

– The importance of following the recommendations of the Musculoskeletal Tissue Advisory Committee with regard to sending cranial vaults to the tissue bank for processing before transplantation should be reiterated.

– A review is recommended of the HSC donor acceptance protocols.

– A review is recommended of the corneal tissue extraction isolation protocols when a multi-organ donor is involved in order to avoid cross contamination.

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