



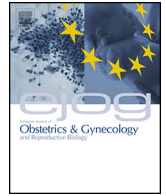
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Suspension of ulipristal acetate for uterine fibroids during ongoing EMA's review of liver injury risk: Unfortunate timing during the Covid-19 pandemic!



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ABSTRACT

Objective: EMA decided that with ulipristal acetate (UPA) treatment for uterine fibroids, should be discontinued due to the associated risk of hepatic failure. We analyzed whether the risk of recurrent symptoms due to fibroids may lead to an increased risk of Covid -19 infection and death, that would exceed the former risk of hepatic failure and transplantation.

Study design, size, duration: We used a Markov model to generate probabilities.

Participants/materials, setting, methods: There are currently about 36,250 treated patients in Europe. We estimated bleeding probabilities, while using or discontinuing UPA, which may induce a need of medical or surgical management in symptomatic patients, and increase the risk of acquiring a Covid-19 infection, and die from it. We also estimated the risk of suffering a hepatic failure and hepatic transplantation.

Main results and the role of chance: Based on our assumptions, ceasing UPA during a Covid 19 pandemic may be associated with a fatality ratio between 4 and 18, due to the Pandemic, whereas pursuing UPA would be associated with a fatality rate due to the pandemic between 1–2, and an added fatality rate due to hepatic impairment of 1. The added risk of stopping UPA may range between 2 and 15 additional deaths.

Our calculations suggest that the decision to stop UPA in the middle of the Covid- 19 pandemic may be untimely, since it may result in an increased risk of Covid-19 infection, due to the recurrence of symptoms and the need for medical and surgical treatment.

Wider implications of the findings: A decision, like the one EMA took need to be taken in a wider health context of a population, than simply analyzing its role as regulating agent for medications.

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Introduction

Uterine leiomyomas, or fibroids, affect between 20–40% of women of reproductive age. The most common symptoms are menorrhagia, leading to iron-deficiency and anemia, which may impair the immune response, increase susceptibility to infections and affect pulmonary, cardiac and renal function [1]. Women with symptomatic fibroids require frequent consultations, imagery tests, and surgical procedures, such as D&C, hysteroscopy, myomectomy and hysterectomy. Ulipristal Acetate (UPA) has emerged recently in Europe as the first choice medical therapy, either as a preoperative treatment, since it successively reduces the fibroid volume and treats the pain and anemia in many instances. In that indication it was often administered for a period of three

months, before surgery was proceeded. Later on, repeated courses of UPA were also recognized as an indication of fibroid treatment in women, who wanted to avoid surgery or had contra-indications to surgery and wanted to keep their uterus intact [2,3].

On March 13, 2020 the European Medicines agency (EMA) decided to suspend ulipristal acetate (UPA) for the treatment of uterine fibroids and recommended that ongoing treatments should be immediately stopped, in all patients, while EMA's safety committee analyses their safety [4]. This decision was motivated by the reporting of liver impairments, including five that led to transplantations, out of over 900,000 treated patients, since 2012 [4].

Whereas this may be justified, the timing seems inappropriate, since we are currently facing a Corona-virus pandemic. Due to UPA cessation, a number of patients may present a recurrence of symptoms, requiring urgent management and treatment, which may include transfusions and surgery. We do not know to what extent some of these patients will increase their risk of Corona

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Table 1
Based on a cohort of 36,250 patients using ulipristal acetate (UPA) of whom 90 % became asymptomatic and 10 % remained symptomatic.

| A. The strategy consists in ceasing UPA (n = 36,250) | | | | | | | | | |
|--|--|-------------------------------|--|--|--|--|--------------------|--|--------------------------|
| Status before stopping UPA | Probability of change to the next status | Status after stopping UPA | Total | Probability of change to the next status | Need for management and Surgery | Probability of change to the next status | Covid-19 infection | Probability of change to the next status | Infection Fatality Ratio |
| Asymptomatic (p = 0.9) N = 32,625 | P = 0.3–0.1 | Asymptomatic N = 3263–9788 | Asymptomatic N = 3263–10151 | 0.001 | No need N = 10,151–3263 | 0.01–0.02 | N = 10–3 | 0.01–0.02 | N=0.01–0.2 |
| Bleeding (P = 0.1) N=3625 | P = 0.7–0.9 | Bleeding N = 22,838–29,363 | Bleeding N = 26,101–32,988 | 0.5–0.9 | Yes=13,050–29,689 | 0.03–0.06 | N = 131–296 | 0.03–0.06 | N=4–18 |
| | 0.9–1 | Bleeding N = 3263–3625 | | | | | | | |
| | 0.1–0 | Asymptomatic N = 363–0 | | | | | | | |
| Total Death | | | | | | | | | N = 4–18 |
| B. Strategy : Continued use of UPA | | | | | | | | | |
| Status before stopping UPA | Probability of change to the next status | Need for Surgery | Probability of change to the next status | Covid-19 infection | Probability of change to the next status | Infection Fatality Ratio | | | |
| Asymptomatic (p = 0.9) N = 32,625 | 0.001 | No N = 32,625 | 0.001 | N = 4 | 0.01–0.02 | N = 0.04–0.08 | | | |
| Bleeding (P = 0.1) N=3625 | 0.5–0.9 | Yes N = 1813–3263 | 0.01 | N = 18–33 | 0.03–0.06 | N = 0.6–2 | | | |
| Hepatic insufficiency | 6/90,000 | N = 2.5 | | | 0.5 | N = 1.3 N = 2–3 | | | |
| Total Death | | | | | | | | | |

contamination, leading to increased morbidity and mortality. The latter could outpace the risk of hepatic impairment.

In this study we analyzed two strategies: The first consists in immediately ceasing all UPA treatments. The second consists in waiting until the Corona pandemic is over before discontinuing medication.

Material and method

Population

We hypothesized, based on IMS data (a company that provides marketing data information for the healthcare industry), that 36,250 patients are current users of UPA and that 90 % of them had become asymptomatic when using the drug, whereas 10 % continued to present menorrhagia [5]. We used a Markov model to generate probabilities.

Strategy A (Stop UPA)

Bleeding or not

We supposed that between 10 % and 30 % of asymptomatic patients would remain asymptomatic, and between 70 % and 90 % would again become symptomatic. On the other hand, we supposed that almost all patients who were symptomatic using UPA would remain symptomatic (between 90 % and 100 %), while few (between 0% and 10 %) would become asymptomatic (Table 1).

The need for medical management and surgery

We estimated that asymptomatic patients would not need medical management or surgery during the Covid 19 pandemic, whereas 70%–90% of symptomatic patients would need some form of medical management (consultations, imaging) and 50–70% would require surgery [6,7].

The risk of Covid-19 infection

Based on the reported cases in Italy, we hypothesized an infection probability of 0.001 for asymptomatic women [8]. We arbitrarily hypothesized that symptomatic as well as anemic women would have a 10 fold increased infection risk due to their prior illness, the need to seek medical advice and the need for surgery (i.e. 0.01)(Table 1).

Finally, we supposed a fatality ratio ranging between 1 %–2 % in women who developed Covid infection, but had no symptoms related to the fibroids, and between 3 %–6 % in the Covid infected patients, whose fibroids had caused anemia or had required recent surgical treatment [8] (Table 1).

We applied the same probabilities using Strategy B, i.e. pursuing UPA, but added the risk of hepatic impairment to the cohort of patients (2). In this instance we would recommend checking the patients' liver tests and discontinue UPA only in the event that they are elevated. But we did not consider this in the analysis.

Number of hepatic impairments

The exact number of cases with severe hepatic impairment is unknown, at the moment, but in 2018, it was estimated that there were 51 cases out of 765,000 treated women, 4 of whom needed a transplant [4]. At the present time, there are about 900.000 women who have been treated and a fifth case of transplantation has been reported. We assumed, therefore, that 60 cases of hepatic impairment occurred in 900.000 treated women, which means about 2–3 cases in a cohort of 36,250 women [4]. In this model we purposely overestimated the risk of death, due to hepatic impairment, since we considered the risk of transplantation to equal the risk of death.

Results

The calculated probabilities and generated numbers appear in Table 1A and B respectively, for the two strategies. Based on our assumptions, ceasing UPA in the middle of a Covid 19 pandemic may be associated with a fatality rate ranging between 4 and 18 due to the Pandemic, while pursuing UPA would be associated with a fatality rate due to the pandemic, between 1–2, with an added fatality rate due to hepatic impairment of 1. The added risk of stopping UPA compared to pursuing UPA may therefore range between 3 and 15 fatalities.

Discussion

We recognize that there are many limitations in this article since certain risks were hypothesized. We maximized the associated risk of hepatic impairment and considered the risk of transplantation to be equal to the risk of death. We used two probabilities for the recurrence of symptoms and the need for medical or surgical management, based on a prospective cohort study in which about 50 % of women who stopped using UPA, underwent a surgical procedure [7]. We did not consider that in case of bleeding recurrence, some patients may have been managed by phone or after blood check first. We also hypothesized that symptomatic and anemic women would have a 10 fold increased infection risk due to their prior illness. Although there are currently no data to sustain this hypothesis, some authors speculated the occurrence of an oxygen-deprived blood disease, with iron metabolism dysregulation, should also be taken in consideration in the pathophysiology of COVID-19 patients [9].

Our calculations suggest that the decision to stop UPA in the middle of the Covid- 19 pandemic is untimely, since it may result in an increased risk of Covid infection and mortality, due to symptom recurrence and the need for medical and surgical treatment. Based on about 30.000 treated patients, this may result in an increase of 14 fatalities. At this time, it is impossible to estimate the incidence of the Covid-19 pandemic, since we are still in an exponential phase. Estimates of infection vary between populations. This heterogeneity may reflect a difference in population susceptibility, in testing strategies and case definitions, in timing and virulence of the disease, in provided health care and prevention measures that are taken or a combination of these factors. They will influence the basic reproduction number (R_0) (which is thought to be around 2.2, meaning that, on average, each infected person spreads the infection to an additional two persons) [10]. Overall, a 6.9 % death rate has been reported in Europe in women, but again, this varies between countries and regions [11]: In some European countries, the cases double every two days, in others, every three days [12].

Besides the heterogeneity in distribution of COVID-19 infection, we need also to add the heterogeneity in incidence of symptomatic fibroids that are treated. Moreover, the highest incidence of COVID-19 do not necessarily coincide with those with the highest number of women treated with UPA, from which the drug was withdrawn.

But the risk of infection is also influenced by the comorbidities of the patients and whether they need to be hospitalized for other conditions [13]. It is possible therefore, that fibroid patients who become anemic have a higher susceptibility to infections such as Covid-19. They may also become less resistant to complications once they have been infected. Similarly, the risk of infection may simply be increased while staying in a hospital, as has been reported previously [13].

Another limitation consists in the fact that we did not consider the complication rates of surgery, which vary between hospitals and populations (between 6.5 % and 9.9 % in one study) [14]. But

more importantly, the failure-to-rescue rate after a hysterectomy increased with successive risk-adjusted mortality quintiles, from 0% at the hospitals with the lowest mortality rates to 4.4 % in the hospitals with the highest mortality rates ($P < .0001$) [11]. Currently, we have no data to suggest that increased mortality rates related to a pandemic also influence surgical mortality rates, but there is good reason to believe that this might be the case.

To conclude, in a time of a Pandemic, the advice would be “stay away from crowds but even more from hospitals, until you really need to be there or you are really needed there”.

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Author's contribution

The first draft, and final manuscript was written by Rozenberg S. The data were analysed by Serge Rozenberg and checked by all the co-authors, who discussed the content of the manuscript and approved it.

Declaration of Competing Interest

There are no competing interests.

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