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Sexual Health & Pregnancy in Autonomic Disorders Live Facebook Chat – August 18, 2014

The following is a transcript of a live Facebook chat hosted by Dysautonomia International, with special guest Dr. Svetlana Blitshteyn. This is mature content intended for adults age 18 and over. The names of all participants have been removed to protect patient privacy. All of the answers below were provided by Dr. Blitshteyn. This information should not be considered medical advice and is provided for general educational purposes only. Please consult your own physician for medical advice.

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- Q: Suggestions for those of us who can't take the pill due to stroke concerns... is hysterectomy a valid option?
- A: It depends on what the reason for hysterectomy is. I would approach any surgery with caution - i.e., unless there are clear indications for surgery.
- Q: Any other suggestions for hormone regulation with out the pill? I have a PFO (patent foramen ovale).
- A: I agree with your doctors and wouldn't use any hormones, whether oral, IUD or transdermal if you have a PFO. If you need to control POTS symptoms during your period, your safest option is to do it with POTS medications, not hormones.
- Q: I've had my tubes tied and have menorrhagia. My OBGYN suggests OCP (oral contraceptive pill) or ablation or hysterectomy as last resort. I tried mirena for one year no luck. I see a pots specialist on west coast. No meds just fluids salt exercise etc. back to work now and want to keep the momentum. Is there any contradiction in OCP usage or with anesthesia for a gyn procedure?
- A: No, there is no contraindication to the use of OCP in POTS patients. There is also no contraindication to anesthesia in the uterine ablation procedure.
- Q: Why so many of POTS patients have "non epileptic seizures" is that related to POTS or not?
- A: It depends by what you imply with the term "non-epileptic seizures." If convulsive activity occurs when you faint, then we attribute this to cerebral hypoperfusion. There are other type of spells that may occur in POTS; it depends on what symptoms/signs are manifested. I think the terminology may be confusing to both doctors and patients since "non-epileptic seizures" often implies pseudoseizures, which then translates as "psychology." A better term to use is "syncope"

with convulsive activity” to distinguish those who faint and convulse from those whose spells are caused by psychological or psychiatric causes.

- Q: My husband doesn't understand why I don't have the energy to have sex, yet I force myself. I get chest pains and still push through. I have a pacemaker and have had many work ups on my heart from three different cardiologist and one was at Mayo Clinic. Can you explain to me why we get these chest pains and why they hurt so bad sometimes. Today I was walking and had to stop three times it hurt so bad, but I relaxed and they got better. How do I make him understand?
- A: I have a number of patients with chest pain and no explanation from the cardiologists as to what causes it. Sometimes beta blockers help, and in some patients, medications for neuropathic pain help as well. As for your husband, clearly he needs to be more understanding and supportive of your chronic illness. One way to help him understand is to take him to your doctor's appointment where they can discuss your health problems with him. Another option is to do couple counseling as it appears that it affects your relationship.
- Q: My worst symptoms hit before and during my menstrual cycle. I will have extreme nausea, dizziness, low blood sugar and increased parasympathetic activity. I have also tested high in testosterone levels. I am not on birth control and have not been since 2011 when I was hospitalized for NCS/POTS after my heart stopped. Is there a way to regulate hormone levels that cause symptoms without using medications such as birth control? Is high or low testosterone or any other hormone typical with dysautonomia?
- A: First, we do not know in your case whether hormones are indeed causing your symptoms. Second, there is no association between testosterone and dysautonomia in women. If you have elevated testosterone, you may want to ask your GYN whether you could have polycystic ovarian syndrome, given the high testosterone level.
- Q: Why every time I have a meal I get very tachycardic and shaky? Is that POTS related?
- A: Yes, it could be, because after you eat, blood goes to your stomach and GI tract to help you digest, which can make you feel more lightheaded and tachy if you already have POTS. Midodrine can help with this. Also, try eating smaller meals more often throughout the day. Larger high carb meals tend to do this the most. You can look up some info on postprandial hypotension (although in POTS we often don't have true hypotension with this post-eating symptom). Gastroparesis can certainly cause chronic nausea, and if you are not able to consume enough fluids and salt, may result in autonomic symptoms of dizziness, tachycardia, etc.
- Q: Would it be physiologically plausible to have POTS during pregnancy and postpartum, and then not again until midlife (--in a different, hypertensive form)? How can perimenopausal or menopausal women pursue more answers about reproductive hormones and POTS?
- A: It certainly is plausible and I do see these women in my clinic. Sometimes a short-trial of HRT (hormone replacement therapy) may be helpful. We do need more studies on hormones and POTS/dysautonomia since there is definitely a relationship. Thus far, we do not have studies addressing perimenopausal/postmenopausal onset of POTS.
- Q: My doctor has said I have vaginismus and will need to consult PT (physical) therapy before sex. Is this a POTS thing?
- A: This is not a POTS manifestation. Vaginismus can be treated with pelvic PT where they work on stretching the vaginal wall without causing pain and use other modalities including relaxation.

- Q: Is it ill-advised to go from a mostly sedentary lifestyle to having intercourse often? Can the symptoms that occur after intercourse, for example palpitations and tachycardia cause any damage to the heart?
- A: No, it does not damage the heart; actually it would be a good exercise.
- Q: Are there any specific red flags to watch for that might suggest a person with dysautonomia isn't healthy enough for sex?
- A: Not really. If you are not having acute heart attack, then you can participate.
- Q: If you have congenital heart disease and POTS is sex risky? Does sex benefit your overall health? Is hyperadrenergic POTS more risky since our blood pressure goes higher?
- A: Generally speaking, if you can climb a flight of stairs, you can have sex. Check with your cardiologist since there are different types of congenital heart disease. Yes, sex is healthy, from both a physical and psychological standpoint. Patients with high blood pressure have sex, so don't worry about hyperadrenergic POTS unless your blood pressure increases to above 180/100.
- Q: Can POTS cause an irregular menstrual cycle?
- A: POTS by itself doesn't cause irregular menstrual periods. But there is one study that suggested that patients with POTS may have a higher rate of polycystic ovarian syndrome, which can cause menstrual irregularities.
- Q: I don't know if this is POTS related or not but I feel like I don't have any feeling inside my vagina. It feels like my vaginal walls are numb. This makes sex not as exciting as I think it can be.
- A: You should discuss this with your OB/GYN first. Some forms of birth control and other medications can give you this feeling. If you have normal bladder and bowel function, it's unlikely to be caused by neuropathy.
- Q: I was told by my cardiologist that metoprolol can do that to you. Is that true?
- A: Metoprolol can reduce sexual drive, but should not typically cause numbness in the vagina.
- Q: Do you know of any beta-blockers that are class B or C as opposed to A?
- A: We just looked up metoprolol tartrate (Lopressor) and it says Class C and cardiologists use it during pregnancy all the time. A doctor will weigh the risks and benefits to mother and baby.
- Q: In the future can I breastfeed on metoprolol?
- A: Generally yes, but please speak with your pediatrician about it first.
- Q: I have POTS, NCS and MALS and have a lot of pelvic/vulvar pain which worsens when I stand for long periods of time... Ha ha-standing. Could this be blood pooling in my abdomen/pelvis? Is there anything that can be done other than lie down or stand on my head?
- A: It may be from blood pooling - if you lie down and it improves, then blood pooling is likely. You may want to try abdominal binders and Midodrine.

The next two questions apply to this slide.

POTS and pregnancy: take-home points

- Women with POTS and physicians who care for them need to be aware that POTS may have a variable course during pregnancy and post-partum period.
- Patients can be reassured that, based on the available data, there appears to be no adverse maternal or fetal outcomes secondary to POTS.
- While there is no "Class A" medication available for treatment of POTS, utilizing medications during pregnancy if necessary to control symptoms does not appear to result in any adverse maternal or fetal effects. In fact, those women who utilized medications during pregnancy perceived their symptoms as either improved or stable more frequently than the women who did not take any medications.

Q: Is this also true for women with EDS?

A: There are many additional issues to EDS, so this information would apply to POTS only. Unfortunately, the few studies on POTS and pregnancy did not separate out those with co-morbid EDS. I believe in my study, we may have had about 10-20% of patients who also had EDS. I would discuss pregnancy-related EDS issues with an EDS specialist.

Q: Which kinds of medications are they referring to in this slide?

A: In my study, most patients used Florinef, beta blockers, and Midodrine.

Q: Why do I get the poisoned / extreme hangover feeling (tachycardia, nausea, feeling dehydrated, extreme fatigue) the day after intimacy, lasting 24 hours? I have tachycardia attacks during and after, since I had arrhythmia a few times after tachycardia I am very scared of this. Should I give up altogether? The terrible hangover feeling and tachycardia are really bothering me, it's too much payback! Doctor suggested me to take extra drugs but I am worried about experimenting with them...Does anyone else have intimacy as a trigger for all the symptoms flaring? How do you keep going through all this, is there a solution?

A: I agree with your doctor - instead of giving up sex, try finding the right medication or a combination of medications to make you feel less symptomatic the day after sex.

Q: What sort of an effect do birth control pills have on POTS symptoms?

A: The answer is "it depends!" Some patients feel that stopping their period is very helpful while others can't tolerate birth control pills due to worsening of symptoms. The same occurs in patients with migraine headaches, by the way.

Q: Do you see a difference in symptoms between masturbation and intercourse in POTS patients? Why is it that an orgasm during intercourse seems to cause more symptoms than with masturbation?

A: Because you are more active during intercourse and it causes more exertion, therefore resulting in more symptoms after the intercourse.

Q: Is there any data or reason to believe that "spastic uterus" (contractions throughout pregnancy that do not dilate cervix) could be POTS related?

A: There has not been enough data/studies on this topic

- Q: Midodrine can sometimes cause supine hypertension. Would that help with the s/s of POTS during intercourse or would it make the risk of supine hypertension increase?
- A: If you have low blood pressure, it's unlikely that a low dose of midodrine will cause you to be hypertensive during intercourse, but you may want to check your blood pressure on midodrine while you're supine and not having sex!
- Q: Any POTSy reason why I can't sleep after orgasm? I get very jittery and tachy, and can't lie still.
- A: This is pretty common. There is a lot of sympathetic hyperactivity during and after sex, so it's possible that this hyper-activation results in insomnia. However, for other people, it can help with sleep, but more often in POTS there is underlying sleep disturbance so it would not be surprising that insomnia will occur after an orgasm.
- Q: Can dysautonomia increase the production of self lubrication? I've had this problem for years, even when not being intimate. I have a clean bill of health but this continues to bother me and can be rather problematic at times. Trying to find a cause when all tests come up negative.
- A: Not really; usually there is an issue of dryness either from medications or sympathetic denervation.
- Q: While having sex of course If I am laying down my heart rate is OK but when I stand it goes crazy and I feel it thumping through my chest during intercourse. Is this dangerous and at what point is it dangerous? At times after sex my heart rate will stay high for a while afterwards if I try to do anything standing up is that normal as well? My last question is if an older adult let's say 22 got POTS out of the blue has she ever seen it go away within time? I know in teenagers it does but how about adults? Has it happened?
- A: No, it's not dangerous. If you feel dizzy standing up, avoid this position. There are no long-term follow-up studies on adult POTS patients yet, but anecdotally, we know of many adult onset POTS patients who got better.
- Q: My husband thinks I don't have any sexual feelings towards him because I don't have a sex drive (never ever want to, can't feel it when we do, sick for three days afterwards), do you have any tips on explaining this to husbands.
- A: Obviously, communication between partners is the key. You want to remain intimate even if you cannot have intercourse.
- Q: I feel like during the first trimester I had what was called a autonomic storm. I couldn't sleep, constant urination every 15 min, elevated heart rate, high and low pressure, flushing, fatigue to the point I couldn't walk and was hospitalized. It was almost like my body freaked out with the hormones. This was during the 5/6 week mark. Any idea why this happens during the first trimester to some of us? I'm scared to try again.
- A: This can happen - your hormones are rising fast, and you may have nausea and vomiting causing decreased blood volume. Perhaps a low dose of a beta blocker may have decreased this sympathetic overactivity period.
- Q: What about sweating? Getting extremely sweaty with very little activity, so with bit more can also be more?? -do beta blockers help or make worse. Clonidine has been mentioned by some to help with extra sweating, but also used to help sleep, what about daytime use?? anything else
- A: Yes, I use both clonidine and beta blockers in patients with increased perspiration. You can use both during the daytime too.

- Q: Can beta blockers such as Metoprolol affect sexual function and does dosage play a role? Can they reduce natural lubrication or desire?
- A: Yes! High enough doses of beta blockers can reduce libido.
- Q: I get very lightheaded the day before and first day or two of my period. I spoke to my doctor about this, and he suggested taking ibuprofen (like Advil), with food and lots of water on these days. Ibuprofen increases blood volume and blood pressure, and as a bonus helps alleviate cramps. Does Dr. Blitshteyn ever recommend this to her patients?
- A: Sometimes, yes. Pre-treat with Advil (with food!) right before their period starts or on the day it starts. You want to minimize the use of NSAIDS if you have gastric problems. Ask your GI doctor whether it is safe for you.
- Q: Can you take beta blockers or other POTS treatment medications during pregnancy? Which one are safe? Is a natural birth; c-section or an epidural safest for mom and baby?
- A: You can take a beta blocker; the most widely studied and used is metoprolol (Class C pregnancy), but I also use small doses of atenolol in some patients. The risk of taking a beta blocker is smaller birth weight of the newborn, but this risk is minimized by the use of low doses and routine ultrasound checks for birth weight. As for delivery, the best way is vaginal delivery with early epidural placement for pain control.
- Q: How do we know if our daughters dysautonomia is genetic and if her kids will get it if she has them. She is the only person with dysautonomia in the family.
- A: Genetic testing is only available for Familial Dysautonomia, a very rare form of dysautonomia that is found in people of Ashkenazi Jewish descent. We do not have genetic testing for POTS or other forms. If you have EDS, there is likely a 50% chance of passing it to an offspring. There is genetic testing available for some forms of EDS, but not for the most common form of EDS associated with dysautonomia, EDS III (joint hypermobility subtype).
- Q: Any suggestions for when I decide to get pregnant and have to stop taking birth control? I have POTS and Endometriosis, both of which flair up during periods (I get the shot so I don't have periods).
- A: If you want to get pregnant, generally you would stop birth control for 3-4 cycles. It make take you longer to conceive given the endometriosis.
- Q: A lot of people with POTS are talking about the MTHFR genes and possible blood clot issues. Do you think girls and women with POTS should be tested for this gene, especially in regards to being on the pill and pregnancy?
- A: Perhaps. Currently, there are no standard recommendations for testing, but it certainly makes sense.
- Q: Would you suggest a panel of tests for any specific clotting disorders for girls and women with POTS?
- A: If you have a personal or a family history of blood clots, early strokes or suspicion for a clotting disorder, you can ask to be tested for anti-phospholipid syndrome (APS) related antibodies. *(Editor's Note: there is more info about APS on the Dysautonomia Dispatch Blog: <http://www.dysautonomiainternational.org/blog/wordpress/what-dysautonomia-patients-should-know-about-antiphospholipid-syndrome/>)*

- Q: My nerves are too sensitive to where I can only handle so much. Less than 2-5 minutes can be barely tolerated. Otherwise it gets me very symptomatic. Any suggestions other than stopping altogether? Losing this part of me is disheartening.
- A: Try lubrication or using a very small amount of lidocaine gel (make sure it is for vaginal use).
- Q: What if you have both POTS and PFD, like myself, and have been advised c-section may be a better option for PFD? What are the added risks of a c-section for a POTS patient? Of course, each case is different so generally speaking.
- A: Honestly, I have not heard PFD as an indication to a C-section, but your case may be unique. Generally, vaginal delivery may improve PFD due to stretching or other factors that we don't know yet.
- Q: Does POTS patients hypersensitivity to pain make pregnancy more miserable and intensified?
- A: Generally not.
- Q: For those that experience an improvement in symptoms post pregnancy, is it typically chronic improvement or do their severity levels return to their original state? Also, for women who have irregular menstruation and bleed constantly without birth control, can they improve after child birth? I would imagine the lack of ovulation makes it difficult to get pregnant in the first place.
- A: In my study on POTS and pregnancy, only a few patients improved after pregnancy compared to before. For many patients, the degree of symptoms returned to pre-pregnancy level, and 50% reported worse symptoms compared to before pregnancy.
- Q: I have NEVER had a true orgasm during intercourse! PLEASE tell me this could possibly be due to Dysautonomia and that there is nothing else seriously wrong with me.
- A: We can't attribute this to POTS or dysautonomia because it's actually fairly common in the general population too.
- Q: Is there a known overlap with endometriosis, libido, POTS and connective tissue disease issues?
- A: We know that patients with POTS may have a higher rate of endometriosis. As for libido, decreased libido is common with many chronic illness, including POTS.
- Q: How does pregnancy relate to POTS? I have been told that it maybe safe during pregnancy but especially with severe pots it may make it worse and can it have an ill effect on the unborn child?
- A: We do not have evidence that POTS is detrimental to the baby. Generally, POTS is not a contraindication to pregnancy.

Q: What can be done about a complete lack of sex drive?

A: Ask your doctor if any of the meds you are on cause a reduction in libido. Also, check out these tips from the power point lecture.

Tips on healthy sex and chronic illness

- Plan sexual activity when you feel less symptomatic (commonly afternoon/evenings for POTS patients)
- Avoid certain positions that reduce blood to the brain or cause blood pooling
- Make sure the room is cool to avoid overheating
- Do not skip medications before sexual activity
- Avoid alcohol or caffeine
- Plan ahead and be well-rested before sex
- Communicate with your partner, both your sexual and medical health needs

Tips on healthy sex and chronic illness 2

- If you become symptomatic with pre-syncope during sex, take a break, cool off, drink Gatorade
- Avoid taking hot shower or hot bath before or after sex
- If intercourse is not possible or not preferable, consider other sexual/sensual activities
- After sex, remain supine, rest, cool off and take medications if needed (i.e. extra beta blocker if persistent tachycardia)

Q: I noticed a question about bladder issues during, what about bowels. Afterwards I have many times where I desperately need to go or the next day is spent on the loo. Is it likely a vagal issue or some other ANS feature, or yet other issue?

A: It can happen to some people. Either this is due to IBS-like increased motility or through local stretch that can possibly result in rectal hypermotility.

Q: A lot of us seem to have mast cell activation issues, which can be associated with elevated prostaglandins. How might that effect pregnancies?

A: We don't have any data on this topic unfortunately.

Q: Are there cases of gastroparesis improving during pregnancy?

A: We do not have enough evidence for or against that statement. Generally, pregnancy hormones relax the smooth muscles of the GI tract and can actually result in gastroparesis-like features in healthy women as well.

Q: Is there anything that can boost our sex drive? There seems to be many of us who have a lack of a sex drive. It is hard because I want to have a sex drive and I want to have a natural craving for sex but I just don't.

A: Check your medications - many can cause reduced libido. Your doctor can for example reduce the dose of a beta blocker or change you from one SSRI to another with less sexual side effects. Check your medications - many can cause reduced libido. POTS itself, as all chronic illness, can decrease libido. The old adage "if you don't use it, you lose it" holds true - do it anyway and your sexual drive may increase.

Q: Is sudden onset of hyperPOTS in perimenopause associated with estrogen deficiency?

A: Yes, possibly.

Q: Can overstimulation from sexual intercourse cause symptoms such as arrhythmia or palpitations in POTS patients? If so should this be considered benign?

A: Sex can increase the sensation of your heart beat in your chest and other places in your body (palpitations).

Q: Regarding the issue of medication use in pregnancy?

A: While it's best not to use any medications during pregnancy, many patients with chronic conditions will use pharmacotherapy, including patients with POTS. It's always best to use the smallest doses possible and the safest ones available. Discuss medications with your POTS specialist and high-risk OB/GYN, who are more familiar with medications during pregnancy than regular OB/GYNs.

Q: Has there being any studies or links between POTS/Dysautonomia and other "typical" pregnancy complications e.g. preeclampsia, peripartum cardiomyopathy, etc.

A: There have been no systematic studies, but there have been isolated case reports on post-partum cardiomyopathy, post-partum hypertension and pre-eclampsia/ecclampsia in patients with autonomic disorders. We do not have data whether prevalence is higher in patients vs. general population.

Q: What should one expect with pregnancy and POTS/dysautonomia? I am hyper POTS, probable EDS and gastroparesis. Are there any risks for baby or mom? Anything I should know or know in general for dysautonomia and pregnancy.

A: Please review several studies that are available on the topic of POTS and pregnancy. Generally, we do not believe that there is any harm or adverse events to the baby. During pregnancy and post-partum, POTS course can be variable, so you need to discuss medication options during and after pregnancy with your POTS specialist. POTS is not a contraindication to pregnancy, as far as we know it.

Q: Is a high risk obgyn necessary for pregnancy if u have POTS? My ob plans on pretty treating me like a normal pregnancy.

A: It depends on how symptomatic you are and what type of issues are you having. If you take medications, I generally refer patients for high-risk OB consult once.

Q: Does having an autonomic disorder increase the chance of sexually transmitted infections and can they be worse in patients with POTS?

A: No it does not increase the chance of a sexually transmitted infections. Having an infection in general can make your POTS symptoms worse.

Q: Do you have general recommendations for POTS patients on pregnancy and delivery? A:

A: Work with your POTS specialist and a high-risk OB/GYN. If you have to take medications, do not be afraid because some are relatively safe. Aim for vaginal delivery with early epidural placement if possible, but also understand that deliveries for anyone are unpredictable, so just "go with the flow."

Q: From your own observance and/or current research, would it be better for those with POTS to have a scheduled c-section or vaginal birth? (Taking all things into account; tachycardia, drops in BP, blood loss)

A: Vaginal delivery with early epidural placement for pain control is always the best way to deliver, but don't be stressed if you have a C-section for non-POTS issues - i.e breach, failure to progress, etc.

Q: Do you need to be off of all medications during the entire pregnancy? I am on a beta blocker and fludrocortisone (lowest dosages). Would getting off medications be dangerous?

A: There are some medications that are safe during pregnancy. Medications can be changed prior

to pregnancy.

Q: I would like to know about 1. hip pain that lasts hours/days after intercourse 2. Fainting (full) during intercourse.

A: 1. If you have hypermobility, then hip pain may be manifestations of this if you are using your hips extensively Try changing positions often and/or use pillows for rest. 2. Fainting during intercourse can occur - make sure your partner is aware and doesn't call an ambulance! Have Gatorade and your medications near you.

Q: Is there any prevalence of Premature Ovarian Failure in POTS patients? Mine started at age 36
A: We don't have data on that topic yet. There are a lot of things about POTS that we would like to study still!

Q: Are there autonomic nerves in the vagina that would cause severely painful intercourse?

A: There are many reasons for painful intercourse with the most common being vaginal dryness. There is also pelvic floor dysfunction that may occur in patients with dysautonomia or fibromyalgia.

Q: Can POTS and can endanger the baby during or after the delivery. Also, what other complications can be expected?

A: No, there appears to be no harm to the baby as we know it.

Q: I have read that pregnancy can be a trigger for forms of dysautonomia or that onset begins after pregnancy. What causes the onset of symptoms after giving birth?

A: We don't have a good answer - many hormonal changes and a huge blood volume shift occur immediately post-partum, resulting in increased sympathetic activity. This is just a hypothesis, and we need more research on the postpartum onset of POTS and other dysautonomias.

Q: Have you noticed any difference in symptoms experienced after sexual intercourse for males with POTS?

A: It depends; some males have no problems, others may have fatigue and post-exertional malaise.

Q: After intercourse I find that I have worsened POTS symptoms. Seems like other women agree. How can we avoid extreme dizziness or passing out? What are some different positions we can do to help prevent major symptoms including joint issues for EDS too?

A: It's not uncommon to have these symptoms during or after intercourse, so you are certainly not alone. Obviously you want to have the room cooled out, to be hydrated and take your medications on time. Gravity may not be your best friend, so try laying down. Switch position often to avoid pain and dislocation of the joints. You want to avoid hyperflexion and hyper-extension of the joints, if possible...

Q: I've heard POTS symptoms get worse during pregnancy for some and better for others. What can we expect and how might we be able to combat the extra/worsened symptoms? Also, what about after giving birth? There are a lot of concerns of taking care of a newborn while having worsened POTS.

A: Yes, the several pregnancy and POTS study that we have do suggest variable course during and after pregnancy, with about 60% of pts doing better during pregnancy. You want to have a support system set up in case you are too sick to take care of the baby. You also want to have a treatment plan during and after pregnancy with your POTS specialist.

- Q: During pregnancy, is there any lack of oxygen to the baby because of Dysautonomia that could potential hurt the baby?
- A: There is no loss of oxygen to the baby.
- Q: Any link between POTS and miscarriage? Had 1 a year ago and am now having trouble getting pregnant.
- A: Not that we know of right now, but in my study, there appeared to be higher miscarriage rate than in general population.