



## Hypersomnia Foundation Video Transcript Released April 16, 2019

### Dr. Isabelle Arnulf: Women & IH

In June, 2018 at the Hypersomnia Foundation's seminal conference in Baltimore, **Isabelle Arnulf, MD, PhD**, gave an expansive presentation on the unique challenges facing women with IH and other rare sleep disorders, drawn in part from her own clinical experience and research. This is the transcript to that presentation, available on our website.

#### **BEGIN VIDEO TRANSCRIPT:**

#### **Introduction: *Amy Desmarais, HF Board Member***

**0:03** Good morning. For both men and women, having a rare sleep disorder and managing its treatment is a challenge. But for women, it can be especially complicated. As they make decisions about contraception, pregnancy, breast feeding, and other issues unique to women, they must also take into account the medications they take for their sleep disorder. How might these medications interact with other choices they make?

We are so fortunate to have Professor Isabelle Arnulf here today to share her research on this subject: Having authored more than 150 publications in peer-reviewed scientific journals, Professor Arnulf is not only one of the world's leading experts on all forms of hypersomnia, including narcolepsy, idiopathic hypersomnia, and Kleine-Levin syndrome, but also Professor of Neurology at the Sorbonne Universités, and head of the Sleep Disorder Service at the Pitié-Salpêtrière University Hospital in Paris, France. She trained with Dr. Michel Jouvet, who studied the function and mechanism of REM sleep soon after its discovery, and completed a postdoctoral fellowship with Dr. Emmanuel Mignot at Stanford University. Dr. Arnulf is the past-president of the French Sleep Society.

Please join me in welcoming Professor Arnulf...

**Presentation: Dr. Isabelle Arnulf, MD, PhD**

**SLIDE 1**

Title slide

**1:59 SLIDE 2**

Thank you. I must confess I have a few relationships of interest, being a speaker bureau of UCB and a consultant for Novartis, and I've also been an investigator in developing several psychostimulants.

**2:00 SLIDE 3**

So, what we know is that 50% of patients with narcolepsy are women, which means that half of them are men. This is for narcolepsy,

**2:11 SLIDE 4**

but when it comes to idiopathic hypersomnia, it is 66-75% of patients who are women. So it's clearly a female-predominant disorder and what is the theory of this [why is this]?

We don't know why. We have no idea about abnormal hormones in women with hypersomnia.

**2:36 SLIDE 5**

What we looked at in our series of 200 patients with IH compared to narcolepsy type 1 patient is to compare the age at puberty both in ...

You can see that the age of puberty is younger in women than in men. But it is the same in IH and in narcolepsy, whether being a man or a woman, so it does not come from at least this part of the sexual development.

**3:01 SLIDE 6**

So, if you don't mind, we will cover together the problem of birth control, then how to be a mother with IH, and the parenthood in general, and a few words about menopause with IH.

**3:19 SLIDE 7**

So let's speak about birth control in IH and narcolepsy.

**3:24 SLIDE 8**

First, you know all the drugs - I put the drugs we have in France; I think you have almost the same: modafinil, armodafinil, methylphenidate, sodium oxybate, amphetamines. You have Adderall (that I didn't put), pitolisant, the anti-h3 drugs [selective [histamine](#) H3-receptor [antagonist](#)/inverse [agonist](#) that enhances the activity of histaminergic [neurons](#)]. All these drugs are used in narcolepsy, but we also use them in IH to almost the same degree.

### **3:50 SLIDE 9**

So if we look on the other hand, the contraceptive methods we have, there are the hormonal methods that you can see here, and it's constituted of estrogen and progestin, sometimes progestin alone. And all these drugs have a theoretical effect on preventing pregnancy, but in real life it's often different, so we call it "pragmatic."

So you can see all these percentages that are given by our government. Combined estroprogestatif [estrogen-progestin, EP] normal dosage is efficacious, given efficacious contraception, in 99.7% of the patients... but in regular use, because you can forget the pill one day – or some days – it's only 91% of contraception [effectiveness]. It means that 9% of women will have a child in the next year. And it's the same for combined low dose of estroprogestatif [low dose estrogen-progestin birth control pills] [and][for progestin-only [pills], that is also called the mini-pill. But vaginal rings also contain estroprogestatif, and they are submitted to the same level of efficacy, as is the transdermal patch. And the implant, by definition, has only a theoretical effect, because it is in use and you cannot forget it! And that's nice.

### **5:20 SLIDE 10**

Then on the other end, you have what we call the barrier methods, which is either a Dutch cap, you know diaphragm with spermicide inside. And you can see the percentage of contraception [effectiveness] is lower in pragmatic use. It's 88%.

Intrauterine device is 99.9 [% effective], and it's in you, you cannot forget it. Condom is a good contraception [method] -98% - unless it breaks - so when it breaks it's 85%.

Withdrawal is the oldest technique used by men, but as you see, it can be, in pragmatic use, not very efficacious.

And the temperature method, used in the 50's and even in the 19<sup>th</sup> century, and is now called the "symptothermia." It means that women are following both their temperature here, as you can see, so that it increases the time of ovulation, here, but also they monitor their vaginal phlegm. And you can see the phlegm. If it's very difficult to extend it, it means that it is blocking the spermatozoid. And then when it is very fluid, it helps the spermatozoid to go to the uterus.

So some women are combining that, and there is quite a revival in France of this method because – I am sure you have the same in the US – many young women don't want to take the pill. They think it's not natural, so we have to explain, as doctors, that it is not natural, but it's working. Anyway, everybody is fine to choose her methods.

### **7:02 SLIDE 11**

So what happens with the interaction between the drug you take for IH or narcolepsy and contraception? There is one drug reducing the effect of the estro -progestatif pills. This is modafinil, and armodafinil, which is almost the same. Because these drugs interact in the liver site where the hormones are destroyed, and it increases their destruction by 30-50%. This is a

problem. So if you have a lower dose of hormones in you [because your liver has destroyed more of your birth control], you have a lower [effectiveness of] contraception.

#### **7:40 SLIDE 12**

So if you are using modafinil or armodafinil, the single hormonal drug that you can take for contraception is normal dose combined EP, which means you have 40-50 micrograms of estradiol in it. Low dose cannot be used alone; the progestin cannot be used alone; vaginal ring and transdermal are exposed to the same problem. For implants, there is an advantage – that it's working, but it's working for a shorter time.

#### **8:18 SLIDE 13**

So the alternative contraception for a woman treated with modafinil or armodafinil is to take a pill with a normal dose of estrogen-progestin, containing at least 40 micrograms of ethinyl estradiol. And I don't know if you have this pill in the US – we had it in France, but they stopped – it was called 10:00 Stediril, but they stopped manufacturing it two years ago. So gynecologists have to make a new estrogen-progestin combination, using estradiol and progestin combined together, but it's not in the same pill.

The alternative we ask to the reference center for contraception in my hospital is to take two tablets of low-dose, not the mini-dose, low-dose pill, containing 20 microgram of 10:30 ethinyl estradiol and levonorgestrel. For example LeeLoo, which is the most prescribed pill in France - and it is the cheapest one, it is two tablets per day instead of one tablet. So it's easy. And the implant can be used, but it will be effective only for two and not for three years, so you have to change it more rapidly.

#### **9:36 SLIDE 14**

Then all barrier methods are compatible with modafinil and armodafinil, even including the Dutch cap of course, but the intrauterine device can be used too, even the one with hormones. I have to specify that some intrauterine devices contain some progestin inside, which is used to reduce the bleeding associated with an intrauterine device. It's not used for a contraceptive purpose; it's just to reduce the bleeding. So you can take it with modafinil or armodafinil because you will still have reduced bleeding; probably a little more [bleeding] than other women, but not that much. And condom can be used. I put withdrawal and symptothermal in gray because they are less efficacious.

#### **10:26 SLIDE 15**

Now this problem with interacting with hormones and modafinil also applies to emergency contraception, Plan B. If you had unprotected sex, or failed birth control, and need to take the morning after pill when being continuously treated with modafinil or armodafinil, don't forget you have to double the dosage of the day after pill to ensure birth control. Otherwise you are not sure of the contraceptive effect.

And remember, it's called the "day after" or the "morning after", but it can be taken immediately after sex – if you have a broken condom for example. You don't have to wait until the next morning. Take it immediately, and if you forgot and don't know, you have five days to use it. So this is quite practical, at least. So twice the dosage emergency contraception – remember when you are on modafinil.

#### **11:27 SLIDE 16**

And this is a little trick some of my patients use. In IH and narcolepsy, patients are really tired, and if you have some severe bleeding during menstruation, you can unchain the blister [pack]. When you are too tired at the end of a cycle and do not want to have menstruation, to prevent fatigue, do not stop the pill, and resume the next blister immediately. It will avoid bleeding, and possible associated lack of iron. And this method has been tested, and it is safe, efficacious, and it has been tested for three blisters in a row. And then you can have your seven days of stopping and resume again. So know it, because some women have really some hard menstruation, and they are so tired, that you can suppress them [menstruation] with no health effect.

#### **12:22 SLIDE 17**

Now from this birth control talk, takeaways you [should] remember: if treated with modafinil or armodafinil, the pills should contain ethinyl estradiol 40-50 micrograms plus a progestin (norgestrel double dose, too; it's a progestin), and all barrier methods or intrauterine device.

And when on modafinil, taking the morning after pill for unprotected sex or a broken condom, double the dosage.

And if treated with Ritalin, Xyrem, or Wakix, do what you want for birth control, but choose it efficacious [an efficacious method], because we will review the problem with pregnancy with it. Speak of all that [discuss] with your gynecologist.

#### **13:10 SLIDE 18**

Then, let's go to pregnancy. When I/we discuss – I'm following patients for 24 years, and I know them when they were teenagers, having their first boyfriends (speaking of contraception), then the husband, then the kid. So we had a lot of questions, and the first one is, "Will I transmit my disorder?"

#### **13:35 SLIDE 19**

And I want to mention something that is sometimes not well understood by patients about narcolepsy – [it's] sometimes [a] heredito-genetic disorder, so people think they will transmit it to their children. So how many cases are there with an affected father and mother, and an affected kid

#### **13:57 SLIDE 20**

With narcolepsy- cataplexy, you can see a review of all the literature on that topic here. And see whatever the number of patient and proband [relative], the person's age of an over-affected member of the family is 1-2 percent... and this is whatever the first-degree person— it can be your brother, your sister, your father, or your child.

#### **14:27 SLIDE 21**

So when you look at [the] [Dr.] Mignot review, 1-2% of subjects with narcolepsy have an affected kindred, vertical or horizontal, which means that if you are just considering your children, it's a more than 99% chance *not* to transmit the disorder. That's important to say. And Ohayon asked to the families of 157 Italian subjects with narcolepsy. He called all the probands one by one, and asked for symptoms by phone, so remember it is a phone diagnosis, it's not a medical diagnosis. And he found that 4% of the children interviewed with a parent with narcolepsy reported some symptoms of sleepiness, not cataplexy, of course. So it means that with narcolepsy you have 96% chance not to transmit symptoms of sleepiness. And in our series, we are following 673 patients with narcolepsy, and we have only 4 families with a parent and a child affected, which is even higher. So please, if you have narcolepsy, make children. [There is] no risk! No risk!

#### **15:53 SLIDE 22**

Now, I feel I will have the question for idiopathic hypersomnia, and unfortunately there is no reliable information on that subject. I'm sure some of you have another kindred affected, but this has not been studied in the general population of IH patients. And long sleep is highly transmitted, so it's hard to know if it's IH or long sleep which is transmitted.

#### **16:21 SLIDE 23**

Now if there is a project of [plan for] pregnancy, we prefer to speak it [discuss it in advance] before the pregnancy has started, to speak about treatment that can be kept and those that need to stop.

#### **16:35 SLIDE 24**

So this is an example of an email I received last year: Dear Dr., (I don't know her.) My name is Valentine, I am 28 years old, and I have been medicated since I am 15 years old for narcolepsy with cataplexy. Every day I take modafinil and venlafaxine (venlafaxine is for cataplexy). It was difficult at first to accept my disorder, (and I am sure that it's difficult for everybody to accept the disorder) but now I don't pay much attention to it. Treatment works. However... I want to be pregnant (sorry, it's a bad translation), and I am getting conflicting advice. My gynecologists said it was not necessary to stop my [medication] regimen. My neurologist said I should stop taking my medication immediately. I use a computer for work, and without the medication, I would be unable to do my job. I am also worried I would be depressed if I have to go off my meds and stay at home during the pregnancy. Could I have a second opinion? Should I halve my dosage, and do I need to stop my medication entirely?

#### **17:43 SLIDE 25**

So, who is right? The gynecologist or the neurologist? In your opinion? [asking the audience - someone calls out “neurologist”]

**17:58 SLIDE 26**

[Laughs] I am happy you think we are right, but uh, I think the gynecologist, yeah, because the gynecologists are always facing the problem of drugs, all the time, and the gynecologist in our case followed the recommendation of the [French] National Site for Pregnancy, which is something made by doctors and government. In France it's called Le CRAT. I am sure you have the same in the U.S., and you can put the drug on it and look at what is known.

**18:26 SLIDE 27**

Because if you look just at the notice of the company [drug manufacturer], everything is forbidden. But with time, the government and the health ministry have developed some registries to know, because there are always some pregnancies on drugs – you cannot always schedule everything. So there are recommendations for some of these drugs. Modafinil, pitolisant, GHB [Xyrem] have not yet any recommendation on the site. Ritalin has some, and amphetamines have some.

And they distinguish taking the drug during the embryo period, which is during month 1 and month 2 of the pregnancy (and it's a time where the embryo is making his organs – he's making his kidneys, his liver, [etc]). And then there is a fetal period from month 3 to month 9, during which it's growing. But the higher vulnerability period is during the two first months, because it's a time of building the organs. And they compare all what is known about pregnancy and modafinil and ritalin, compared to the normal rate of birth defects, and you know what? There is no zero risk for any pregnancy, even without any drug. Humans make/have some birth defect babies.

And the percentage is around 2% of pregnancies that is conducted to the end. So each time the government, with registry, is comparing how much birth defects are in the general/untreated population, and [when] we have a specific drug in an exposed woman - is the risk higher or lower?

It's how they do [it], so it does not come from the company [drug co]. It comes from a registry, a national registry, from all doctors seeing pregnancy and drugs.

**20:22 SLIDE 28**

So, what they say for modafinil and pregnancy is what we know from studies in animals, and we know that there were no birth defects in non-human animals, which is first, very good news. And then they say that data of women exposed to modafinil during pregnancy, at both states, embryo and fetus, is small, but reassuring. No problem yet. They don't give the numbers– if they are around 100, in France now. You probably have much more here. During pregnancy, the recommendation is if stopping the drug seriously worsens the patient condition, it is not justified to stop it during pregnancy. And this recommendation is held since ten years now, so we have

implemented it in our patient population. So if pregnant when on modafinil, we assure everybody that there is no problem ([greater] risk of birth defects), and as usual, inform the delivery team.

### **21:27 SLIDE 29**

So, since this advice ten years ago, we say that to the patients. Some want to stop, which is perfectly acceptable. And some don't want to, because they cannot live without it, and we leave it. And consequently, we suggest the following: if routine life is not possible without a stimulant – because you work, because you drive (when you drive a car, being sleepy is much more dangerous), or because you have serious symptoms – and you're already on modafinil, keep it. No change of dose. They don't recommend to split the dose; they say if you give it, you give it. No changing the dose.

Using other stimulants, I recommend to switch to modafinil before pregnancy, so it's part of the plan we have together. That's why I want to see my patients before the beginning of pregnancy. If some are on Ritalin or amphetamines, I ask them to switch to modafinil, and we leave the modafinil during pregnancy. But I recommend stopping it two weeks before delivery, because when the baby is in you, it's your kidney and your liver which is eliminating the drug. But when the baby is born, it's out of you, and he still has 5-7 days of modafinil in his blood, on his little kidney and little liver, so it is difficult to eliminate for him.

So I prefer they stop it two weeks before delivery, (because it's a time usually when you are on maternity leave) to avoid getting [the baby] overdosed with modafinil after birth. And if routine life is feasible without any stimulant, stop the medication, but avoid driving a car, rest as often as you can, and take early maternity leave, which is probably not possible in every country....I've learned before that you [in the U.S.] have only three weeks of maternity leave here? [audience replies] Six weeks! Hey ok, ok. [laughs]

### **23:37 SLIDE 30**

And as physicians, we should report every pregnancy where the mother is taking medication to this center, because the more information we will have in the national database, the better for the future mothers. We will know better about this risk, and you know the higher number of exposed people, and the more you know... So this is what we do with Le CRAT.

### **24:04 SLIDE 31**

This is baby Lucas. And mother had IH, and she was on modafinil. That is what I report to the center, national center. She was on 300 milligrams of modafinil. They conceived the baby in August. She was on modafinil since 2012, and she stopped it two weeks before term. There was a normal delivery on term, and then I give also constant [report] of the baby. He is 3 kilo, Apgar score of..., and I saw him at two months and he is communicative. He's holding [up] his head. And I have to monitor progress every year, to say, to have, the longest time of information for the woman because the immediate problem that you can see since birth, but we don't know for the long term. We have to implement. So I have now some patients with ten year old babies

that have been exposed to modafinil, and it was “safe.” I mean, we need more [information] of course, to know, but we have to [continue to] report.

### **25:13 SLIDE 32**

So for methylphenidate and pregnancy, they say that there is no birth defect in non-human animals and that data of women exposed to methylphenidate during pregnancy are numerous and reassuring. But because of the amphetamine properties of methylphenidate, they ask to take an alternative treatment. So we follow, we stop Ritalin, and we switch them to modafinil.

### **25:39 SLIDE 33**

For pitolisant (pitolisant is the new Wakix drug), there have been some birth defects in one animal species. There have been some... unscheduled – wanted but unscheduled – pregnancies, and they gave birth to normal babies. But it is only two, so you cannot play with that [risk]. So it is contraindicated, to be stopped until we have more information; stopped. And it is [takes] five days to be eliminated from the body.

### **26:12 SLIDE 34**

For sodium oxybate, there was no information on the site. I sent an email, but I don't yet have any information., So we use only the company information, which indicates that that there is a risk of miscarriage. In animals exposed to sodium oxybate, there were more early miscarriages than in non-exposed animals, and they say there could be more early miscarriages in women exposed to sodium oxybate.

So I would recommend to avoid exposure during the first two months. It's scheduled as “Risk B” here in U.S., meaning that the problem is during the [first] two months [of pregnancy] and then after, there is no evidence of abnormality in the fetal period. But again, not many information, so no information. I would say, avoid [it], anyway.

### **27:10 SLIDE 35**

So, the problem is that, except for modafinil and some anti-cataplectic drugs, the key problem will be when we decide to be pregnant, when do you stop the medication? In all women, the average time between the desire to start a pregnancy and real pregnancy [becoming pregnant] is on average six months. I've been pregnant immediately after stopping the pill for my two children, but my sister needed two years to get pregnant. So, I wish you are like me, but it's chance! We don't know our fertility.

So you have to be able to stop and wait, but it's nice if you know about how long you can take your drug until it is dangerous for the egg. And the conception occurs for women between the 11th and the 18th day of the cycle; it's on average the 14 days. And then it's not immediately that there is an implantation of the... egg.

### **28:28 SLIDE 36**

You have here a uterus. Here is an ovary, making the oocyte... and then when you've got [have] sex, the spermatozoa come in here, and they meet the egg here in the [fallopian tubes] (we call that the "trompe of Fallope" – is it the same name in your...trompe like Trump). And then the new embryo, the fertilized egg, is not implanted yet. It's floating here in the trompe [fallopian tube] and making a small journey: Day 1, Day 2. Meanwhile, it's dividing, making more and more cells, and then at D8, it's implanting inside the uterus at the place where it will develop as an embryo and a fetus.

So there is eight days during which the fertilized egg is doing its organs but is not exposed to your blood and to you drugs. So I call it "the safety zone."

### **29:35 SLIDE 37**

So let's make it clearer. That's day 1 of your cycle. Day 28 for regular women with regular menstruation should appear here, and during the beginning of the cycle you have no egg, no oocyte. Then, you make your egg, and it can be fertilized by the spermatozoa between day 11 and day 18. Then it's not implanted until day 19, if you have ovulated at the 11th day. And the 26th day of your cycle, if you ovulated here. As soon as the egg is implanting in the uterus, you start to make some beta-HCG hormone, which makes a blue test positive. So the test is positive when [the egg] is implanted, not before.

So you can start to determine your ovulation time with temperature, and then use a positive blue test as soon as 19 days of your cycle to know if you are pregnant or not.

So we have this "safety zone" for drugs. Now the drugs that you are using are not eliminated in one day, except for Xyrem, from your body. They are eliminated after 5 half-lives. The half-life is different from one drug to another. The shortest half-life is Xyrem. Xyrem is eliminated very quickly. It's less than 4 hours, sometimes 6 hours. so 5 times 6 hours (if you take the maximum), it's 30 hours. So it's one day and a half – even lower than that. So this drug can be taken quite late in the cycle.

And then methylphenidate is eliminated between 4 and 6 days. And pitolisant and modafinil are the longest – you have also 5-7 days of elimination. So if you're pregnant, it's ok. If you're not pregnant, you can restart it at every cycle. It's what our patients are doing if they cannot stop it.

### **31:57 SLIDE 38**

So I would recommend to monitor your central temperature if you have a pregnancy project [want to become pregnant], to localize your ovulation time over three months. And then when you know your ovulation time, you can stop Xyrem between the 19th and 26th days of your cycle and pitolisant the 11th. If you want to stop modafinil (you are not obliged), 11th day as well.

If you have [an] irregular, very irregular cycle, you cannot use this method; you have to stop the drug very soon – 10th day of the cycle.

### **32:35 SLIDE 39**

Now you may use antidepressants either for cataplexy or for concomitant depression, and what we know for pregnancy is that the oldest [drug] is the safest. Clomipramine (it's one that we use for serial cataplexy), it's the oldest drug, and there have been numerous use cases during pregnancy, and there are low risks of withdrawal for infants at birth, even for dose higher than used in narcolepsy. And it can be used during breastfeeding because the amount that goes into the milk is very low. So it's safe, for cataplexy, to keep people on clomipramine.

Then, using the most common SSRI, or SNRI, there's a lot of data with no birth defect, but there's signal on the site [Le CRAT], too, that there is a risk of withdrawal for infant. There are transient, not severe, syndromes – syndromes of withdrawal in children, including tremor, hyperexcitability, sleep disorder, lack of muscle tone, and difficulty eating. So that they recommend that the delivery would be in a kangaroo unit. I'm sure you have the kangaroo unit, too. It's for special delivery, where there is more monitoring. You don't stay one or two days at the hospital; you stay four days, and they're monitoring better the child. So it needs that your neurologist is interacting with the gynecologist [to plan for] for delivery.

### **34:08 SLIDE 40**

Maternity leave. As we said before, if medication is stopped, and mother is too tired for continued working (in case of disorders like narcolepsy or hypersomnia [IH]) it's possible in France to have a paid leave (whereas in your country...), at least during nine months. So I always tell my patients, when you're pregnant, phone me, call immediately and then I stop you for nine months. You will do what, one or two babies in your life? That will be two times nine months leave – that's not a big deal in regard of doing these things.

My experience is when pregnancy starts, is that the fatigue of the pregnant woman is much more accepted by the society and understood by the society than the fatigue of hypersomnia. Because pregnant women are working for the humanity. So everybody tells [her], "Oh, rest, rest, please, make your child, rest." I wish you would hear that during all your life, because I think the sleepiness of pregnancy has nothing to do with the sleepiness of hypersomnia.

### **35:19 SLIDE 41**

So, it depends from one case to another. Some are better during pregnancy, probably because of the hormones, and some are worse because of stopping the medication; it's very different from one woman to another. And then, if you have to remember the takeaways:

- If treatment is needed, the safest compromise is modafinil (plus clomipramine if cataplectic).
- And clomipramine can be taken during breastfeeding.
- It's advisable to stop the modafinil two weeks before the delivery.

- Advisable to stop methylphenidate, Xyrem, and pitolisant. And there's this risk B that I see in the U.S., that Xyrem can be taken after the start of the third month.

### **36:10 SLIDE 42**

Now, the gynecologist wrote me, "Dear colleague, One of your patients (Mrs. C) is pregnant and under my care. She's 25 years old, she's... 24 weeks of pregnancy, and this is her first pregnancy. You treat her for narcolepsy. Are there any specific risks for delivery? (which is good interaction that we have). Sincerely." So to answer her, I have the recent study made in Europe.

### **36:41 SLIDE 43**

We interviewed all our patients, female patients, who had pregnancies, and there were 246 responders. And some of them had their pregnancies and children before having developed narcolepsy, and some had it after. [Some had children before, and some had children after.]

And what was interesting in this large series is that for delivery, there was no difference between narcolepsy and non-narcolepsy women. It was spontaneous in most cases, triggered in one fourth of the cases. Caesarian [section] was not more used in narcolepsy than in non-narcolepsy women. And there was only 1% of cases of cataplexy during delivery. And the weight and the size of the newborns was the same in both groups, in both pregnancies.

Then, after birth, babies were more often to breastfeed if mother was narcoleptic (almost 80 percent), and for a longer time. Note that these data were obtained in a European country where it's easy to have some leave when you have a child.

### **38:03 SLIDE 44**

And there were also USA-BOND [Burden of Narcolepsy Disease], by Jed Black, study with 9000 people reported to have narcolepsy in U.S. (at least on the registry), and they were compared to healthy controls, and there were no differences for pregnancy, delivery, and perinatal period. [<https://www.ncbi.nlm.nih.gov/pubmed/24768358>]

### **38:29 SLIDE 45**

So I responded to the gynecologist: "Pregnancy and delivery for narcoleptic women is the same as for any women. There are no added risks, except maybe to use extra care when giving the baby to the mother for the first time, because you can have a cataplexy of happiness!"

### **38:50 SLIDE 46**

Now baby is there. Should we breastfeed him or her, or use formula?

### **38:57 SLIDE 47**

As you know, drugs are passed down in mother's milk, and this is true for modafinil, methylphenidate, and sodium oxybate (but it has a short half-life), pitolisant, venlafaxine, fluoxetine. Clomipramine is allowed. So it is ok to resume stimulant when done with

breastfeeding, except for clomipramine and sodium oxybate [which can be used throughout breast-feeding], with some caution.

#### **39:23 SLIDE 48**

And this is a recent study that has been conducted by a woman having narcolepsy, on Xyrem. And she accepted [agreed] to have some measure[ments] in her milk, taking either 3 grams twice a night or 4.5 grams twice a night, and as you can see the level of Xyrem were almost undetectable before she takes the Xyrem. The small dosage, 3 gram, increased [the level] after intake, and here after the second intake, too, which is expected because they accumulate. And it's the same, but higher, for the higher dosage. And you can see that this is seven in the morning, so it's still high; then ten, eleven, sixteen, it resumed to lower dosage - and even with 3 grams there is nothing in the milk here the next day.

So, from this experiment, what do we know? The milk of the evening is ok for the baby, before taking the first intake. No breast milk at night for the baby (use formula at that moment). And the first milk of the morning should be pump and dump (except for those using only a single dose of Xyrem; in that case, you can give the [morning] milk); then breastfeed the baby all day long. So it's interesting – this woman, we should thank her to have given this information for breast milk!

#### **40:57 SLIDE 49**

Then, you know that baby hypersomniacs; they sleep in bouts, and I would recommend sleep when the baby sleeps. My grandmother used to say, "You have to be like a cow in the grass. You make your milk, you calve your baby, and you sleep, and everybody is caring for the rest. Be quiet as a *cow*.." (Sorry, I'm not saying it well.)

#### **41:33 SLIDE 50**

But you know that we are all exhausted with these babies, because it's a lot of care. And this is not a hypersomniac woman; it's a normal woman, and she is exhausted with her baby, as shown there.

#### **41:46 SLIDE 51**

So, the questions of my patients are always the same: "What if I fall asleep (or I have a cataplexy) when breastfeeding or feeding the baby?" There are many solutions for that.

#### **41:59 SLIDE 52**

This includes breastfeeding in the lying position, like you can see here, and using also this (I don't know how you call them? [Sling?]) You can use them to either breastfeed or give the formula. And the baby will be safe, which is important because it can be long to breastfeed. Some children are taking their time, so you might fall asleep, and it happens to every woman, every mother, believe me, even non-hypersomniac.

#### **42:39 SLIDE 53**

And the mother doesn't have to feed the baby all the time; get help from the partner and family. I would say it's extremely important to have a supporting partner and family, when having this project, and remember it's easy to pump the mother's milk and to put it in the fridge or the freezer. Somebody else can give it to the baby when the mother sleeps or is too tired. Use it. It's easy – it's very easy to pump your milk, and it's [been] done for centuries.

#### **43:13 SLIDE 54**

Parenting with idiopathic hypersomnia may be your problem. For example, a recurrent question is, "If I take Xyrem, will I hear my baby crying at night?" Maybe not, because especially during the two first hours of the drug, there is a hypo [low]-arousability. So make sure you have a partner or family to help when, during the night, and same thing for sleep drunkenness.

#### **43:42 SLIDE 55**

Now, one of my patients [Marion] said, "When I sleep (I have two little girls), when I sleep on the sofa in the living room for my scheduled nap – I need this nap, really I need it! – my two daughters come and disturb me. They want to play; I want to sleep. I get angry with them, and then I regret being angry. I feel guilty."

And this is very typical. You feel guilty to sleep in front of your children at times they want you. So what would you answer to Marion? There is a little problem when you see the figure here [on the slide]. Where is she sleeping? On the sofa, and, yeah, the living room is a common room, so little children understand that you are available for them, so sleep in the bedroom for privacy and explain to your children that your naps are "mom therapy." So now she sleeps in her bedroom, and she has no fights with her little girls because she's sleeping. The door is closed, and she is sleeping, and they should not disturb [her].

#### **44:53 SLIDE 56**

Menopause occurs also, and I have only a single slide.

#### **44:59 SLIDE 57**

Menopausal hormonal therapy consists of estrogen and progestin at lower dosage than for birth control, but we have the same problem. So you need to double the dosage if you are on modafinil. Like for example, if you take one press of estroge1 (usually, you prescribe that), if you're on modafinil, you take two press.

#### **45:24 SLIDE 58**

So, this is to finish. This is my family, father's side. There was some birth control, but we like children. Thank you very much!

#### **Audience Question 1:**

"I have been on – I started with Ritalin, and I had bad side effects along with modafinil and armodafinil, and now I'm on Ritalin (or Adderall, excuse me). So I'm wondering if I had bad side

effects taking both modafinil and armodafinil, with the hormonal changes of being pregnant, like, could I have a better effect going on that when I'm pregnant, potentially? Like does the hormone potentially make it better?"

Dr. Arnulf: "No. No, if you had a side effect with modafinil, you will still have them during pregnancy. So, no. Better not taking anything. It's usually because we are using modafinil, and it works, but not very well, so we are constantly switching the patient to something else, in routine. So when it comes to pregnancy, you can restart it if it had worked before, even if it was not big [help]."

**Audience Question 2:**

"Do you schedule c-sections because of their taking off medications 2 weeks before? What if the baby comes early or is late?"

Dr. Arnulf: "No."

"So it's still natural delivery?"

Dr. Arnulf: "It's still natural, and as you've seen, there are no higher c-section rates in patients with hypersomnia, so... It just... Two weeks is a very, very safe zone because modafinil is eliminated within 7 days, so it's to be sure, because you can have premature birth."

**Audience Question 3:**

"Do you see a correlation for your patients that have IH also having menstrual headaches?"

Dr. Arnulf: "No, but I think I didn't ask very well. We look at pain in general in patients with IH and with narcolepsy. As you know, it's increased in narcolepsy. It's known. And we have the same rate of pain in IH. So it seems that being sleepy increases your pain in general, but we have not yet gone in detail of, 'Is your hypersomnia symptom increasing at time of premenstruation, or does it change during pregnancy?' Nothing serious to answer you, but I think it's an interesting project to do in the future."