

ADVERSE EFFECTS OF GONADOTROPINS USED IN INFERTILITY TREATMENT

Bogdan Ioan Vintilă¹, Anca Butucă², Claudiu Morgovan³,
Andreea Loredana Vonica⁴, Luca Liviu Rus⁵, Andrei Cătălin Muntean⁶,
Anca Maria Juncan⁷, Felicia Gabriela Gligor⁸

Abstract:

Introduction: Infertility represents a problem for more and more couples all over the world, including in Romania. Thus, more and more women need to resort to drugs to treat infertility, treatments which are not without adverse reactions (Boivin et al., 2007). Modern therapy brings significant benefits in the treatment of infertility. Despite all the benefits, the controlled ovarian stimulation treatment does not lack the possibility of adverse reactions to the administered drugs.

Objectives: The aim of this study was to determine the potential adverse reactions experienced by patients during the treatment with gonadotropins followed by assisted conception

Methods: A study was done based on a questionnaire which included the adverse reactions comprised in the SmPCs (Summaries of Product Characteristics) of the original drugs, and also based on the adverse reactions frequently reported in clinical studies. The questionnaire was distributed in the online environment, from May 2018 to July 2018, in Romania, to patients to whom at least one of the analysed gonadotropins (corifollitropin alpha, follitropin alpha, follitropin beta, follitropin alpha/follitropin beta, menotropin, urofollitropin) was administered during the controlled ovarian stimulation treatment, in the routine practice of assisted human reproduction technology.

Results: The results show that a total number of 319 events suspected of being adverse reactions was reported, grouped on the highest MedDRA level, SOC (system – organ- class), with an average of 8.18 adverse reactions (AR)/patient.

Conclusions: The results of the study demonstrate the fact the disorders appeared after drug administration in the controlled ovarian stimulation treatment in the context of the routine practice of assisted human reproduction technology, were considered adverse reactions by the patients.

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Introduction

Infertility represents a problem for more and more couples all over the world, including in Romania. Thus, more and more women need to resort to drugs to treat infertility, treatments which are not without adverse reactions (Boivin et al., 2007).

A study done by the World Health Organization (WHO) in 190 countries between 1990 and 2000 showed that 48.5 million couples from all over the world have had this health problem called infertility.

In 2001, WHO declared that infertility should be considered a world problem, and eight years later it was officially declared “a disease of the reproductive system defined by the incapacity to obtain a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse”, in the fertile phase of the menstrual cycle (Hoffman et al., 2017).

During a meeting of assisted reproduction specialists attended by gynaecologists specialized in in-vitro fertilization, statistical elements regarding fertility in Romania were discussed. According to the National Statistics Institute, fertility in Romania has started to have an accentuated descendent trend. At the moment, the rate is 1.57 children to a woman (in 2015), classifying Romania among the European countries with the lowest fertility values. It is assumed that, with this rhythm, in the year 2050 our country will reach a population of just 16.3 million inhabitants, as opposed to approximately the current 19.8 million (National Institute of Statistics, 2018).

¹Faculty of Medicine, “Lucian Blaga” University of Sibiu, Sibiu, Romania, bogdan.vintila91@gmail.com

²Faculty of Medicine, “Lucian Blaga” University of Sibiu, Sibiu, Romania, anca.butuca@ulbsibiu.ro

³Faculty of Medicine, “Lucian Blaga” University of Sibiu, Sibiu, Romania, claudiu.morgovan@yahoo.com

⁴Faculty of Medicine, “Lucian Blaga” University of Sibiu, Sibiu, Romania, loredana.vonica@ulbsibiu.ro

⁵Faculty of Medicine, “Lucian Blaga” University of Sibiu, Sibiu, Romania, liviu.rus@ulbsibiu.ro

⁶Faculty of Medicine, “Lucian Blaga” University of Sibiu, Sibiu, Romania, andreicatalin.muntean@ulbsibiu.ro

⁷Faculty of Medicine, “Lucian Blaga” University of Sibiu, Sibiu, Romania, ancamaria.juncan@ulbsibiu.ro

⁸Faculty of Medicine, “Lucian Blaga” University of Sibiu, Sibiu, Romania, felicia.gligor@ulbsibiu.ro

all authors have equally contributed to this work

Modern therapy has brought significant benefits in the treatment of infertility, but despite all the benefits, the controlled ovarian stimulation treatment does not lack the possibility of adverse reactions to the administered drugs.

Monitoring drug safety, also known as pharmacovigilance, is essential to detecting, evaluating, understanding and preventing adverse reactions and other problems regarding drugs (Butuca et al., 2018). Because adverse reactions cannot be completely detected during the process of development and pre-marketing, nowadays a special emphasis is placed on post-marketing monitoring, which allows for a better pharmacotoxicological evaluation (Butuca et al., 2018; Cuc et al., 2015).

The ovarian hyperstimulation syndrome (OHSS) remains a major complication both for the patients and for the doctor using human assisted reproduction techniques (HART), because of the morbidity and possible mortality (Kasum et al., 2011, Kol, 2003). The incidence of OHSS, clinically significant, is of 2 to 3%. However, up to 30% of the patients treated with HART can develop milder forms. The syndrome affects approximately 6020 patients a year in the United States and Europe, and the risk of dying is estimated 1:450,000 to 1:500,000 (Alper et al., 2009; Brinsden et al., 1995; Nevesa et al., 2013).

Data and methodology

In this study the interviewing method based on a questionnaire was used. Thus, a questionnaire was developed based on the adverse reactions referred to in the Summary of Product Characteristics (SmPC) of the original drugs, and also based on the adverse reactions frequently reported in clinical studies. To analyse this information, observational, comparative and interpretative methods were used. A language appropriate for the patients was used in writing this questionnaire. The questionnaire was given to patients in Romania to whom at least one of the analysed gonadotropins (corifollitropin alpha, follitropin alpha, follitropin beta, follitropin alpha/follitropin beta, menotropin, urofollitropin) was administered.

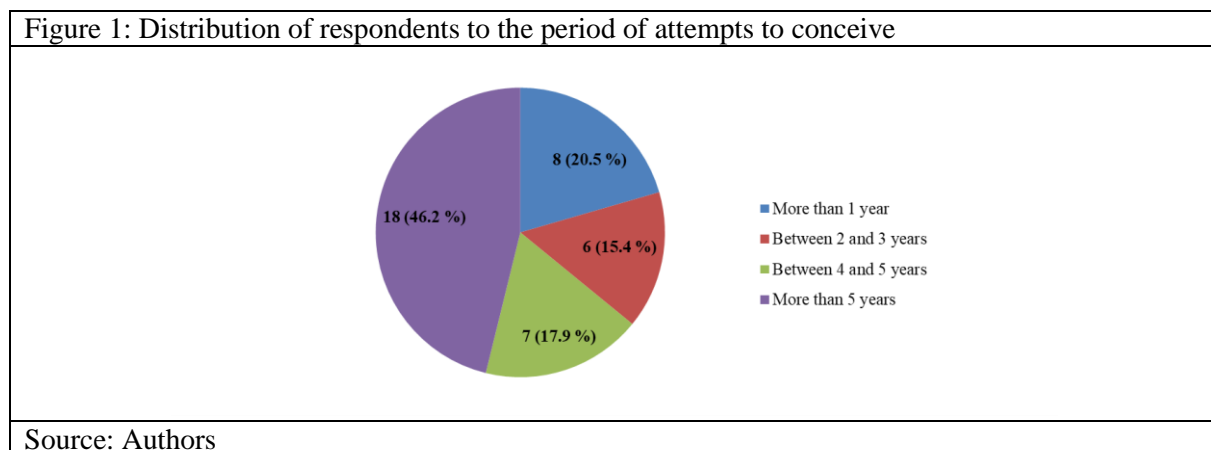
The questionnaire was distributed in the online environment, from May 2018 to July 2018, in administered during the controlled ovarian stimulation treatment, in the routine practice of assisted human reproduction technology. The questionnaire was distributed to three groups of persons who were dealing with an infertility problem and who have undergone a gonadotropin treatment for this. In the introduction the aim of the research was presented, and the participants were assured about the confidentiality of their responses provided. The time estimated for completing the questionnaire was 5-7 minutes.

The questionnaire is made up of 20 items, out of which 11 had closed answer variants, which offered a single variable, and 9 items had open answer variants, ensuring freedom of expression without the risk of suggestibility. The closed answer variants for some questions were written according to the Likert scale (1-5). The answers to the open questions were afterwards coded in order to allow for a quantitative interpretation of the results and to be entered into the calculation software.

The quantitative interpretation of the data was done in the data management software “Microsoft Excel”, by using the functions: Count If, Sum If, VLOOKUP and inserting graphs.

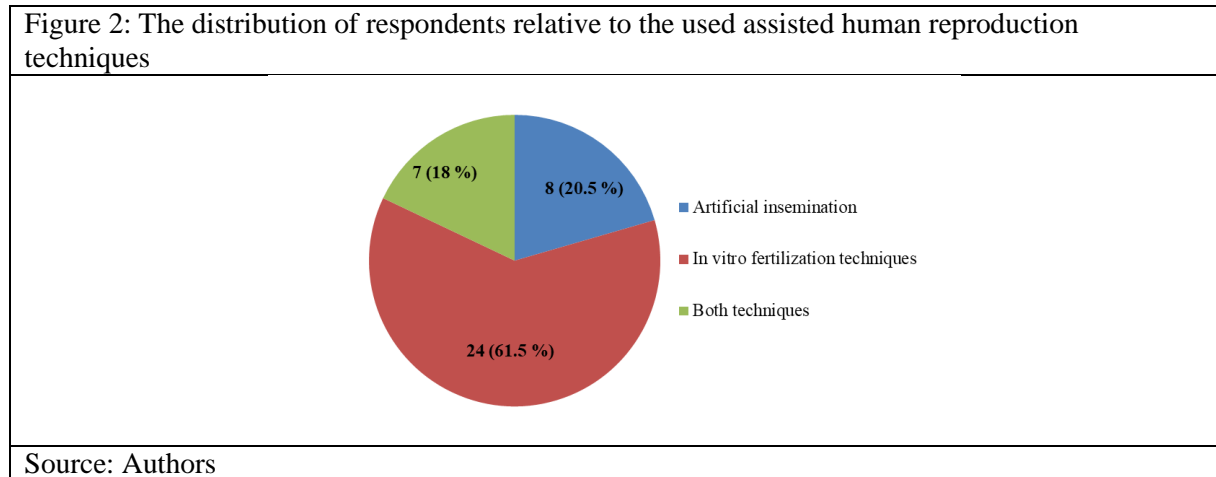
Results and discussion

After the questionnaire was release, 39 persons in total responded, all of them women between the ages of 27 and 45 years old. The answers to the questions are presented as follows.



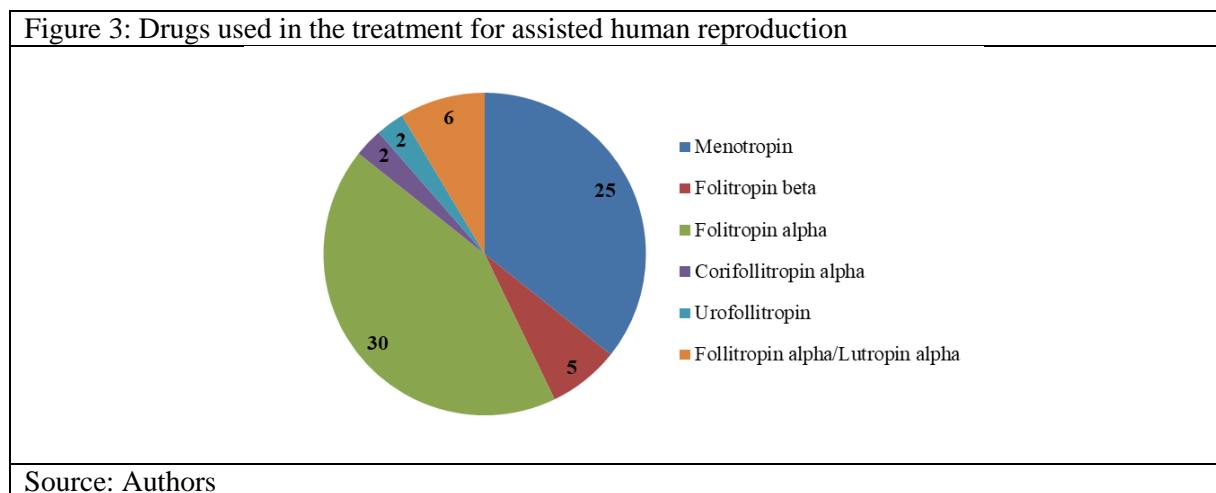
Of the 39 persons that filled out the questionnaire (Figure 1), 18 (46.2%) declared that the prior period of time dedicated to trying to conceive (naturally and through assisted human reproduction techniques) was more than 5 years, while 8 (20.5%) answered that the period was more than 1 year, but less than 2 years.

Figure 2 presents the distribution of respondents relative to the tried assisted human reproduction techniques, which shows that 7 (18%) of all the patients that filled out the questionnaire have tried to conceive both through in vitro fertilization techniques, and through artificial insemination, and 24 (61.5%) have only used in vitro fertilization techniques.



Regarding the drugs used in the treatment for assisted human reproduction, shown in Figure 3, out of the total number of persons who filled out the questionnaire, 30 (76.92%) have said that they used follitropin alpha, alone or combined with other gonadotropins, and 25 (64.1%) were administered menotropin, both alone and combined with other drugs.

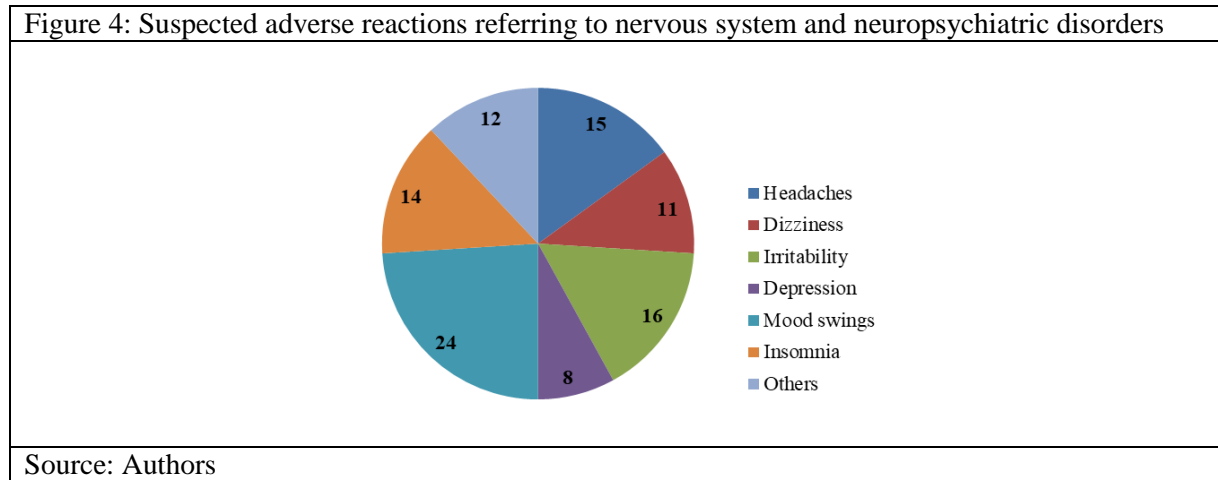
Out of the total number of 70 administered drugs, 16 (53.3%) patients used a combination of follitropin alpha and menotropin. Other drugs used in combination with follitropin alpha in the treatment were: menotropin + follitropin beta + follitropin alpha - 1 patient (3.33%); menotropin + corifollitropin alpha + follitropin alpha - 1 patient (3.33%). Out of all the drugs administered, menotropin represents 35.71%, meaning a number of 25 patients. Out of all the patients that used this drug, menotropin was used as monotherapy for one patient (4%) and in combination for 24 patients (96%); for example, menotropin + urofollitropin – 1 patient (4%); menotropin + corifollitropin alpha – 1 patient (4%); menotropin+ follitropin beta – 1 patient (4%).



By analysing the answers of patients referring to nervous system or neuropsychiatric disorders suspected of being an adverse reaction to the gonadotropin treatment, Figure 4 shows that 24 (61.5%) of the total number of respondents say that they suffered from mood swings, followed by 16 (41%) who suffered from irritability, 15 (38.5%) from headaches, 14 (35.9%) from insomnia and 8 (20.5%) from depression.

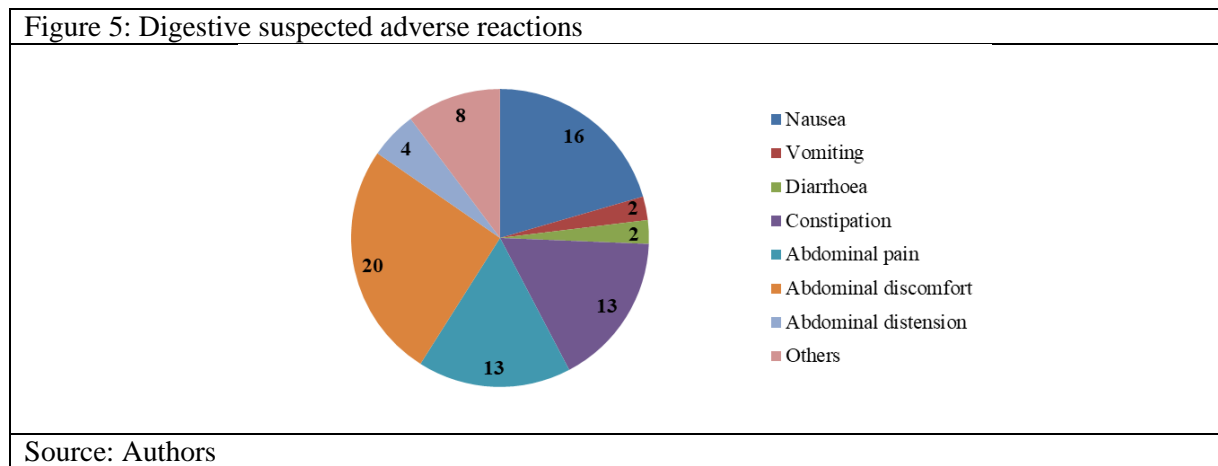
It must be mentioned that each patient has reported more than one adverse reaction, 100 events being signalled in total, in average 2.56 events per patient.

From the structure of the suspected adverse reactions to the gonadotropin treatment referring to the central nervous system and to neuropsychiatric disorders, it appears that the most frequent reported adverse reactions are mood swings, representing 24 (24%) of all of the events signalled in the questionnaire, followed by irritability, representing 16 (16%) events.



Of the gastrointestinal disorders shown in Figure 5, the most frequent adverse reactions reported by the patients in the questionnaire were abdominal discomfort in 20 (51.3%) cases, nausea in 16 (41%) cases and abdominal pain in 13 (33.3%) cases.

A total, 78 suspected digestive adverse reactions were signalled, abdominal discomfort being present in 20 (25.64%) patients, followed by nausea in 16 (20.5%) patients, and by constipation and abdominal pain in 13 (16.66%) patients each.

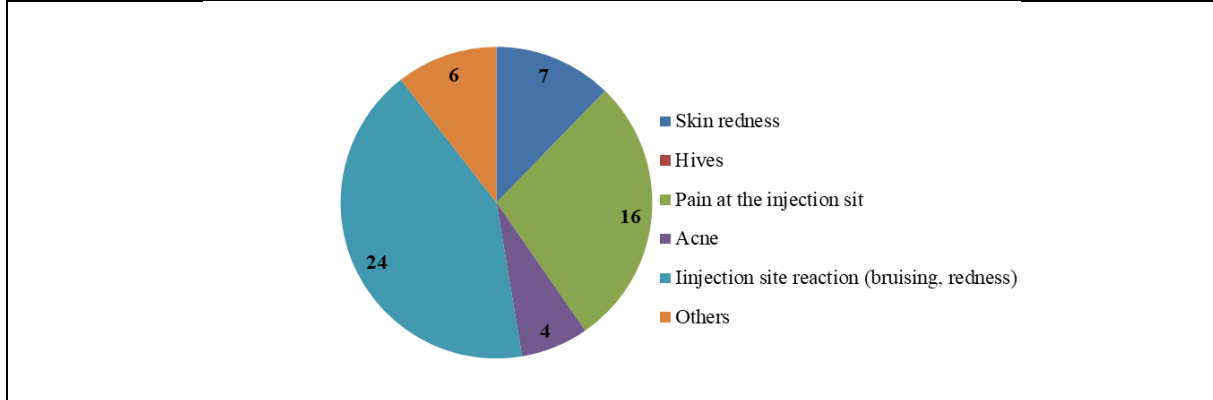


The adverse events suspected at locally or in the skin are shown in Figure 6, where 24 (61.5%) patients accused reactions at the site of injection, in the form of redness or bruising, and 16 (41%) patients accused pain at the injection site. 4 (10.25%) patients said that they developed acne, while 7 (17.95%) patients noticed redness of the skin.

A total of 57 adverse events were reported, on average 1.46 per patient, out of which 24 (42%) represent injection site reactions and 16 (28%) injection site pain.

One of the disorders of the genital apparatus or breast that was considered a possible adverse reaction by the patients, shown in Figure 7, is pelvic pain (in the ovaries), presented by 25 (64.1%) of all respondents. Breast tenderness is another symptom accused by the 17 (43.6%) patients. 9 (23.1%) patients suffered from ovarian hyperstimulation (fever, fluid in the abdomen, pelvic pain), which is considered by specialists as one of the most serious adverse reactions of the treatment for ovarian stimulation, requiring hospital stay.

Figure 6: Suspected adverse reactions reported locally or in the skin



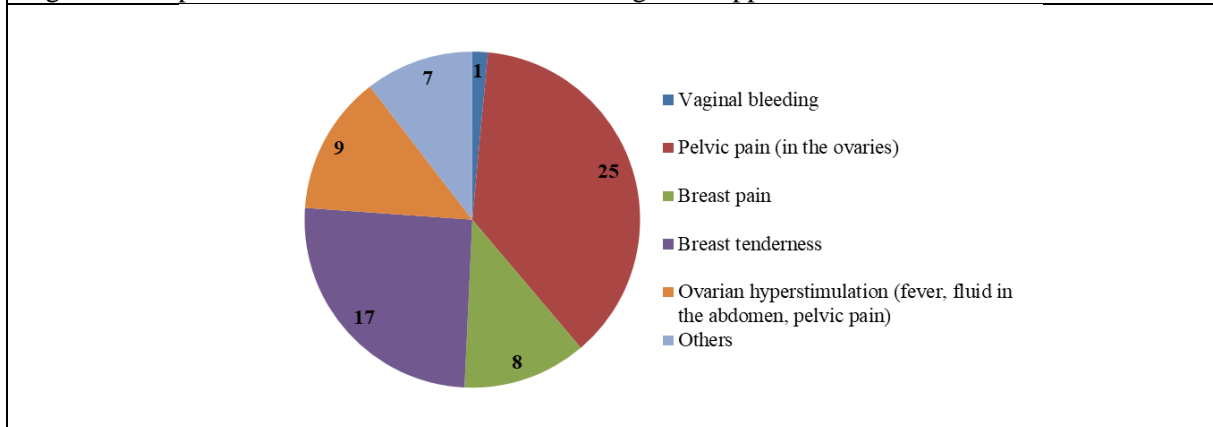
Source: Authors

There were 67 suspected adverse reactions reported in the genital apparatus or breast, on average 1.72 per patient. Of these, 25 (37.3%) represented pelvic pain, 17 (25.37%) breast tenderness, and 9 (13.43%) ovarian hyperstimulation syndrome.

In the questions regarding the severity of adverse reactions and regarding which of the adverse reactions presented in the questionnaire, grouped in the SOC level (system-organ-class) bothered them the most, some of the answers given by patients were: pain caused by ovarian hyperstimulation with all its symptoms, weight pain, abdominal distension, headaches, depression, irritability and injection site pain. During the treatment these symptoms severely bothered 6 (15.4%) patients, while 20 (51.3%) patients said that some of these reactions were present, but were of a moderate severity.

In 27 (69.2%) cases these reactions disappeared or improved after finalizing the treatment, 21 (53.8%) patients discussed these adverse reactions with their doctor, and 9 (23.1%) needed treatment.

Figure 7: Suspected adverse reactions related to the genital apparatus or breast



Source: Authors

According to literature, ovarian hyperstimulation syndrome (OHS) remains a major complication both for patients and for the doctor using assisted human reproduction techniques (HART), because of the morbidity and possible mortality (Kasum et al., 2011, Nevesa et al., 2013). The incidence of OHS, clinically significant, is of 2 to 3%. However, up to 30% of the patients treated with HART can develop milder forms (Alper et al., 2009, Brinsden et al., 1995, Nevesa et al., 2013).

To the question “Do you read the information leaflets of the drugs that you use?”, 28 (71.8%) patients answered that they always do.

At the end of the questionnaire the patients were asked to evaluate how much their health preoccupies them, on a Likert scale from 1-5 (where 1 signifies not at all and 5 signifies a lot). 30 (76.9%) patients declared that their health preoccupies them a lot.

In Table 1 are represented the 24 musculoskeletal system and connective tissue symptoms that were reported, out of which 11 (45.83%) represent muscle pain.

System	Arthralgia (joint pain)	Muscular pain	Bone pain	Total
Musculoskeletal and connective tissue	9	11	4	24

Source: Authors

The general adverse events reported (71 events) frequently refer to tiredness - 22 (30.98%) and weight gain - 18 (25.35%).

System	Tiredness	Loss of appetite	Weight gain	Increase of appetite	Hot flushes	Others	Total
General disorders	22	6	18	6	10	9	71

Source: Authors

Conclusions

A total number of 319 events suspected to be adverse reactions were reported, grouped on the highest MedDRA level, SOC (system-organ-class), on average 8.18 AR/patient.

The most frequently reported were nervous system and neuropsychiatric symptoms – 100 (2.56; 31.35%), followed by general disorders - 71 (1.82; 22.57%) and genital apparatus or breast 67 (1.71; 21%).

In the SOC the most frequent of all of the reactions reported in the questionnaire (accused by over 50% of the women) and the most severe were the ones regarding the disorders at the genital apparatus or breast: pelvic pain - 25; 64.1%), followed by reactions at the site of injection and mood swings -24 (61.53%) cases each, nausea- 20 (51.28%) and tiredness - 22 (56.41%). These adverse reactions are frequent and well known in the gonadotropins class.

The results of the study demonstrate the fact that the disorders that appeared after administering these drugs in the controlled ovarian stimulation treatment, in the context of the routine practice of assisted human reproduction technology, were considered adverse reactions by the patients.

Prescribing drugs is a very important responsibility for doctors, but reporting suspected adverse reactions and taking part in their monitoring systems must also be promoted as a fundamental professional task.

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