



In Vitro Fertilization Revealing Intracranial Meningioma: Case Report and Online Enquiry Among French ART Specialists: Who and When to Screen?

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Abstract

Background: We report the first case of meningioma dramatically revealed during endometriosis indicated IVF treatment. This 5 cm large meningioma in a 32 years old woman provoked general convulsive crisis, and a brachial deficit member. Any hormonal treatment or pregnancies are now contraindicated to this young woman. This case aware our ART team, and raises many questions. Do ART specialists have to establish a meningioma screening strategy before ART? Who to screen? If a meningioma is diagnosed, do we have to prohibit ART to the patient?

The National Agency of Medication Security (ANSM) published in 2021 use restrictions and screening recommendations concerning Chlormadinone Acetate (ACM) and Normegestrol (NMG), after those of 2018 concerning the use of cyproterone acetate (PCA), faced with the risk of developing meningiomas. Due to the pathologies responsible for their infertility, patients treated with ART are likely to have been exposed to these molecules.

Objective: To assess the practices of ART professionals in patients who have been treated with ACM/NMG/PCA and to identify a preventive course of action before ART in these patients at risk of developing a meningioma.

Material and Methods: We sent a multiple-choice inquiry by email, via our professional associations, to French ART specialists. 123 anonymous responses were analyzed; 39% worked in a private hospital, 37% in a public hospital, and 23.6% in a city office; 80% had more than 5 years of senior ART activity.

Results: 61% did not check in patient inquiry a prior use of PCA, ACM or NMG before ART. After previous exposure to these molecules, 26% were unaware of the exposure time after which a brain MRI should be offered. 25% retained the indication for imaging after 24 months of treatment, compared to 21.9% after 12 months and 10% after 6 months.

Concerning the minimum gap between the end of these treatments and an ART: 84.1% estimated it at 6 months, 8.4% at 12 months and 6% between 18 and 24 months.

Conclusions: Faced with the heterogeneity of the results, we propose to systematically search during medical inquiry:

- Prior exposure to ACM, PCA or NMG. If exposure is confirmed for more than 2 years: Realize a brain MRI to rule out a contraindication to ART.
- A minimum period of 6 months between the end of the treatment and the start of ART should be observed.
- A history of meningioma under progestogen. If necessary, we recommend performing an MRI and discussing the file in a multidisciplinary consultation meeting before authorizing any treatment in ART.

Case Presentation

A 32 years old patient was referred on February 2020, for 3 years of primary infertility, with severe painful endometriosis and post chemotherapy premature ovarian failure. Indeed, she was treated for a sacrococcygeal teratoma when she was one-and-a-half-year-old. She underwent then a curative surgery and a chemotherapy protocol treatment with Cyclophosphamide (cumulative dose

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Received Date: 18 Jan 2022

Accepted Date: 09 Feb 2022

Published Date: 23 Feb 2022

Citation:

Khaïat A. *In Vitro* Fertilization Revealing Intracranial Meningioma: Case Report and Online Enquiry Among French ART Specialists: Who and When to Screen?. *Ann Infert Rep Endocrin.* 2022, 5(1): 1027.

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4660 mg/m²).

At the beginning of our care, endometriosis was multiple on MRI, 3 cm torus nodule, rectovaginal 1 cm nodule, fundus posterior adenomyosis. Hysterosalpingography showed tubal retention.

The ovarian reserve assessment retrieved Anti-Mullerian Hormone (AMH) levels at 0.24 ng/ml, and an antral follicles count was 6 in total.

Our Team indicated IVF treatment after 6 months of medical therapy with Dienogest (2 mg/J), tobacco quitting, and anti-inflammatory diet endometriosis.

This successfully diminished pain, she started a long agonist protocol on September 2020.

Despite 2 mg of Nafareline during 15 days, the sonography control showed a spontaneous ovulation.

We decided to trigger the ovulation with injection of Human Chorionadotrophine (HCG) alpha 250 mg, and to go on with Nafareline until next period.

On October 10th, two hours after HCG, she felt paresthesia in upper and lower limbs. She went to nearby emergency room, the emergency physician suspected only secondary effect of the treatment, and did not suggest a cerebral imagery.

On October 30th, after her menses, she started her IVF ovarian stimulation with 300 UI of Menotropine per day. After 9 days of stimulation, estradiol level was 558 pg/ml, the ultrasound showed two mature follicles, and ovulation was triggered with HCG alpha 250 mg.

Before the HCG triggering shot, the patient had a generalized convulsive crisis. A Magnetic Resonance Imaging (MRI) realized in emergency diagnosed a voluminous 5 cm large subcortical meningioma.

Anticonvulsive treatment with levetiracetam in addition to corticosteroid was established.

The neurologist contraindicated both a spontaneous and induced pregnancy for this patient.

Four months later, the patient had new convulsive crisis despite her treatment, and she kept a brachial deficit member since her first crisis.

This dramatic case has been a real awareness for all our medical team, and has raised many questions.

Do we have to establish a meningioma screening strategy before ART? Who to screen?

If a meningioma is diagnosed, do we have to prohibit ART to the patient?

Introduction

Meningiomas represent 1/3 of central nervous system tumors. The incidence is age dependent, and median age is 66 years old [1]. Studies showed that risk of meningioma which need surgery is three times higher in women between 35 to 44 years than to 24 to 34 years [2,3]. About 80% of meningioma express progesterone receptor and about 40% express estrogen receptor. The risk of developing a meningioma under hormonal treatment exist and is both dose and time dependent [4]. Their growth is slow, estimated about 1 mm by month, but is very influenced by estrogen and progesterone hormones [5].

In France, in 2018, the ANSM (National Agency of medication security) published recommendations to prevent development of meningiomas in women previously treated with Cyproteron acetate [3].

A risk of meningioma is published for women previously treated with chlormadinone and normegestrol too, and ANSM published recommendations 2020 to help health professionals concerning these treatments too.

Due to their multiple indications in ART population (adenomyosis, endometriosis, polycystic ovary syndrome PCOS), many women we meet ought to have previously been treated with progestin's for a long time before they come to us. As far as we are concerned, we consider it very important to track down meningioma and define a medical attitude in case of confirmed meningioma too.

Material and Methods

We tried to evaluate, through online enquiry, the practice of health professionals specialized in ART 6 months after French ANSM recommendations publication [3]. We asked the following questions. Are these recommendations well known and followed? What is the ART specialists' attitude towards women who had been previously treated with progestative medications before ART; Normegestrol (NMG), Cyproterone Acetate (ACP) or chlormadinone (ACM)? Are ART specialist concerned with this issue? Do our colleagues search for these previous treatments? Do they prescribe MRI? Do they contra-indicate ART? If not, what would be the reasonable delay after discontinuation of these treatments before ART?

We submitted to physicians ART specialists a short multiple choices survey on SurveyMonkey.fr.

Descriptive data of the participants.

123 doctors took part to this survey; all were ART specialists, and 39% worked in private hospitals, 37% in public hospitals, and 23.6% in doctor's office. Almost a third of them had more than 20 experiences in ART (30.08%), and about half had an experience between 5 and 20 years. 24 young doctors, with an ART activity who started less than 5 years ago also took part in this survey.

Results

Among the 126 participants, 61% were searching during their medical inquiry of infertile women, if they already had taken ACP, ACM or NMG.

If women had been exposed to those molecules, 26% did not know after how much time a cerebral MRI should be undertaken to search a meningioma.

25% of the participants chose to prescribe a cerebral MRI after 24 months of treatment, against 21.9% after 12 months, and about 10% after 6 months.

We also wanted to evaluate the minimum reasonable delay after discontinuation of these treatments before ART. 90 doctors (84.1%) estimated a time of 6 months was the most secure. For 6% of the participants this time should be longer, about 18 to 24 months.

Finally, regarding the patients who had a previously treated meningioma and need ART, 53.6% of the doctors could not decide if they would allow an ART. 13% contraindicated an ART, and 33% would agree to help them get pregnant.

Discussion

The link between meningioma and use of ACM, NMG or ACP is now well known. Studies showed a dose effect relationship and a regression of the lesion at the discontinuation of the treatment [6,7]. In 2020, a large epidemiological study was permitted to quantify this risk: A woman taking one of these treatments for more than 6 months has about 3.3 times the risk of developing a meningioma compared to the baseline risk. The risk increases with the duration of treatment, the dose used and the patient's age: with NMG, the risk is increased by a multiple of 12.5 after five years of treatment and with ACM, it is increased by a multiple of 7 for 3.5 years of treatment [7,2].

Progestin's have many indications, especially in patients referred for infertility. In patients suffering of endometriosis for example, the treatment is effective on pain, and well tolerated. Furthermore, compared to GnRH agonists, progestin has less anti estrogenic effects [8,9].

In PCOS patients, Cyproterone acetate is effective on hirsutism and menstrual cycle regulation. Moreover, metabolic tolerance is interesting compared to contraceptive third generation progestin's regarding cholesterol level for example [10].

Considering their indications, tolerance and efficacy, women counseling for infertility are very likely to have been previously treated with progestin for a long time. Clinicians have to be aware of the risk of meningioma for these patients.

In the literature, there is no recommendations concerning women with meningioma who need an ART. We may be concerned with hyper stimulation's effect on tumor size, despite no case was previously reported in literature. We may be concerned with the amount of estradiol and progesterone levels during pregnancy too. Saitoh et al. [5] presented the case of a pregnant woman with a meningioma: the size of the tumor was two times bigger in only 110 days related to the hormonal receptivity of the tumor [5]. Moreover, we know that a meningioma revealed during pregnancy may induce maternal and fetal risks such as prematurity or caesarian delivery [11].

Our survey showed that among 123 ART professionals, only 60% were asking to patients if they had previously taken ACM, ACP or NMG. Despite information being emailed to all doctors by the ANSM in October 2020. We may think it's linked to an oversight. Indeed, infertility consultations are very long and need a very detailed inquiry. Moreover, when women consult for a pregnancy desire, most of the time they stopped their hormonal treatment for at least six months so they can easily forget.

In mars 2021, the ANSM has defined the indications that should lead to realize a cerebral MRI in case of exposition to ACM, ACP or NMG. The recommendations are

- To prescribe a MRI at the beginning of the treatment, only if there are some risks factors (neurofibromatose type II, antecedent of encephalic radiotherapy).
- To prescribe a MRI after one year of treatment by ACM, ACP or NMG and then five years later. In case of pursuit of the treatment, patients should have a cerebral MRI every two years.

When we asked to ART professionals the duration of treatment before an MRI, only 23% said one year, in accordance with the ANSM recommendations, and 26% did not know. These results may be in

link with the lack of information during the COVID-19 pandemic. Indeed, for almost a year, there was no discussion between doctors and no information meetings. The transmission of information only by mail is very difficult and can easily be missed.

Concerning the minimum reasonable delay between the discontinuation of the treatment and an ART treatment, almost 90% thought that 6 months was safe. It allows time to check if some symptoms of meningioma appear, and to conduct a cerebral MRI in case of symptomatology before a hormonal treatment.

Half of the ART professionals who participated to this survey did not know if they would allow an ART for women who previously had a diagnosis of meningioma. This result shows all the interest of a multidisciplinary discussion with neurosurgeons, endocrinologists and gynecologists. The heterogeneity of the results obtained through this survey shows that French ART specialists need recommendations in their practice for this topic.

We try to focus clinicians' interest on this poorly known topic, and wish that the French ANSM recommendations could be generalized, not only in France.

Meningioma could be systematically researched when women have been exposed more than five years prior to ACM, ACP or NMG, especially in context of adenomyosis or endometriosis or PCOS.

In this case, a cerebral MRI could be conducted to make sure there is no contra-indication to an ART.

When ACM, ACP or NMG are discontinued, a minimum time of 6 months delay before the beginning of a cycle of ART should be observed.

In case of previous treated meningioma a multidisciplinary discussion must occur, with gynecologist, neurologist, neurosurgeon and endocrinologist. Both the ART and pregnancy may anyway be contra-indicated definitively.

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