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### Freeze-All Policy: Is It Right for Everyone?

Dr. Roque:

Hello, it's really a pleasure to be here in this continuing medical education to talk about the Freeze-All policy. This is really a fascinating thought process in reproductive medicine. And for those of you who haven't met me before, my name is Matheus Roque, I am from Brazil, and we are going to evaluate in the next few minutes, the rationale of freeze-all strategy, its effectiveness, and finally, we evaluate if this strategy should be offered for all of the patients who are in IVF treatments.

So, from the beginning, it is important that the delivery of a healthy baby, it's important to have a good embryo, a good quality embryo. But the embryo quality is not only...it's not only the embryo quality that is of fundamental importance to achieve a pregnancy, we also need a good embryo endometrial interaction, and, a good endometrial receptivity to achieve our goal during IVF treatments. And it is also of fundamental importance to think about and discuss about the facts of controlled ovarian stimulation over the endometrium when you talk about our IVF treatments. And if we go back in the past in 1997, Ubaldi and his group, they published one study evaluating the endometrial dating. They performed endometrial biopsies during IVF treatments on the day of oocyte retrieval, and what they found on that study was that when the endometrial advancement was over 3 days, no pregnancy was achieved. And they could correlate these advancements with the progesterone levels. The patient with high progesterone levels, progesterone levels over 1.1 on the trigger date, these were the patients that were more susceptible to have endometrial advancement. And the way that we can analyze, you can evaluate the endometrium has evolved, and in 2005, the group from Horcajadas, they evaluated endometrial gene expression during controlled ovarian stimulation. They evaluated oocyte donors in one natural cycle and then in stimulated cycle and they observed that there were over 200 genes that were over or under expressive during ovarian stimulation. And finally, they concluded that ovarian stimulation affects endometrial receptivity. And this group, they continued with these studies, and in 2011, Labarta, they published that, they also correlated these endometrial advancements and the alteration in the gene expression, endometrium gene expression, they correlated with progesterone levels and they performed the endometrial biopsy in patients with progesterone levels over 1.5 on the day of oocyte trigger and patients with levels under 1.5, and what they found was that the superficial large hormone levels can affect the endometrial receptivity. And when you think about these hormone levels when you look at this image about implantation, we can see that the estradiol, progesterone also the receptors they are presenting many steps of implantation, and if you think that the superficial large hormone levels are present during an ovarian stimulation, we can think that we can have endometrial advancement and peri-implantation modifications during our IVF treatments and during a fresh embryo transfer. That it can affect implantation, but not only implantation, and now the process of pregnancy that this decidualization, placentation, and finally, the parturition. Thus, we could have problems during all the pregnancy and not only for implantation. And this is the reason to discuss about the freeze-all policy. This is the reason that we need to think if this strategy is viable...if it is a strategy that is effective for all of the patients, and this is question of our presentation, if this strategy is for all of our IVF cycles?

Then we need to move to effectiveness, and in 2013, it was published this metaanalysis. This metaanalysis included three randomized clinical trials, two of them from Shapiro. This doctor, that probably he is the father of freeze-all. Many, most of his studies concerned about freeze-all; they were published by the Shapiro group, and what we could observe in this metaanalysis is that the ongoing pregnancy, and clinical pregnancy rates were increased by over 30% in patients who needed to freeze-all cycle when compared to a fresh embryo transfer. However, we can have some problems with metaanalysis, and after he published this study, one year later, one of the studies from Aflatoonian, it was retracted from the literature due to some methodological flaws in the study. And we just keep with these two studies from Shapiro. We don't have a difference. We just have difference in clinical pregnancy, but ongoing pregnancy we don't have difference.

Then we need more randomized clinical trials, and last year in 2016, a Chinese group they published the largest randomized clinical

trials evaluating the freeze-all strategy, and they evaluated this strategy in PCOS patients and they found an increase in the probability of live birth in patients who needed the freeze-all. We can see this in this picture, in this figure, that the risk rate was 1.17 in patients who submitted to a freeze-all cycle and this benefit in live birth it was mainly based on a decrease in miscarriage in patients who submitted to freeze-all cycle. Then what we can conclude in this RCT is that it is the largest RCT until now that was published evaluating the freeze-all, is that we can have an increase in the live birth and a decrease in the miscarriage in patients submitted to freeze-all cycle when compared to fresh embryo transfer.

This year it was published by another group, a randomized clinical trial evaluating this strategy in patients submitted to PGS genetic screening and embryo transfer on day 5 and one can see in this graph is that the ongoing pregnancy and the live birth it was increased in patients submitted to freeze-all cycle when performed in a PGS study.

Then these are the randomized clinical trials of viable up to now, and we can have another observational study evaluating this strategy, and in 2015 we published this study, it was a retrospective study. Until that time it was the largest study in freeze-all and we could observe in this study went from cleavage stage to transfer, and all of the fresh embryo transfer they worked from only the progesterone levels on the trigger date. It was lower than 1.5 we could observe an increase, a relative risk of 1.33 for implantation rates and 1.28 for ongoing pregnancy rates and when performed the logistic regression we could see that the freeze-all strategy it was an independent factor related to the outcomes that in that study was ongoing pregnancy rates.

Then it seems that we have some evidence showing the benefit of freeze-all. We have a few randomized clinical trials that have been published. We just state up to now with those 3 studies from Shapiro, one of them evaluating normal responders and the second study evaluating the high responders. We have this study published last year evaluating the freeze-all in PCOS patients that it was published in the *New England Journal of Medicine* and then this year we have one study published in *Fertility and Sterility* evaluating this strategy in PGS cycles.

Last year in ASRM there was one more study that evaluated the freeze-all that was published by Wong group from Vietnam that they didn't show any benefit of this strategy of freeze-all in normal responders, but it was only an oral presentation. There is just one abstract. They didn't publish it until now.

And then finally, it is important to evaluate if this strategy is for all. Based on those studies evaluating they have based science and those studies evaluating the clinical evidence of freeze-all, most of the doctors, or many doctors, can imagine that it can be applied for all of the patients. However, we need to evaluate with caution many of these studies. If you look back to that study from Horcajadas one can see that they concluded that ovarian stimulation can affect endometrial receptivity, but that study it was from an oocyte donor, and the minimum number of oocytes it was between 13 and 18 oocytes retrieved. Also the patient with the high estradiol levels on the trigger date. On this study published last year in PCOS patients, what we can see is that the number of retrieved oocytes is over 14 oocytes, and the mean number is between 14 and 14.4, and the estradiol levels over 4000 on the day of oocyte trigger. Then it seems that in some specific group of patients, in fact, the ovarian stimulation may affect the endometrial receptivity. But it seems that it is not for all of the patients. We don't have big studies evaluating in poor responders and actual normal responders. We just have these studies evaluating high responders, also the studies evaluating the endometrial receptivity and the endometrial dating. Most of them are based on high responders.

And then this year it was published in Cochrane, a review from Wong, that we can see when evaluating the cumulative live birth that there is no benefit in performing the freeze-all strategy for the patients submitted to IVF cycles. In this study, in this metaanalysis, it is included the 2 studies from Shapiro. They have since published from Chen and one study from Ferraretti that's from 1999. Thus, we can have also some concerns about the inclusion of this data from Ferraretti, although it was a randomized clinical trial evaluating this strategy, it can have some bias effect here, because if we imagine that in 1999 probably our results with frozen-thawed embryo transfer, they were not so effective as we can achieve now.

Then, I just have these concerns or these comments about this metaanalysis and the inclusion of this study. Then we have this question, if the freeze-all strategy is for all of the patients? We don't know exactly but one can see in the recent evidence is that this strategy is not for all of the patients.

When we look back for the retrospective studies, this study it was submitted to *Ultrasound in Obstetrics and Gynecology* we presented this study in this year, in 2017, and we evaluated the freeze-all strategy in poor responders following Bologna criteria. And in this group of patients, we didn't observe any benefit in performing the freeze-all strategy. In January of this year we published in *JARG* a study evaluating—it was a retrospective study—evaluating the freeze-all strategy in normal responders, but considered these normal responders Chen, the group, and group one those patients between 4 and 9 oocytes were retrieved and group two between 10 to 15 oocytes were retrieved. In what we found is that in the first group between 4 and 9 oocytes, is a sub-optimal group. We don't have any

benefit in performing the freeze-all. In the normal responders when considered these normal responders between 10 and 15 oocytes, in this group of patients we can have a benefit when performing freeze-all. That's if we put this data together we can see that in patients with a low number of oocytes, there is no benefit in performing and in patients with over 10 oocytes retrieved, in this group of patients we have a benefit. However, this data is from our center and these we don't know exactly if we can separate all of this data for all of the patients. What we can see with this data is that the freeze-all is not for all of the patients. It is necessary individualization and there are some recent studies published that go back on this idea of individualization, and these recent studies published in *Fertility* we can see that they have evaluated the patients with recurrent implantation failure, and in this group of patients they observed that there was a benefit in performing the freeze-all in patients with previous recurrent implantation failures.

However, another interesting study, a really good study pictured there, is from the cohort study, a matched cohort study evaluating American data, IVF data, and what they found in general, is that the freeze-all course is of benefit when, from and when, evaluating all of their data, however, when they performed stratification of these patients, we can see that patients with progesterone levels at the trigger date lower than 1, there is no benefit in performing this strategy. They only found a benefit in patients with progesterone levels over 1 on the trigger date, and this benefit it was dependent on the patient's age. With patients lower than 35 years-old, there was benefit; however, the benefit looks even better in patients over 35 years-old. Thus, it seems clear with all of this data, in the past years, the idea that the freeze-all could be employed for all of the patients and we saw this rationale in this presentation and the reasons that the ovarian stimulation may affect endometrial receptivity and its effectiveness. It really depends on the ovarian response and hormone levels. Then, the idea is that this strategy is not for all of the patients and we will need to think about the individualization, as we are thinking about the individualization for other parts of the treatment like ovarian stimulation, the lab techniques. We also need to think about the individualization, we are selecting the best strategy for embryo transfer for our patients.

Thank you very much.