# Recurrent Miscarriages - Causes and Treatments

Almost half of all pregnancies end in a miscarriage, most of them occurring within few weeks of conception.

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While there are a number of known risk factors such as maternal age, history of miscarriage, and infertility, there are others like alcohol consumption and smoking that remain controversial.

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We are talking to fertility expert Dr. Kristin Bendikson about the latest developments related to causes and treatments of recurrent miscarriages.

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**Full Transcript:**

**Shweta Mishra –** Good evening and welcome to CureTalks. I am Shweta Mishra, your host, joining you from India; and this evening on CureTalks' 102nd episode and our fifth talk on fertility and reproduction, we are discussing recurrent miscarriages – causes and treatment.

Miscarriage – Medically defined as spontaneous abortion of the fetus before 20 weeks of gestation, is cited as the most frequent problems in human pregnancy. American Society of Reproductive Medicine (ASRM) has recently redefined "recurrent" pregnancy loss as two or more pregnancy losses. According to a national survey analyzing perceptions of miscarriage, Couples pay a huge emotional price due to lack of knowledge, of the reasons, that led to the miscarriage. So knowing the cause is important. But unfortunately, doctors are still struggling to find a cause for almost 50-75% of women who miscarry. Today, We are talking to our eminent guest Dr. Kristin Bendikson, a fertility specialist, teacher, and researcher, to learn about the known causes of recurrent miscarriages and to know what is being done about the ones that are called "unexplained miscarriages". We will also delve into questions related to available tests and treatment options, as well as new developments in diagnosis and treatment.

On our earlier shows we talked to Dr. Mousa Shamonki of UCLA about the "The Risk factors associated with infertility in men and women". We discussed "Fertility preservation in young adult cancer survivors" with Suleika Jaoud and Dr. Andrea Reh, and We also discussed "Psychosocial and Emotional aspects of infertility and infant loss " with psychotherapist Helen Adrienne.

Our expert today, Dr. Kristin A. Bendikson is an Assistant Professor of Obstetrics and Gynecology in the Division of Reproductive Endocrinology and Infertility at the USC Keck School of Medicine, as well as serves as the associate fellowship director for the infertility fellowship. Dr. Bendikson joined USC Fertility after finishing her residency at Harvard Medical School and completing her subspecialty training in Reproductive Endocrinology and Infertility at Cornell University. She specializes in recurrent pregnancy loss, endometriosis, and polycystic ovarian syndrome, failed implantation, and egg freezing. She is opening

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USC's Center for Pregnancy Loss this spring and aims to provide the highest quality care for her patients. I welcome you to CureTalks, Dr. Bendikson.

**Dr. Kristin Bendikson –** Thank you, Shweta.

**Shweta Mishra –** Its our pleasure to have you, doctor. Yes.

**Dr. Kristin Bendikson –** Ah! Its very nice for me to be here. Can you hear me okay?

**Shweta Mishra –** Yeah. Yeah. We all can hear you okay, doctor. Thank you.

**Dr. Kristin Bendikson –** Wonderful! Wonderful! Why I am so happy to be here today to shed light on this important and often neglected issue of miscarriage, specifically recurrent miscarriage, I think its important when we talk about miscarriage that we…, I know you defined it a little bit in the intro, but just really to think about the term "miscarriage" and when people use that term, they are usually referring to a loss of the pregnancy that occurs in the first trimester, which is the first three months of pregnancy. Miscarriages are very common. They occur in 15% to 20% of all pregnancies. So, they are much more common than people think or are aware of. I believe that many people are unaware of how often miscarriages occur because often times its something that a woman keeps private and doesn't share with even her closest friends.

**Shweta Mishra –** Right.

**Dr. Kristin Bendikson –** Having more than one miscarriage in a row is less common and are further referred to recurrent pregnancy loss. Fewer than 5% of women will suffer two consecutive miscarriages and only 1% of women will suffer from three consecutive miscarriages. In my practice at USC Fertility, I see a lot of both fertile and infertile women who have suffered from a miscarriage or multiple miscarriages. In my consultations with these women, I find that they really focus on three things that they want me to answer for them. One, why did this happen to me? Two, can we treat it? And, three, what is the chance that this is going to happen again? I think its important and what I always tell my patients is that the more miscarriages a woman has in a row, the more likely it is that she is going to miscarry in the subsequent pregnancy. So, if you think about the background, risk of having one miscarriage is about 15% to 20%. After a woman has suffered two losses in a row, the chance of a loss in the next pregnancy increases to about 30% and after three losses in a row, the chance of another miscarriage actually increases to about 35%. The chance of miscarrying just gets higher and higher the more losses that a woman has; however, for that very same patient, instead of actually thinking about the fact that they have a 35 chance…, 35% chance of miscarrying, if instead you focus on the likelihood that they will actually have a baby with their next pregnancy, the chances are high. So, even when they have had three miscarriages in a row, the chance of having a baby with that next pregnancy is 65%, which is really good.

**Shweta Mishra –** Great! That's nice to hear. Yeah.

**Dr. Kristin Bendikson –** The majority of miscarriages are caused by non-inherited genetic abnormalities. People refer to these types of abnormalities as chromosomal abnormalities, and they account for two-thirds of miscarriages. Genetic material in all of our cells is packed into these tiny structures called chromosomes. When the egg and the sperm come together during fertilization, an embryo is made. This is just a term for a fertilized egg. Both the egg and the sperm are supposed to contribute one set of chromosomes to the embryo. If there is an error in the egg or sperm development, it may lead to the amount of genetic material in the embryo being abnormal. It means there is either too many or too little chromosomes in that embryo, and we call that a chromosomal abnormality. Chromosomal abnormalities are most often caused by random errors in the development of a woman's eggs, not in the sperm; and this eventually leads to an abnormal amount of chromosomes in the embryo. Its these types of chromosomal abnormalities that are random and not inherited that are the cause of most miscarriages. Now, this is true for a woman who has one random miscarriage, and its also true for a woman who has had multiple miscarriages.

**Dr. Kristin Bendikson –** The majority of chromosomal abnormalities happen as a function of egg quality. So, they… These chromosomal abnormalities can happen in women of all ages, but its going to happen more often as the woman gets older. In fact, age is the most important risk factor for miscarriage in a healthy woman. So, unlike sperms that are constantly created in men, all of the eggs in a woman that you will ever have are present in her body from before the time she was born. Therefore, as a woman ages, her eggs age, just like any other cell in her body. As the eggs age, they are more likely to have a mechanical failure as they develop, which leads to the egg contributing too much or too little genetic material to the embryo, meaning that there is either duplicates or an incomplete set of chromosomes. Therefore, that embryo will end up having an abnormal amount of genetic material, which we call that chromosomal abnormality.

The chance of miscarriage in any woman is greatly impacted by her age. The older a woman gets, the more likely it is for her to miscarry. The risk of a single miscarriage is only 15% in a 35-year-old; however, by the age of 40, it increases to 30%; and by the age of 40, the miscarriage rate is over 60%. There is some evidence to suggest that male age may also slightly increase the chance of miscarriage. If this is true, the cause is unknown as we do know that embryos are not more likely to be chromosomally abnormal when the male partner is older. Another very common cause of sporadic miscarriage is a congenital anomaly in the baby, also known as the birth defect. A congenital anomaly is a condition that occurs when there is an abnormality in how the baby is formed as its developing. Significant birth defects that are not compatible with life often cause early miscarriages. For example, if there is a severe abnormality in the development of the brain or the heart, this could cause an early miscarriage. Chromosomal abnormalities and even severe congenital anomalies are most likely to cause miscarriages that will happen before the tenth week of gestation. The further along a woman is when she miscarries, the more likely it is that there is another factor that's actually causing the loss.

**Dr. Kristin Bendikson –** When a woman has only one miscarriage, its very common to never know why they miscarried. Part of this is because a workup to assess why it happened doesn't usually occur at this time because the odds of getting pregnant and having a baby with the next pregnancy is really good; however, even with one miscarriage, it is important for a woman to meet with her obstetrician so that they can review together the woman's medical history and lifestyle and make sure that there isn't something obvious that needs to be addressed at that time that could impact the next pregnancy and the health of the next pregnancy. Even with the first loss, it is possible to test the tissue that passes with the miscarriage and send it to a lab to assess for chromosomal abnormalities. For most women, that information may not be useful because the likelihood is is that they will have a baby with their next pregnancy; however, I would argue that you never know which patient is going to have multiple miscarriages. So, having that information could be extremely valuable in the future, so you might as well stand off that information to begin with.

**Dr. Kristin Bendikson –** When a woman has recurrent losses, we can identify a cause of their losses in about 50% of couples. Unfortunately, many of these causes are treatable. Structural issues within the uterus can lead to miscarriage. This is a very common cause of recurrent miscarriage. Women can be born with an abnormally shaped uterus or throughout their life they can develop non-cancerous lesions called polyps or fibroids. Women can also develop scar tissue within their uterus as a result of infection or from a previous surgical procedure. All these uterine issues are associated with a higher chance of miscarriage. The good news is that in many of these situations, the uterus can be repaired surgically. If, however….

**Shweta Mishra –** That's good.

**Dr. Kristin Bendikson –** Yeah, its wonderful! If, however, the uterine issue cannot be fixed, the couple does have the option of using gestational surrogacy to get pregnant. Gestational surrogacy is when the embryo of a couple is actually transferred into another woman who has healthy uterus so that she can carry the pregnancy for them. In order to use a gestational surrogate, the couple needs to go through in vitro fertilization or IVF to get embryos from their eggs and sperms that can be put into the healthy uterus of the surrogate. So, even though the surrogate carries the pregnancy, the baby is 100% genetically related to the intended parents. So, gestational surrogacy can solve an unfixable uterine issue. There are also several immunologic diseases that have been postulated as increasing the chance of miscarriage; however, the only

disease that has been proven to cause miscarriages and pregnancy loss is antiphospholipid antibody syndrome. This is a disorder in which the immune system attacks the proteins in the blood that leads to an increase in blood clotting, which can result in that woman having either a blood clot in her leg or it can also result in having multiple first trimester miscarriages. Locally, this disease can be treated very effectively to decrease the risk of miscarriage by putting the mom on baby aspirin and a blood thinner. So, this is also another example of an easily treatable issue.

**Dr. Kristin Bendikson –** Endocrine imbalances have also been associated with miscarriage. Poorly controlled thyroid disease has been associated with pregnancy loss and infertility, which can be corrected with medical management of the thyroid problem. Likewise, uncontrolled diabetes can lead to increases in miscarriages as well as certain birth defects. A very common endocrine disease is called PCOS, which stands for polycystic ovarian syndrome. PCOS also increases the chance of a miscarriage. PCOS affects 5% to 10% of women; and its caused by an imbalance of sex hormones, specifically an increase in the amount of testosterone that leads women to have irregular periods and it also increases the chance of miscarriage. The risk of miscarriage for a woman with PCOS may be three times as high as the general population, so that's pretty significant. The reason why women with PCOS are more likely to miscarry is not fully known, but its thought to be related to how the hormone imbalances affect the uterine environment. Unfortunately, there is not a way to reduce the chance of miscarriage for women with PCOS.

**Dr. Kristin Bendikson –** Lifestyle factors can also contribute to the risk of miscarriage. These include extremes of body weight, being either underweight or overweight; however, exercise is not associated with miscarriage. Anything that can contribute to an extremely toxic environment inside the uterus will also increase the chance of miscarriage, like excessive amounts of drugs, alcohol, caffeine, and any amount of smoking. A rare but treatable cause of recurrent miscarriage is an inherited genetic abnormality where one of the parents has an abnormality in their genetic makeup that they keep on passing down to the baby each time they get pregnant, which, therefore, leads to these repetitive losses. These abnormalities can easily be tested for in the parents; and we can treat them by using something called pre-implantation genetic diagnosis with in vitro fertilization so the couple can go through the in vitro fertilization or IVF to have embryos created in the lab and then we can actually test those embryos for that specific genetic abnormality to determine which embryos are normal and which are abnormal. This way, we can transfer back only the normal embryos into the uterus and avoid transferring back those abnormal embryos and therefore avoid having another miscarriage.

**Dr. Kristin Bendikson –** Likewise, IVF can actually be used to treat the most common cause of miscarriage, which is chromosomal abnormality. By screening the embryos to make sure that they have the correct number of chromosomes in a process called pre-implantation genetic screening, we can avoid transferring back chromosomally abnormal embryos and therefore again gravely diminish the chance of a miscarriage. In extreme cases when the egg quality of a woman is very poor, often times a function of her age, an egg donor can be used to help the couple have a baby. With egg donation, a young woman will go through IVF and donate her eggs to a couple that either has infertility issues or recurrent miscarriages. By utilizing eggs from a young woman, the chance of miscarriage is decreased because the egg is younger and healthier and less likely to have a chromosomal abnormality. The eggs from the donor are fertilized with the sperm from a male partner, and then the resulting embryos are transferred back into the uterus of the female partner. Although the baby will not be genetically related to the female partner, she still, the woman, will still have the opportunity to carry that pregnancy and so that is really important to many women.

**Dr. Kristin Bendikson –** I think its important to understand that day-to-day stress and anxiety that is part of normal life is not thought to cause miscarriages. Its unclear if extreme levels of stress can increase the chance of miscarriage. Certainly, there is very clear data that suggests that having a miscarriage in and of itself can be emotionally traumatic, and it can take longer to heal from a miscarriage mentally than actually physically.

**Shweta Mishra –** Right.

**Dr. Kristin Bendikson –** Women experience a multitude of emotions when they have a miscarriage, from anger to numbness and depression; and I think its really important to take the time to grieve and to heal and to seek support from those around you that can help you through this difficult time.

**Shweta Mishra –** Right.

**Dr. Kristin Bendikson –** After many years, in my practice, caring for both infertile and fertile patients who have suffered from miscarriage or late pregnancy loss, I really noticed a profound lack of centralized resources for these patients; and I felt compelled to take action and create a center where patients could receive care from professionals who specialize in different treatment modalities in a coordinated fashion and so, therefore, that's the reason that I am launching the USC Center For Pregnancy Loss later this spring.

**Dr. Kristin Bendikson –** Okay.

**Dr. Kristin Bendikson –** Its going to be the only center in Southern California that is dedicated to providing group healthcare to those patients who have endured pregnancy losses. At our center, we will be having experienced, multidisciplinary team which includes physicians of all specialties, nurses, therapists, acupuncturists, and other mindfulness professionals who will be able to expertly guide patient to achieve a healthy baby. Our experts of all types will be formulating individualized plans to help patients who previously had not had a clear path to treatment to achieve their goal, the baby, while at the same time really helping those patients heal from the grief of their previous loss.

**Shweta Mishra –** Right.

**Dr. Kristin Bendikson –** Women who have suffered from any type of pregnancy loss have unique needs because they both are history and what they have gone through and I think that, you know, we're going to take our approach at the USC Center For Pregnancy Loss to address both past and future in all treatment modalities is really unique; and we will be taking a holistic approach addressing the patient's needs and both their mind and their body, preparing the patient for a healthy pregnancy and so with the launch of our center, we are going to be able to provide compassionate and extraordinary…, extraordinary care for those patients who have either suffered from recurrent early pregnancy loss as well as a single loss later in the pregnancy in the second and third trimester. I think that these women need care. I think that there is a lack of care for these women certainly in any kind of coordinated fashion. So, I mean, I think in summary, the most important thing is just to really remember that miscarriages are extremely common; and the best news is that there are many treatable causes of miscarriage and that in most cases, with or without treatment, the likelihood is that with the next pregnancy the couple will be able to have a baby.

**Shweta Mishra –** Now, that's so good to hear, Dr. Bendikson, and you described it so beautifully and just one question I wanted to ask you is does low folic acid intake also…, can that also lead to miscarriages? We know that it leads to spina bifida in babies, but can that be a reason for miscarriages?

**Dr. Kristin Bendikson –** Uhmm… I think it is unlikely.

**Shweta Mishra –** Okay. All right. All right. All right. At this point, I want to bring in our co-host for today's show, Fran Meadows. Fran is an author and infertility advocate, and she became a mom through IVF to her one son. She works with women fighting infertility by providing hope and inspiration and a friend to lean on, and she has authored the book titled The Truth Behind The Secret Infertility. And we have on our panel today with us Davina Fankhauser who has a very, very impressive work profile in the field of fertility advocacy. She is a 15-year long former infertility patient who has now two children with IVF. She has extensively lobbied for infertility health benefit, national funding, and family building legislation at the state level. She has led strategic efforts to update the Massachusetts definition of infertility and see cryopreservation of eggs become a required benefit of infertility and available to other patients with medical need. Davina founded Fertility Within Reach in 2011 through which she trains people to advocate for infertility. She also has oncology patients preserve their reproductive health through her non-profit program,

Banking on the Future. Davina is a member of many prestigious societies and also a recipient of many prestigious awards like the Congressional Award, RESOLVE Advocacy Award, and many others. So, I welcome to the…, welcome you both to the show, Fran and Davina; and before we begin into the panel discussion, I would like to remind my listeners that we will be discussing questions sent in via email at the end of the show. So, you can mail your questions to priya@trialx.com; and if you want to ask a question live, please press 1 on your keypad and we will bring you live on air to ask them, or you can post your questions on CureTalks' website as you listen to the show. So, with this, Fran, I hand it over to you now to take the discussion forward.

**Fran Meadows –** Great! Thank you, Shweta, for having me again today and welcome to Dr. Bendikson and to Davina. Thanks for having me here to ask some questions and, Dr. Bendikson, for the first thing, I would like to firstly thank you for taking the initiative to open up about the Center For Pregnancy Loss that you will be launching shortly because I think its really a good way to start a discussion, open up those resources for patients that have suffered with pregnancy loss like myself. So, thank you for that.

**Dr. Kristin Bendikson –** Oh, you are welcome, really! I am…, I am very excited and hopeful that its going to be useful for many patients.

**Fran Meadows –** I am sure it will be, it will be. (Laughter) And with that, for myself, I…, I suffered with a very late pregnancy loss at 25 weeks; and this topic is something very sensitive, near and dear, and its also something where I want to continue the conversation for so many other women that I have been hearing stories of miscarriage or late pregnancy loss; and with that, my first question for you is, for a woman that goes though her regular pregnancy checkups and their screenings until a few days before they are going into labor or being scheduled for a C-section, why do full-term stillbirths still happen with all the monitoring and, you know, how could they be prevented?

**Dr. Kristin Bendikson –** Sure. Stillbirths that occur very late in a healthy pregnancy are rare and when they do occur in a healthy pregnancy, a lot of the time unfortunately there is an unexplained cause and we really don't understand exactly why it happened. Two causes that we do know that can happen in very late pregnancies are an umbilical cord abnormality or a placental abruption which is when the placenta prematurely separates from the uterus. With both umbilical cord abnormalities or placental abruption, the onset of both of those things is very sudden, which is why there is a warning sign and then because there is not a warning sign, there is no way to predict that its going to happen and therefore, its very hard to prevent. On the other hand, there are some causes of stillbirths that can get picked up early, for example, fetal growth restriction, which is commonly a result of placental dysfunction. This is still a very common cause of stillbirth; and if the woman is having routine prenatal care, her doctor should be able to diagnose if the baby is not growing well and is growth restricted and then take measures to assess the baby's well being and deliver the baby early if the baby is having issues and in this scenario, a stillbirth could be prevented, but unfortunately, many of the causes of these very late stillbirths are unpreventable because they can't be predicted.

**Fran Meadows –** And now if somebody were to, like myself, have a stillbirth and then, I mean I did go on to have a…, a full healthy pregnancy after my stillbirth, would there be other indications of, you know, maybe, you know, I would suffer like a miscarriage like if I were to get pregnant again if I did have a stillbirth or is that kind of rare?

**Dr. Kristin Bendikson –** No. So, your… Because you had one stillbirth does not mean that you would…, are more likely to have a miscarriage in the future and I think a lot of your chance of having another stillbirth would be dependent on why it happened in the first place. If they couldn't figure it out or maybe it was because of some placental abruption, you know I think its worthwhile to explore, for example, with the placental abruption, you know, make sure that the uterus has a normal shape and doesn't have some kind of congenital anomaly that would predispose you to having a placental abruption. I think many placental abruptions are random and it is just horrible if it happened to you, but probably it wouldn't happen again, but for other women who have a structural abnormality in the uterus, they maybe are more likely to have that

happen.

**Fran Meadows –** Right. Right. And, so…, so going through fertility treatments, I…, I went through to conceive and then I lost my first child and, of course, you know, the first thing I was thinking was its my fault. What did I do wrong? You know, but then I thought afterwards did this happen because of fertility treatments and medications and are there indications that fertility treatments can cause pregnancy loss or…, and…, on the other hand, do you believe that when somebody is on like progesterone and oil, are they effective in helping prevent miscarriages because this is something that I have heard.

**Dr. Kristin Bendikson –** Sure. So, there is not an increased risk of miscarriage or stillbirth after fertility treatments; however, advanced maternal age is an independent risk factor for both miscarriage and stillbirth. So, older women who are more likely to have…, older women are more likely to have a miscarriage because of worsened egg quality leading to the higher rates of chromosomal abnormalities and older women are actually also more likely to have stillbirth and that is even after accounting for medical issues that are more likely to occur in older women that are associated with stillbirth. So, the fertility treatments per se don't increase your risk for miscarriage or stillbirth. I do think that sometimes very, very early miscarriages are caused more early with fertility treatments because we are monitoring the pregnancies so much more closely and carefully than in a spontaneous environment.

**Dr. Kristin Bendikson –** For women who have had multiple miscarriages, there is good data that suggests that supplementing with progesterone actually does not improve their outcomes and this is specifically for miscarriage. I am not talking about progesterone in terms of pre-term labor because that is a different animal. In terms of progesterone for miscarriage, there is actually a pretty recent study of over 800 women that showed very well that the progesterone didn't improve outcomes; however, there certainly are smaller studies that do indicate that progesterone could be beneficial for women who have had multiple miscarriages.

**Dr. Kristin Bendikson –** In certain situations where the ovary is not able to produce enough sustained progesterone secretion, then in those situations, progesterone is absolutely beneficial; and this can occur when there are mild medical issues like thyroid disease that are impacting progesterone secretion. Progestins which is how the…, how we deliver progesterones to use the type of medication, so progestins can be administered both through vaginal suppositories or through intramuscular shots and both of those are equally efficacious and both of those are actually superior to taking oral progestin therapy. So, you know, in the end, progestins don't necessarily improve outcomes in all of the research that's out there. It is a very common treatment for women with recurrent loss; and a lot of that is due to the fact that, you know, progesterone supplementation is unlikely to cause any harm in the pregnancy. There are very few side effects. So, many physicians feel that its worth prescribing even if there is only a small chance that it could have a positive impact on another pregnancy.

**Fran Meadows –** Great! That's really great information, I am sure, for so many people who are, you know, listening in. So, I mean, thank you for all that information and, you know, its a really great resource for other people to hear, you know, talking about this conversation. So, thank you for that.

**Dr. Kristin Bendikson –** Oh, you're welcome.

**Fran Meadows –** And at this time, I am going to introduce Davina to come in and go ahead and ask the questions. Davina, are you there?

**Davina Fankhauser –** I am here, Fran. Thank you so much an

d…

**Fran Meadows –** Hi! Thank you for being here.

**Davina Fankhauser –** Thank you. Thank you, Shweta, for inviting me and, Dr. Bendikson, thank you for your time and your expertise. This subject is very important to me. I was someone who… I have experienced 10 pregnancies and I have been lucky enough to come out with two children through IVF, but I…, I am extremely passionate about it and I hope to educate as many people as possible so they don't have to go through, you know, necessarily what I went through or Fran went through. I was wondering, you know, when…, when I miscarried, I would feel my body was letting me down or that my body was meant to be pregnant and sometimes I would feel hesitant or feel loss of hope and I was wondering, does that ever impact the body's ability to become pregnant or to sustain a pregnancy when you tend to feel a bit down like that.

**Dr. Kristin Bendikson –** Sure. No, I think the amount of anxiety, hopelessness, and actually even emotional detachment that a woman experiences when she has had pregnancy losses in the past do not contribute to her ability to either get pregnant or to her having another miscarriage and I think that that's really, really important for people to know because I think anyone who has suffered from one loss or multiple losses, whether it be early or late, all of those feelings I think are normal and are very common. So, its important to know that those feelings are okay and they're not going to make things worse for your next pregnancy. I often find that many patients of mine who had miscarried feel extremely anxious and ambivalent and sometimes super disconnected from a current pregnancy until they pass the point in the pregnancy where they miscarried previously. So, I think its really important to acknowledge these feelings, try not to squelch them, know that they are there, they are real, and that they are very common.

**Davina Fankhauser –** Thank you. Thank you. You know, one of the things I have always wondered about it because I seemed to always get pregnant, I would get pregnant once a year and then I would miscarry in my first trimester and…, and way back then the doctor would say, "Oh, its just your normal, you know, percentage chance of…, of miscarrying," but, you know, after three, four, five miscarriages, I am thinking, really, if this is my odds, so I am wondering after how many miscarriages should a patient receive a thorough exam and what does that evaluation consist of and is it covered by insurance, all those kind of questions.

**Dr. Kristin Bendikson –** Sure. I think even after one miscarriage, its advisable for a woman to meet with her obstetrician to discuss, you know, what factors surrounded the miscarriage and to review the woman's clinical history so that they can identify medical issues that could have possibly contributed to the loss. Obviously, you want to rule out anything that is out of the normal that could be fixed. You know, I also think its really important to meet with the doctor so that the woman gains an understanding of why miscarriages occur and understanding that, you know, her chances of conceiving with the next pregnancy are very good, so to give her that hope. After two miscarriages, it is recommended to see a specialist who can proceed with a more thorough and complete workup; and the evaluation is going to basically run down all of the known causes of recurrent miscarriage and rule that couple out for every single one of them so that, one, you can understand why the multiple miscarriages have happened; two, identify if there is something that you can fix and so that evaluation is going to consist of blood work. So, in the blood work, you are going to test for ovarian reserve, which is related to the woman's age. You are going to rule out medical and hormonal issues. You are going to look for those inherited genetic abnormalities that I talked about, and you are also going to rule out antiphospholipid antibody syndrome which is that one blood clotting disease that I talked about. You will also be looking at the uterus and to make sure that the uterine cavity is normal and there are multiple different radiologic tests to do that and I think that many insurance carriers will cover this, but some won't and I think that you have to just look in to figure out if your's does or not.

**Davina Fankhauser –** Okay. Yeah, thank you. So, I wasn't sure if this was considered in infertility workup or, you know, working up causes related to OB-GYN issues.

**Dr. Kristin Bendikson –** Yeah, I…, I think that, you know, it really again depends on the insurance carrier…

**Davina Fankhauser –** Yeah.

**Dr. Kristin Bendikson –** …and some of these tests can get run by the routine obstetrician/gynecologist. I mean, often times you can even go see a fertility specialist and then they can just make the recommendation

and then your OB-GYN who maybe is within your insurance plan can actually run those tests for you and that's what I do with a lot of my patients. I just want them to get the workup done. It doesn't matter if they are doing it at my office or through their own obstetrician.

**Davina Fankhauser –** Accha. Well, so…, one…, after one of my losses, I ended up having a D&E versus passing everything naturally and I was wondering what are some of the risks associated having a D&E versus passing everything naturally?

**Dr. Kristin Bendikson –** Okay. So, I'll explain a little bit for the audience so they make sure that they know what a D&E is or D&C. So, when someone gets diagnosed with a pregnancy that's no longer growing inside the uterus, they have several options at that point. The woman could go under a D&C which is the type of procedure that's performed in the first trimester, and this is a very simple procedure where the remaining pregnancy tissue is removed from the uterus. Another option is that a woman can take some oral medication that will induce the miscarriage to occur so the woman will pass the pregnancy on her own, but the medication will just make it happen really quickly; and then the last option is that the woman could just wait and see and try and let the miscarriage happen when its going to happen and happen on its own timeline. They are…, they are all safe; and the choice that the woman decides upon sometimes will depend on how far long she is in her pregnancy because the farther along in the pregnancy she is, the more bleeding that's going to occur when the…, if the woman is passing it on her own. So, sometimes when it gets to certain point its kind of inadvisable to pass the pregnancy on your own just because it will be so uncomfortable and so unpleasant. A lot of times it depends on the personal preferences of the woman herself, whether she just prefers getting it all over with really quickly while she is asleep during the procedure or if she wants to be able to just pass it on her own, but she doesn't want to wait for it to happen naturally. She wants to kind of do it over a weekend when she is not at work and she knows she can be at home, so that's when taking the medications can be very effective and they are all safe options. A lot of it is just really due to personal preference.

**Dr. Kristin Bendikson –** Whenever I think the pros of having a surgical procedure that has been kind of put forth is that, oh, if you do the D&C procedure, we can get genetic tissue testing done and I think that its actually important to know that you can get genetic tissue testing done on the products of conception whether you have a procedure called the D&C or if you pass the pregnancy at home because even if you pass the pregnancy at home, you can collect the tissue and bring it into the office and we can send it off. In both of those cases, we can send that tissue out to a lab that will test it and it will…, they will be able to determine if the loss is because of a chromosomal abnormality or not and so I think that that is really important and I am not sure what you went through, but typically when people refer to the procedure of the D&E, that's when its…, the procedure that removes the pregnancy in the second trimester pregnancy and that's the surgical procedure that women undergo because women…, when women have a loss in the second trimester, they still have the option of medical induction or they can go through the D&E and again both of those are safe, although actually in the second trimester, the D&E procedure is left with and so actually that is chosen more often than the medical induction.

**Davina Fankhauser –** Okay. Well, I do have a thank you for that clarification and I do have a followup question.

**Dr. Kristin Bendikson –** Sure.

**Davina Fankhauser –** I remember this happened to me once where it was like a Friday evening and I miscarried and I basically, I kept the tissue and put it in a baggy and put it in the refrigerator. Is that what you are supposed to do if the doctor's office is closed for the weekend?

**Dr. Kristin Bendikson –** Yeah. Yeah. So, the…, the best thing is literally to go out to…, put it in a bag, you can do that and put it in the refrigerator but go out to a pharmacy and get some saline which is just salt water you can get that people use for flushing their eyes out and you can actually get like a little plastic cup from a pharmacy and put the tissue in that. I think its really important to understand what your obstetrician has in

terms of their capabilities of sending the tissue out for genetic screening because there is a lot of amazing technology that's out there now and there are these new genetic screenings that are being done and so its important to make sure that the best and most advanced testing is being done and many obstetricians unfortunately are using these outdated genetic tests that often times will actually fail to diagnose the tissue and/or give you ambiguous results and so, especially when tissue, if you have passed it on a Friday night, you are not going to go into your doctor's office by Monday. With these old testing modalities, they are more likely to not get a result and they are also more likely to not get a result if, for example, the…, you know, the…, the pregnancy loss was diagnosed at six weeks and then you didn't pass it for eight weeks. The new testing that we have at our office and is available at many fertility centers, those problems are not issues anymore and so it doesn't matter if the pregnancy loss was diagnosed at six weeks and you are now passing it at eight weeks. We can still send the tissue out; and we'll get a result every single time and we're not going to get an ambiguous result where they give you result…, they tell you, well, we're not really sure what this means and we can't tell you for sure if its normal or not.

**Davina Fankhauser –** Can you clarify like what is old and what is new because how will a patient know if the doctor is using the old technique?

**Dr. Kristin Bendikson –** So, the old…, the old genetic…, the old genetic testing is where they literally culture out the tissue and they just send it for a karyotype, wherein they just kind of look at the chromosome. The new genetic screening is through very… and not something that's typically done through a hospital. The new genetic screening is the type of screening that's done when we are testing embryos with IVF where they use very advanced modalities, something called competitive genetic hybridization or SNP arrays or next-generation sequencing to diagnose, to specifically find abnormality they can determine and separate out maternal tissue from baby tissue. So, I think it is the best way to actually maybe determine with your doctor or if they have those newer technologies or not is just to ask them, how are you going to be testing the genetic material and if they say karyotype, then that's not what you want. I mean you can get that and if you get a result and its okay, but I think it is often times its just…, you spend a lot of money and you don't get the answer that you want.

**Davina Fankhauser –** Fantastic! Thank you for that. So, I…, I was wondering, so what do you think are the best treatments for someone who experiences recurrent miscarriage?

**Dr. Kristin Bendikson –** Well, I think you know the…, the treatments for recurrent miscarriage are really going to depend on the cause and so I think that this is where understanding, you know, what the cause is and understanding is this related to maternal age and if that's the scenario and its a chromosomal abnormality issue, then IVF with pre-implantation genetic screening can be very effective. Or, if this is a uterine structural issue…, so, for example, there is a congenital anomaly of the uterus called the uterine septum. So, women are born with these abnormal-shaped uteri and typically that's not anything that you would ever have picked up in a public exam or an ultrasound, you would never know you have it and these women suffer from high rate of miscarriage and in fact if you have a uterine septum, the chance of having miscarriage is about 25%. In these women, if you…, you can go in with a very simple surgical procedure called the hysteroscopy which is where we put a camera through the cervix and go into the uterus and you just cut and remove that septum. Its so simple! The miscarriage rate is decreased by 90%.

**Davina Fankhauser –** Wow!

**Dr. Kristin Bendikson –** And so, its…, its amazing and so I've…, I have seen this multiple, many times in patients and its just a very effective, simple thing that can really dramatically change that outcome and I think another one of those kind of very effective treatments is with antiphospholipid antibody syndrome. I think by treating women who have this syndrome, all we have to do is treat them with baby aspirin and a blood thinner and their chance of miscarriage is decreased by 70%.

**Davina Fankhauser –** Wow!

**Dr. Kristin Bendikson –** So, for those…, you know, for those two scenarios we have great treatments that can be very meaningful for the pregnancy outcomes in the next pregnancy.

**Davina Fankhauser –** That… This is so helpful. I wish I had known all of this when I was trying to build my family. I have one more question for you…

**Dr. Kristin Bendikson –** Sure.

**Davina Fankhauser –** …and it may be really odd, but I heard that eliminating mycoplasma can help someone who miscarries. Have you heard of this? I am wondering…

**Dr. Kristin Bendikson –** Yeah. I have absolutely heard of it. So, there are certain infections that can lead to miscarriage. So, for example, if a woman can track a disease like listeria, toxoplasmosis which is from cat litter, or herpes – all of those can cause sporadic miscarriages in the first trimester. There are no infections that actually cause recurrent miscarriage. People have hypothesized that certain infections like mycoplasma and ureaplasma cause miscarriage, but there is no good research that supports these.

**Davina Fankhauser) –** Thank you so much and I know Shweta has questions for you, but I just want to thank you again for…, for this information. Its amazing! Thank you.

**Dr. Kristin Bendikson –** You're welcome.

**Shweta Mishra –** Thank you, Davina, for handing me over; and you had some great questions which will make a very informative talk today and; Dr. Bendikson, you talked about aneuploidy or chromosomal abnormalities and you really explained very well what goes wrong there, but is there a way to stop that from happening in later pregnancies if suppose we know that that was the case in the previous one?

**Dr. Kristin Bendikson –** I know. Well, you know, as of right now we don't have a way to prevent chromosomal errors from occurring in embryos. Its not something we can predict either with their current technologies, for example, like an ultrasound or blood work, and…, and its because chromosomal errors don't occur until the very final stages of the egg development which happens at the time of ovulation and fertilization each month. So, these stages of development when the errors occur are very late in the process and they are not something that you can see months ahead. You know, currently, there is lots of interesting research taking place, trying to figure out how we can think better about chromosomal errors. For example, there is research looking at mitochondrial levels and embryo and how that affects aneuploidy. Mitochondria are the energy-producing organelles in our cells, but we are really a long way off from figuring out a way to completely prevent aneuploidy. I think solving that issue is akin to preventing aging. (Laughter) You know, but at the current time, the best thing that we can do is test the embryos for chromosomal abnormalities in the setting of IVF with preimplantation genetic screening and, you know, by doing this we can greatly decrease the chance of miscarriage by avoiding transferring back those embryos that have the abnormalities.

**Shweta Mishra –** Right. So, you… So, do you compulsorily do the PGD for each and every embryo ?

**Dr. Kristin Bendikson –** We…, we don't for our infertile patients. For patients who specifically have recurrent miscarriage, I actually talk to them about what their options are and…

**Shweta Mishra –** All right.

**Dr. Kristin Bendikson –** …not everyone…, not everyone wants to do preimplantation…, preimplantation genetic screening and remember, even without treatment, even for someone who has suffered four miscarriages, there is a decent chance that she will have a normal pregnancy in her next pregnancy if she just tries again, but I think that sometimes what it comes down to is that people are just so tired of miscarrying that the thought of going through another miscarriage is just untenable and so in those

situations, PGS can be very useful.

**Shweta Mishra –** Okay. All right. All right. So, my next question relates to IVF. Do you think that the use of frozen eggs is one of the causes of increased miscarriages in people who are trying to conceive through IVF…

**Dr. Kristin Bendikson –** Yeah.

**Shweta Mishra –** …and is there a study which shows such a correlation?

**Dr. Kristin Bendikson –** Yeah. No, there is no evidence that using frozen eggs increases the chance of miscarriage.

**Shweta Mishra –** Okay. Oh, all right. I think I saw some study in JAMA or some publication which shows that lower live birth rates are related to use of frozen eggs or… Is that true?

**Dr. Kristin Bendikson –** So, when they say that the clinical pregnancy rates with frozen eggs get worse, its still _____[00:53:42]_____ out, but it still be that they might be slightly lower than IVF, but that's not because people are miscarrying. Its just that their chance of getting pregnant is actually little bit lower.

**Shweta Mishra –** Right.

**Dr. Kristin Bendikson –** Yeah.

**Shweta Mishra –** All right. Okay, okay. All right. So, my next question also relates to IVF and I wanted to know if the correlation between the date in the embyronic development on which the embryos are transferred, for example, the day 2, day 3, or day 5 embryos and recurrent pregnancy loss, is there a correlation?

**Dr. Kristin Bendikson –** Yeah. So, after IVF, the embryo is kept in the laboratory for it to develop and we can transfer it back into the uterus at any time between day 2 and day 5. When the embryo continues to develop normally at day 5, it should reach a particular stage of development called the blastocyst. Unfortunately, embryos that are chromosomally abnormal become blastocysts all the time. So, therefore, transferring embryos back at day 5 instead of day 2 isn't going to avoid transferring back a chromosomally abnormal embryo. Even how the embryo looks on day 5, whether its a good quality embryo or poor quality embryo based on the physical features of the embryo is not predictive of chromosomal abnormalities. So, really the only way to decrease pregnancy when choosing which embryo is to put back is to test them with pre-implantation genetic screening and that is actually performed at the blastocyst stage. So, you have to let them develop for five days in the lab.

**Shweta Mishra –** All right. Okay. All right. So, next question is about DNA fragmentation in sperms. So, first of all, I want you to…, I would like you to explain to the audience what DNA fragmentation is and what is the possibility of a sperm with fragmented DNA fertilizing an egg to form a viable embryo and has a high DNA fragmentation rate of sperms been shown to be one of the reasons for miscarriages?

**Dr. Kristin Bendikson –** Sure. So, DNA fragmentation is a measure of the integrity of the DNA within the spermatogenetic material within the sperm. During the time that the sperm travels from the testicle to the ejaculate after its been formed, it can get damaged. DNA that is more fragmented is more likely to be damaged during sperm transport. The DNA fragmentation test is a way to assess the state of the DNA in the sperm; however, the issue is that existing data does not support a consistent relationship between abnormal DNA fragmentation and poor reproductive outcomes. There are a few studies that have looked at the relationship of DNA fragmentation to pregnancy loss and a recent med analysis did find an association between DNA fragmentation and pregnancy loss after IVF; however, there isn't any evidence to suggest routine testing of DNA integrity because there is no use and…, and useful way of using that information in

order to predict the pregnancy outcomes. So, I think that researchers are currently looking at the use of antioxidants and are retrieving sperm directly from the testicles as a way to improve DNA integrity, but as of now, there are not reliable ways to…, and proven ways to check DNA integrity at all. So, therefore, DNA fragmentation testing is not recommended in patients with miscarriages.

**Shweta Mishra –** Okay. All right. I think my next question is on immune abnormalities and I have a listener's question on the same topic. I think I'll read out the listener's questions.

**Dr. Kristin Bendikson –** Sure.

**Shweta Mishra –** What are the treatment options that are available for immune abnormalities that cause recurrent pregnancy losses and what are the recent developments in this field that can be…, that we can be hopeful about?

**Dr. Kristin Bendikson –** Okay. So, the most common immunologic disorder is the disease that I talked about already, the antiphospholipid antibodies, and antiphospholipid antibodies are proteins in our bodies that have been created to impact our blood clotting system. Phospholipids in specifically are substances that are required for the blood to clot. So, if the body mistakenly identifies these phospholipids as foreign, its going to form antibodies against them; and these antibodies can increase the body's tendency towards clotting. We think that antiphospholipid antibodies can cause miscarriage by causing clotting in the blood in the placenta and that obstruction to blood flow leads to tissue death within the placenta. The only antiphospholipids that are associated with miscarriage are the ones associated with antiphospholipid antibody syndrome, and so I think that is really important to understand. There are a lot of companies and physicians that market potentially harmful and difficult remedies to fix supposed immunologic issues for patients with recurrent loss; and these companies and physicians are preying on the patient's desires to do anything, pay anything, and take anything in order to have a baby. So, treatments like steroids and intravenous immunoglobulins that are prescribed to fix certain immunologic causes of recurrent miscarriage do not work and are potentially dangerous to the patient. So, I actually get really upset when I find out patients have really been…, because I had had this happen many times where patients have been swindled into paying just exorbitant amount of money for useless tests, for all sorts of immunologic tests that have no bearing, and treatments that could actually cause complications in a future pregnancy.

**Shweta Mishra –** And you mentioned the baby aspirin, so people with antiphospholipid antibody are supposed to take baby aspirin?

**Dr. Kristin Bendikson –** Yeah. Baby aspirin and…, and a blood thinner.

**Shweta Mishra –** Okay. All right. Okay. At this point, I guess, Fran, do you have anymore questions for the doctor?

**Fran Meadows –** Maybe one last question, just kind of going to the emotional aspect of it. I know as doctors you guys are people too with feelings (laughter) and I am sure that in your…., you know, I am sure in your office you'll be screening for miscarriage or stillbirth with many of your patients and my curiosity is, how do you separate your professional and personal feelings when something like this happens in your office?

**Dr. Kristin Bendikson –** It can be very challenging. (Laughing)

**Fran Meadows –** I am sure.

**Dr. Kristin Bendikson –** I think its…, I think its really hard to separate out personal and professional feelings when a patient has a loss. I am really attached to my patients and personally connected with them and so these losses are devastating for them, but they are devastating for me, they are devastating for everyone that's involved in their care at our office and especially if that patient has gotten pregnant after a longstanding infertility and fertility treatment. So, I think in answer to your question, I…, I don't fully separate

my professional and personal feelings, but, you know, I think that that's what makes me an empathetic and caring doctor and I think you can still be a compassionate and sensitive doctor and kind of open your stuff up personally and at the same time provide excellent, kind of objective medical care.

**Fran Meadows –** Right and I am sure. I mean…, I know like I said, going…, going through my experience, it was very hard for me to even talk into the doctor's office after the fact.

**Dr. Kristin Bendikson –** Yes, its very common.

**Fran Meadows –** Its like you could just…, you could just feel like, you know, the faces…, like you could tell like, I think, you know, like even being in the hospital afterwards I find that doctors in hospitals with their staff, sometimes…, I mean the people I've…, I've run into when I was there, I didn't feel they were well equipped to deal with these tragedies…

**Dr. Kristin Bendikson –** Yeah. Yeah.

**Fran Meadows –** …and they didn't have compassion or professionalism and that was bothersome to me and that's why like…

**Dr. Kristin Bendikson –** Sure.

**Fran Meadows –** ….I said I really think that your center for pregnancy loss is really going to be a great way to kind of make people heal and, you know, experience their feelings and express how they are feeling but yet find their way of healing on their own and balance and that's kind of like what I did, you know, afterwards and I think that, you know, there should be a lot more protocols in place, I guess, from hospitals because sometimes I feel you know when I was there, it was just kind of like they just noted like on the door, like don't go in there, don't go in there.

**Dr. Kristin Bendikson –** Yeah. No, absolutely… Yeah, absolutely you're so right. I mean the majority of hospitals have protocols in place to guide staff members to help them manage, kind of the medical and social logistics when the patient has a stillbirth and every labor and delivery unit I have ever worked on they have that binder that has, you know, the medical protocols for the doctors and the medical protocols for the nurses and then outlines for the nurses to…, to kind of guide them through all the logistical steps that need to be addressed and, you know, the packet for the patients that have resources for them, etc., but that being said, I mean its hard…, its hard to teach compassion and sensitivity to people and I think that something to kind of keep in the mind is that stillbirth is not that common and so that, you know, its not something that every doctor or nurse or staff member has…, with the floor has dealt with on a regular basis, so their ability to manage that situation kind of in a compassionate, efficient, and sensitive way may not be perfect and I think certainly there are some personalities that just don't even know how to handle that situation because they're just so emotionally charged…

**Fran Meadows –** Right.

**Dr. Kristin Bendikson –** …, but I think that that being said, I think there is absolutely more room to improve training of staff dealing with stillbirth and so I think that when you have events like this that are rare, its really important to provide repetitive end services for staff members and whether that be lectures or mock drills or role playing, anything to just kind of remind them over and over again of kind of what needs to happen because they can't just like put a binder behind the desk and expect them to be compassionate.

**Fran Meadows –** Right and I agree. I agree that there should be like…, kind of, I mean it sounds terrible, but kind of like hands-on training where people have like an experience where they discuss and see how they would be able to handle it if it happens on their shift or something of that sort. So, I think…

**Dr. Kristin Bendikson –** No, I think with…, with medical care, they are really moving towards that. The…, the

medical students that go through now go through their training, they have to talk to actors in terms of delivering bad news and…

**Fran Meadows –** Right.

**Dr. Kristin Bendikson –** …dealing with a difficult situation and they get graded on how they do that and they get immediate feedback with that and so I think that at least from the physician's side, hopefully with the next generation of physicians, we are going to be a little bit better, but I do think that that takes efforts on departments that you are dealing with the staff that you have now and so I know even at USC, we brought in an expert, her name is Kiley Hanish, and she has this Return to Zero Center For Healing. She came and talked to our department about this very issue because I really wanted her to sit down with a resident and really talk to them about what it was like. She…, you know, she personally suffered a loss and to really explore with them kind of how she felt and what she really needed from the people that were taking care of her at that time.

**Fran Meadows –** Yeah. So, I am actually familiar with the movie, I saw it on Lifetime. So, it…, it brought a lot of feelings and memories back. So, I mean, I…, I think with hope that there will be more training and compassion and like you said, its…, its something that's very hard to deal with on a professional level or personal level, on every level, so thank you for sharing that.

**Dr. Kristin Bendikson –** Yeah.

**Shweta Mishra –** All right. Thank you, guys. Thank you so much. I think we need to wind up the discussion now because we have reached the end of the hour. Dr. Bendikson, thank you so much for being here with us today; and it was a wonderful discussion, and we wish you all the best with your new center for pregnancy loss. I am sure its going to be a help to the patients as well as to the caregivers. ….and, Fran, thank you so much for co-hosting with me and, Davina…

**Fran Meadows –** Thank you.

**Shweta Mishra –** …thanks and congratulations for all you do with the infertility community and I must mention that you are doing a commendable job with your Banking on the Future program.

**Davina Fankhauser –** Thank you.

**Shweta Mishra –** I hope… Yeah. I hope this discussion would serve as a good reference for many who are searching for authentic information on the recurrent miscarriages; and, audience, I thank you for your support and we look forward to having you all join us on our next CureTalks show on 31st March, 2016, at 5 p.m. eastern time to discuss emerging immunotherapies in myeloma treatment with Dr. Saad Usmani. For more information on this show and other upcoming shows, please visit our website, www.curetalks.com, or you can email at priya@trialx.com. The link for today's show will be sent in via email to all the participants. So, until the next show, thank you very much, everyone.

**Fran Meadows –** All right. Thank you.

**Dr. Kristin Bendikson –** Thank you.

**Davina Fankhauser –** Thank you.

All right. Bye. Bye.

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