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Released: 03/29/2015
Valid until: 03/29/2017

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Improving Fetal Outcomes Through the Use of PGD/PGS

Announcer:

Welcome to CME on ReachMD. This is the Omnia Education activity, Improving Fetal Outcomes through the use of PGD and PGS. Your host is Dr. Michael Tucker. Dr. Tucker will speak with Dr. Robert Anderson, Medical Director at Southern California Center for Reproductive Medicine in Newport Beach, California, and Dr. Brian Kaplan from Fertility Centers of Illinois in Chicago, Illinois. Dr. Robert Anderson receives consulting fees from Serono and is a speaker for Illumina, Inc. Dr. Brian Kaplan receives consulting fees from Actavis, Ferring, Good Start Genetics and Serono.

Dr. Michael Tucker has nothing to disclose. This CME activity is supported by an independent educational grant from Illumina, Inc.

After listening to this activity, participants should be better able to understand the latest advance in preimplantation, genetic screening and diagnosis that will optimize fetal outcomes in ART, utilize appropriate screening and diagnostic protocols according to evidence-based guidelines and incorporate latest technologies into clinical decision-making.

Dr. Tucker:

Most of the embryos created during the process of in vitro fertilization, IVF, will not implant. Nearly all of these failures are the result of genetic defects in the embryos; thus, the creation of embryos via in vitro fertilization has led to the need to identify possible genetic defects in these embryos before pregnancy occurs. Preimplantation genetic testing is a technique used to identify these embryonic genetic defects. There are currently 2 pathways for doing so. The first is preimplantation genetic diagnosis, PGD, and PGD refers specifically to when one or both genetic parents have a known genetic abnormality and an embryo is tested to determine if it also carries a genetic abnormality. Now the second pathway is preimplantation genetic screening or PGS for short. PGS refers to techniques where embryos from presumed chromosomally-normal genetic parents are screened for aneuploidy, abnormal chromosomes.

Please join us as Dr. Robert Anderson and Dr. Brian Kaplan discuss the latest advances in preimplantation genetic screening and diagnosis that will optimize fetal outcomes in ART. And they will also discuss the appropriate screening and diagnostic protocols and incorporate these latest technologies into clinical decision-making.

Drs. Anderson and Kaplan, welcome to the program. PGD and PGS have become routine procedures in many IVF clinics. Can you provide an overview of just what these procedures do and what genetic disorders or abnormalities can actually be identified by these procedures? Dr. Anderson?

Dr. Anderson:

We've gotten to the point now in our clinic where probably 95% of our IVF cycles are using preimplantation genetic screening. Initially, we were biopsying day 3 embryos and transferring back day 5 embryos in the same cycle. Obviously, there were a lot of problems with that mostly due to mosaicism and self-correction; so in 2011 we pretty much replaced that with blastocyst biopsy, and that allowed us to get more cells to make the diagnosis, which made it more precise. When we started this treatment, we were biopsying embryos on day 5 and transferring them back on day 6 fresh with a less than 24-hour turnaround we realized that we were getting more pregnancies when we didn't transfer them in fresh. There were some patients who needed to have their embryos frozen. They were at risk for

hyperstimulation or they had a poor endometrial development or they were making too much progesterone prior to the retrieval. And we started to realize that we did much better with that method. So, we dropped off the fresh transfers all together, and just done frozen embryo transfers following PGS. It allowed us to also make use of the day 6 embryos, we find we have just as good a chance of being euploid as the day 5 embryos do, and our pregnancy rates are identical as well.

We're getting roughly around 80% implantation rate with embryos that have been screened in that way and then transferred as frozen. So it's been a tremendous value in our practice allowing us to do single embryo transfer on just about everybody with better success rates than I've ever seen in the almost 30 years I've been in the field.

Dr. Tucker:

Excellent. Dr. Kaplan, can you perhaps speak a little more to the genetic diagnosis of perhaps single gene disorders which the biopsy techniques can help?

Dr. Kaplan: If I could just expand on Dr. Anderson, because our experience has been predominantly in PGS and we have a very similar philosophy that Dr. Anderson has. It has been that for many years our field was measured by pregnancy rates, and that was our ultimate goal. And in the beginning, the only way we could achieve pregnancy rates was increasing the number of embryos we transferred into our patients today where instead of pregnancy rates being our ultimate goal, it's become how do we take home a healthy baby? This is really where PGS plays such a critical role because the ultimate goal is a single embryo resulting in a single delivery of a healthy baby at full term. It is obvious that there are certain transformative technologies that have occurred over the last 10 years that have allowed us to apply PGS, which has now maximized that probability of taking home that single healthy baby. It's important for those in the field and outside the field to understand that you have to have those technologies in place before you can apply something like PGS. You have to have that good foundation, the first being the ability to grow embryos to the blastocyst stage, which has changed our field in many ways and allowed us to limit the number of embryos, and number two the ability to transfer embryos that have been cryopreserved with an evolved technology of vitrification into a more natural physiological milieu is proving to be as effective if not more effective than transferring the embryos into our standard fresh cycles.

The benefits to that transfer allows us to do PGS or PGD without the time restraint. Not only are we achieving higher implantation rates with that approach, we are achieving healthier babies with lower incidences of prematurity and complications in pregnancy as a result of that environment being more physiological than the hyper stimulated endometrium in our controlled ovarian stimulated cycles. So genetic technology together with the IVF technology has been truly a godsend to our field.

The paradigm has changed tremendously in the goal to achieve a singleton pregnancy; the only way we can really do that to a large degree is by transferring the single embryo. In order to transfer a single embryo, we have to be able to select which embryo to transfer. It is clear that just morphological assessment and temporal assessment of embryos is inadequate to assess genetic competence, and it is well established that as women age, the incidence of aneuploidy goes up dramatically; and even in normal, young, fertile women, we know there's aneuploidy in those embryos, as we see it from our donor egg data, so that the main reason for failed implantation is aneuploidy. So the logic of transferring a normal ploid, euploid embryo makes sense from an intellectual point of view. I think the controversy is are we technologically at that point where we can now offer it to all our patients? I am a strong proponent that there is data there, and that I think in my practice a PGS is increasingly being utilized to obtain that goal.

I think with PGD looking at a single gene abnormality is more obvious to most of us because we are now identifying a known genetic abnormality, and it is less controversial. But our experience has been predominantly in the PGS area.

Dr. Tucker:

Thank you, Dr. Kaplan. Now, you've both more or less cut to the chase of my next question, which was: Traditionally, in all forms of preimplantation, genetic, diagnosis or screening, there have been earlier options during embryo development, options to biopsy at

earlier stages; for example, even as early as the unfertilized egg stage doing polar body biopsy or indeed on day 3 pulling out a single cell. Can you perhaps address what the limitations or were there any apparent benefits to these earlier stage biopsies and why clearly now you both promote the concept of going to the later stage blastocyst for biopsy? Dr. Anderson?

Dr. Anderson:

The initial thinking about day 3 biopsy was that that gave us plenty of time to still be able to transfer back a fresh embryo because you could wait until day 5 and it would be plenty of time to do the actual testing; the drawback of that--there are several. One is that you're only using 1 cell, and there were studies that showed that if you remove 2 cells that up to 30 to 40% of the time they differed in their genetic makeup, so there was a significant amount of mosaicism that I think may have led to some missed diagnoses.

Secondly, the embryos at that stage are more susceptible to damage from the biopsy procedure, removing a larger percentage of the cells when you only have 6 to 8 to work with compared to the day 5, day 6 embryos that have hundreds of cells, and when you remove 5 to 10 from them they don't suffer much in the way of damage. I don't think you can undervalue the ability of the embryologist who's doing the biopsy in the process as well, so not only do you have to grow blastocysts well, you have to be able to vitrify embryos well, but you've got to have a team that can reliably remove the cells from the blastocyst and still have them be viable. There's a learning curve with that just like any other kind of technical component in the laboratory, but once the embryologists are skilled at it, it really becomes quite routine.

As I mentioned before, ability to realize that embryos will implant better in an environment that's more like the physiologic state in terms of the amount of estrogen exposure than in the hyper stimulated state where the super physiologic levels of estrogen are present, we're better off really biopsying the embryos when they're day 5, day 6 and then vitrifying them for later transfer. The days of the day 3 biopsy are probably over. The randomized controls studies that came from that—and a lot of them were done with FISH as well—they really didn't show much advantage compared to not doing them, that's definitely changed with the advent of our ability to do comparative genomic hybridization and working with day 5 and day 6 embryos.

Dr. Tucker:

Dr. Kaplan, could you perhaps speak to how the actual cellular makeup of the blastocyst differs than from earlier stage embryos and how that may benefit the actual removal of the cells from the blastocyst versus earlier stages, that is in terms of the trophectoderm being biopsied as opposed to the inner cell mass?

Dr. Kaplan:

From the polar body point of view, there is an appeal to that because it theoretically would be less invasive. There are really no studies to show how safe polar body, the actual biopsy is, they'd extrapolate which will get to day 3 transfers which Richard Scott did show in New Jersey in a randomized controlled trial that patients who had a single blastomere removed showed low implantation rates when it was controlled versus trophectoderm. There was, a dramatic effect of removing a single cell from a day 3 embryo. With a polar body, not only are you removing that cell, the disadvantage there is what are you actually measuring and what is the effect of the biopsy excluding the male component, and it also in multiple studies has shown to fail to identify approximately 40% of genetic errors when doing aneuploidy screening and so that the accuracy from a prognostic point of view is much worse. So for me as a clinician and not as a technician in the lab, the 2 key aspects that I would want to know before applying a technology is, number one, am I getting as detailed and accurate information prognostically of the future embryo —and I think polar body does not give you that—and secondly, is there any harm to that biopsy on reducing just from a pure mechanical or traumatic effect reducing the implantation rate? So with polar body having less of a role, day 3 became much more of a commonly used technology. And we did a lot of day 3 biopsies and our results were decent. However, from many randomized trials, particularly out of Europe, and now Richard have shown detriment to day 3 biopsy. So the mosaicism rate, the accuracy of the analysis and predictability has decreased. And so from those 2 factors, I think when it comes to predicting the health of this future child and the less traumatic effect of the biopsy itself seems to be and our advice would be the only way to do PGS at this point in time.

Dr. Tucker:

It appears that during the days of day 3 biopsies that perhaps there were certain numbers of embryos that were deemed normal that were transferred and those that were deemed abnormal were perhaps discarded, so by moving to the biopsy of the blastocyst stage, it appears the trophectoderm is the favored stage at which to biopsy now.

Can you perhaps just give me some indication of the differing technologies which underlie, the PGD and the PGS process in terms of use of perhaps array CGH for whole genome amplification as well as other suitable techniques?

Dr. Kaplan:

The chromosomal aneuploidies, which we define as the gain or loss of an entire chromosome, contributes to the vast majority of pregnancy losses and failed implantation in both natural and ART conceptions. The most significant factor for this is maternal age and initial PGD for aneuploid screening involve the blastomere biopsy from a cleavage stage embryo with FISH technology examining selected panel of chromosomes. Only the chromosomes most commonly observed in pregnancy loss and aneuploidy deliveries were analyzed. Most meta analyses eventually showed no beneficial effects following FISH screening of biopsied blastomeres. There is a clear need for technique that could analyze all 23 pairs of human chromosomes. Recent advances in molecular biology and various platforms have allowed us now a comprehensive chromosomal screening, a full karyotyping of the embryo, and these studies have involved CGH and has extended to array CGH, array technologies, and most recently in some labs quantitative real-time PCR. The new generation sequencing will probably replace all of those technologies, but the ability now with whatever technology is state of the art to analyze all 23 pairs has been a tremendous advancement in adding PGS to our patient population.

Dr. Tucker:

If you're just tuning in, you're listening to CME on ReachMD, the Channel for Medical Professionals. I'm

your host, Dr. Michael Tucker, and today I'm speaking with Dr. Robert Anderson and Dr. Brian Kaplan about Improving Fetal Outcomes through the Use of Preimplantation Genetic Diagnosis and Preimplantation Genetic Screening.

So, just to return to the differing tests that are available currently, do either of you wish to hazard any statements as to the different commercial platforms that exist in terms of their similarities and differences with regard to identifying aneuploidy we've spoken earlier about the ability to undertake overnight screening so that you can actually replace embryos, blastocysts on day 6 while still fresh. But Dr. Anderson clearly seems to have moved away from fresh transfers; but nevertheless, the ability to undertake the overnight screening may limit access to some of those commercial platforms. Any comments?

Dr. Anderson:

We did take advantage of those initially. We desired a 24-hour turnaround. And I assume you're talking about maybe some regional problems that some clinics might face in getting the cells to the laboratory and getting the results turned around quickly with those platforms. But if you aren't interested in a 24-hour turnaround, then it makes available to probably every clinic the ability to get a good diagnosis and still be able to use them in the way that's going to maximize their pregnancy rates. So I'm not so sure that if you move away from fresh transfers that's going to be as much of an issue anymore.

Dr. Kaplan:

I agree very much with Dr. Anderson. We have the ability to do a turnaround. We have in-house capabilities. We look to that data and with the data from multiple centers including Shapiro's data showing that frozen cycles placing embryos into a more controlled environment was actually as effective and even had long-term advantages. We don't see the need anymore to do same cycle transfers in a fresh environment even though we have that capability. So the ability to transfer the embryo to subsequent cycles, I believe the only negative or down side of that is cost. And I think our centers have to evolve over time to how do we incorporate a patient now, first of all from an expectation point of view that she has to wait to do a frozen cycle, the extra cost of a frozen cycle; is there a cost for

freezing embryos for a longer period of time I think it's really just a matter of explanation and expectation of the patient, knowing when she goes into the cycle that this will be a frozen cycle in a subsequent month.

Dr. Anderson:

We're going to find, that it's a much more cost-effective approach because what was happening when we were doing fresh transfers is we had lower pregnancy rates, so that meant that a significant percentage of the patients had to come back to do a frozen cycle subsequently. As Dr. Kaplan has mentioned, the efficiency of this whole process has been improved so dramatically, what we're seeing for a lot of our patients is that they only have to go through the most involved and costliest part, the egg retrieval stage, once. And if they have a number of euploid embryos obtained from that cycle, they may be able to get all the children that they ever want by doing 2 or 3 subsequent frozen embryo transfer cycles at 2 or 3 years apart, and in the long run, spending a lot less money than they would have if they had been putting back unscreened embryos multiple times and getting negative results and then only hit and miss getting the positive.

In our clinic since we've moved to this entirely, we've actually adjusted the price somewhat so it isn't as expensive as a fresh cycle plus a frozen cycle tacked together would be. We've kind of hybridized the cost so it makes it more affordable, and we've had a very good response from our patients.

Dr. Kaplan:

I think there's an added benefit, and in some of these patients who are a little bit on the hyper stimulated side and you often need a lot of embryos for PGS, you lower the risk dramatically of hyperstimulation syndrome by transferring in a cryopreserved cycle. And there's still some controversy. There are still some centers which are not quite comfortable with Lupron Trigger and its effect on the subsequent luteal phase. And if our results which have not been as good with Lupron Trigger in fresh cycles, you take that variability out of the equation in a subsequent frozen cycle. I think transferring embryos in a frozen cycle with or without PGS, we are very strong proponents for all those reasons.

Dr. Tucker:

Is there any resistance? What is changing or has changed in recent years to make the confidence, your professional confidence, grow in the cryopreservation techniques that we now apply? It almost seems that you're suggesting that embryos now can be cryopreserved with very little fuss with good survival rates. Could either of you speak to the quality and the type and the nature of cryopreservation now as compared to, say, 10 years ago?

Dr. Anderson:

I don't think there's any... couldn't be a bigger difference. The slow freezing technique for embryos was hit and miss, and I found that even with blastocyst freezing, when you went to thaw them out you really never knew what you were going to get. Sometimes the embryo survived completely intact and looked exactly like it did when it was frozen, but sometimes only part of the embryo survived, and sometimes the entire embryo didn't survive even though they looked pretty good when they were frozen. With the advent of vitrification, that just changed everything; I don't remember the last time we had an embryo that didn't survive the vitrification process. And it's rare to see an embryo that doesn't look just like it did when it was vitrified.

We show the patients on a screen in the transfer room what the embryo looks like under the microscope, they look like fresh embryos. There's very seldom any difference between what that embryo looked like when it was frozen and what it looked like when it was warmed. The transition from slow freezing to vitrification, like what we saw with the same experience in freezing eggs, has had a profound effect on your ability to recover embryos.

Dr. Kaplan:

Our experience has been the same. Vitrification has really transformed, IVF in many ways in our ability to freeze. We have found the same results as Dr. Anderson where there's very little lack of survival, from vitrification, and that was one of the biggest factors which gave me the comfort level of doing PGS in a subsequently frozen cycle.

What transformed my thinking as well, was the years of sitting with patients in 35- to 40-year-old age group, which is a large percentage of our patient population, having an implantation from IVF and with the enormous miscarriage rates they've had to deal with, and dealing with that woman of 38 who's gone through IVF and who loses that pregnancy at 7 or 8 weeks from aneuploidy with a subsequent D&C and delay in attempting another cycle, and by the time she starts over again, you're looking at 4, 5, 6 months. The time is so critical in that age group. The dropout from our patients which I think is significant—and the vast majority of the reasons for dropout of our patients who are not coming back for further technology or treatment has not been shown to be financial but been shown to be emotional and the stress of going through all of this, miscarriages are probably at the pinnacle of that. To use whatever technology is available to lower their probability of that early loss was, a very important part in treating my patients. We need to be more sensitive to that temporal timeline in the first trimester because it has tremendous ramifications from the patient point of view, from our point of view, from continued treatment, from cost point of view.

Dr. Tucker:

Thank you. So in terms of patient pushback or resistance to cryopreservation, that seems very minimal, I presume. Are there any studies which either of you could refer to as to the actual healthy, live birth outcomes from cryopreservation in the sense that this might give confidence that this is a healthy route to go as opposed to a fresh transfer?

Dr. Anderson:

We've now been doing only frozen transfers for several years and we haven't had one adverse outcome. There's certainly been minimal evidence that cryopreservation had much of a difference in neonatal outcomes compared to fresh embryo transfer. There maybe was some birth weight issues, but other than that it seems to be pretty safe and effective.

Dr. Tucker:

Interestingly, what comes to mind is a Danish study showing a large for gestational age outcome from cryopreserved embryos. Now, they were reviewing data which was largely from slow freezing versus vitrification. But interestingly, one of the major complaints about gestational outcomes from in vitro fertilization traditionally has been the offspring have often come in as small for gestational age at birth, and quite the opposite was even suggested from cryopreserved embryos. Perhaps we're looking at overall a potentially healthier outcome by transfer of frozen thawed or vitrified warmed embryos in subsequent more natural physiological cycles.

Dr. Kaplan:

There's a meta-analysis that did show compared to fresh transfers that FET pregnancies showed significant reduced risk of preterm birth, perinatal mortality, placental abruption and previa.

Dr. Tucker:

In 2013 the American Society for Reproductive Medicine, the ASRM, and Society for Assisted Reproductive Technologies, SART, issued a publication entitled, *Criteria for Number of Embryos to Transfer, a Committee Opinion.* Now, the overall purpose of this publication was to provide guidance as to the number of embryos to be transferred in IVF cycles so as to reduce the number of higher order multiple pregnancies. Could you comment on this ASRM/SART statement, and how IVF clinics can incorporate these recommendations into your daily practice, with a view to our subject in this particular discussion of genetic diagnosis and screening?

Dr. Anderson:

I strongly support the recommendations of ASRM and SART to lower the number of embryos transferred. I've certainly been doing this long enough to remember the days when transferring back 4 or 5 embryos was not out of the question, and certainly we had adverse outcomes to show for it. But in those days, our ability to select the best embryo was really lacking. And with the advent of preimplantation genetic screening and our ability to now select the best embryo for transfer, it's allowed us to embrace these guidelines and to transfer, at least in our hands, a single embryo probably 90% of the time. I still occasionally will transfer 2 embryos in patients who have embryos that have come from cycles that preceded PGS, so they were unscreened, but very seldom do we ever transfer more than a single embryo when they've been screened. The data is clear that our treatment in the past with multiple embryo transfer led to a lot of adverse outcomes and a lot of extra medical spending in caring for these neonates in the NICU and subsequent problems that some of them developed, and these things will be completely alleviated when our industry as a whole is able to put into place routine single embryo transfer for all of our patients. And I think the only way to realistically do that and achieve the kind of results that our patients expect is to use preimplantation genetic screening in the process.

Dr. Kaplan:

The guidelines I think are essential. I'm a very strong supporter of those guidelines. My only concern is that the guidelines and the reality of our field differ dramatically. If you look at the SART data, the number of single, elective single embryo transfers is well under 20%; so although many of us advocate it, in practicality I don't think it is still done to the degree it should be done. The role of PGS is the ability to educate patients and for the patients to be more comfortable in deciding to transfer a single embryo because a lot of the pushback, as we all know, in transferring embryos comes from our patient population; and many patients because of the time and the stress and the cost are more interested in getting pregnant than looking at the long-term health of a twin pregnancy. And PGS allows not only the physicians but the patient who's the ultimate consumer and pays for this to also feel more comfortable transferring a single embryo. Our patients have to be educated, this is part of the armamentarium, which is very strong, in showing patients that if you transfer a single embryo that's selected more accurately that you have a very high probability of pregnancy and a healthy outcome.

Dr. Tucker:

Well, I very much want to thank our faculty, Dr. Robert Anderson and Dr. Brian Kaplan, for outlining for us the latest advances in preimplantation genetic screening and diagnosis that will optimize fetal outcomes in assisted reproductive technology according to evidence-based guidelines as the data grows and also for discussing the appropriate screening and diagnostic protocols incorporating these latest technologies into their clinical decision-making.

Dr. Anderson:

Pleasure.

Dr. Kaplan:

Thank you very much.

Dr. Anderson:

Thank you.

Announcer:

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