Identification of Candidates for Progesterone: Why, Who, How, and When?

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Question 1:

Could you please expand on your statement about second-trimester stillbirth as an indication for progestogen prophylaxis? Is this regardless of the etiology of the stillbirth?

Response from Dr. Iams:

Many second-trimester stillbirths, especially those before 24 weeks, are intrapartum deaths of otherwise normal fetuses whose gestational age is simply too early to justify cesarean birth. The exact percentage is uncertain, but support for this observation can be found in reports from the NICHD Stillbirth Collaborative Research Network (see Stillbirth Collaborative Research Network Writing Group, JAMA 2011;306:2469-79 and Stillbirth Collaborative Research Network Writing Group, JAMA 2011;306:2459-68). Thus, the answer to the second question is no. It requires a careful medical history to ascertain if the fetus was alive at the time of arrival at the hospital; if there were any preadmission signs and symptoms suggestive of parturition (see article); or, the opposite, if there were any signs and symptoms of demise before parturition (intrauterine fetal death diagnosed followed by cervical ripening and long induction-to-delivery time). A detailed medical history is also needed to ascertain if there was obvious fetal anomaly, polyhydramnios, or uterine anomaly. Questionable cases of intrapartum deaths include a history of light bleeding, oligohydramnios, prior fluid leakage, or when no records are available.

When the mother has had parturition symptoms and the fetus was alive at arrival, it is appropriate to prescribe progestogen in future pregnancy. When the fetus had an obvious anomaly, it is not appropriate to prescribe progestogen in future pregnancy. For all others, we follow with cervical scans every 2 weeks from 16 weeks to 24 weeks, and initiate progestogen treatment only if the cervix is less than 25 mm (25 mm is used instead of 20 mm due to the history of stillbirth).

Question 2:

In the setting of a patient with a history of preterm birth presenting late to prenatal care, what is the latest that progestogen prophylaxis should be started?
**Question 3:**

In your practice, how would you treat a woman receiving 17 alpha-hydroxyprogesterone caproate for a prior preterm delivery who shows cervical shortening at her 26-week sonogram?

**Response from Dr. Iams:**

There is no evidence-based answer to this question. We use 24 weeks but will initiate progestogen treatment as late as 24+6 weeks if the cervix is short at the initial visit, again using 25 mm rather than 20 mm. Please note the discussion in the text explaining why I think a short cervix identifies women who are “progestogen” candidates—a history of spontaneous preterm birth is a marker for finding short cervixes, but women with a history of preterm birth who do not have short cervix in their next pregnancy do not benefit from “progestogen” (see O’Brien et al, Ultrasound Obstet Gynecol 2007;30:687–96).

**Question 4:**

If a clinic chooses universal transabdominal screening of cervical length between 18 weeks and 24 weeks, is there an ideal time to aim for during that window? What patient characteristics decrease the accuracy of the transabdominal measurement compared with the transvaginal?

**Response from Dr. Iams:**

This is another question for which there is no evidence-based answer. Some stop cervical sonograms at 24 weeks because those greater than 24 weeks are no longer candidates for cerclage. If cervical shortening is significant after 24 weeks (defined as more than 5 mm shorter than previous examination), my first question would be to look at the images again because not all images are of equal quality. Thus, two common reasons for a big difference in cervical length are that one image is poor or has been measured incorrectly. If the images are good and the calipers are properly placed, then this is a patient who might be a candidate for steroids. Since one can’t obtain a fetal fibronectin after a cervical sonogram, we have started to collect a fetal fibronectin swab at 24–26 weeks before cervical sonogram. Thus, if there is any question about significant shortening, we can send the fetal fibronectin to help guide steroid treatment decision. This is the only time we use fetal fibronectin in asymptomatic patients. Remember that a cervical sonogram is the “best” predictor of preterm birth at any time in future (best equals not that good but better than others); however, fetal fibronectin is a better predictor of the next 2 weeks, so a short cervix and a positive fetal fibronectin could be a good reason for steroids. We don’t like waiting for overt symptoms/signs to treat with steroids because that policy misses about 1 in 3 who deliver early (see Mercer et al, AJOG 2001;184:S6).

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**Response from Dr. Iams:**

This is another question for which there is no evidence-based answer. The later one does a cervical sonogram, the more likely one is to find all who have short cervixes; however, the later one initiates treatment, the less likely one is to be successful with the “progestogen” treatment (see Markham et al, Obstet Gynecol 2014;123:34–9). The best time is probably 20 weeks, but this is just my opinion in the absence of evidence. I am not sure of the answer to the second question. Reported experience with transabdominal scans to measure cervical length is mixed and clinical use of transabdominal scans is nil. Obviously, maternal body mass index and habitus and prior abdominal surgery would limit transabdominal accuracy. I have limited, mostly negative, personal experience with trying to image and measure the cervical length via transabdominal scanning. I have obtained some good images, but the percentage for which that is possible is questionable (see Friedman et al, Am J Obstet Gynecol 2013;208:190.e1–7).
Question 5:

Do you recommend any variation in screening or management in the patient with cervical shortening due to LEEP/cone history versus other risk factors?

Response from Dr. Iams:

No (see Conner et al, Obstet Gynecol 2014;123:752–61). Women with dysplasia have the same preterm birth risk as women with dysplasia treated with LEEP/cone biopsies. The associations of spontaneous preterm birth with a history of dysplasia, bacterial vaginosis, urinary tract infections, and sexually transmitted infections are, in my opinion, all markers of a patient whose “immune defense” is altered, damaged, and not okay. Huge numbers of women are exposed to genital tract microbes. Most defend themselves, are never symptomatic, and recover without treatment. A smaller number become ill, and a still smaller number have persistent colonization and injury. These “mark” a woman as being at risk for preterm birth. That’s why treatment of all these infections has had no effect on preterm birth rates. It’s the host defense, not the bad bugs ascending into the uterus during pregnancy.

Question 6:

Does a positive fetal fibronectin test play any role in decision making regarding the addition of vaginal progestogen prophylaxis?

Response from Dr. Iams:

None. There are no data to suggest that at all.

Question 7:

Is there any role for use of a pessary as an adjunct to either 17 alpha-hydroxyprogesterone caproate or vaginal progestogen prophylaxis?

Response from Dr. Iams:

I don’t know. The European data are interesting but not conclusive (see Iams, BJOG 2014 Mar;121:463). We consider a ring or cup pessary when there is progressive cervical shortening to 0 mm before 24 weeks in a woman with a history of two births prior to 26 weeks who is being treated with progestogen and already has a cerclage in place. I’ve done that four times in the last 3 years: one failed soon after, one was amazingly successful and led to birth at 38 weeks, one was removed 2 weeks later at 21 weeks for discomfort and spotting (she is now at 28 weeks), and the fourth one was placed recently at 18 weeks in a woman who is still pregnant.

Question 8:

What do you currently offer to the patient with a multifetal gestation and cervical shortening or history of preterm birth?

Response from Dr. Iams:

There are two risk factors at work in this setting. The first is uterine stretch, which can lead to a short cervix that is not dangerous, does not respond to “progestogen” treatment, and is often made worse by cerclage. The other is a history of a previous preterm birth, which often but not always means increased risk for recurrent preterm birth and is marked by a short cervix in the next pregnancy (see Iams JD et al, AJOG 1998;178:1035–40; recurrence risk of preterm birth is <10% in women with a cervix >35
mm in the next pregnancy, about 15% if cervix is a little shorter than average (25–35 mm), and 35% if cervix is <25 mm).

How to apply that here (all dichorionic diamniotic twins):
A. Nulliparous woman with twins and a short cervix <25 mm is given no treatment other than education for signs/symptoms of preterm labor. No bed rest, but no physically demanding work either.
B. Multiparous woman with prior singleton preterm birth <32 weeks who now has twin pregnancy is given the same treatment as any woman with a prior spontaneous preterm birth, should offer “progestogen,” and, if the cervix shortens <25mm, offer cerclage too. This patient has two risk factors (stretch, for which there is no treatment, and a history of preterm birth/short cervix, for which “progestogen” and maybe stitch are the treatment of choice).
C. For a multiparous woman with prior preterm birth of twins who now has a singleton pregnancy, if the twin preterm birth was <32 weeks, she has increased risk of singleton preterm birth in the next pregnancy. Care is uncertain. Whenever care is uncertain, follow closely with cervical sonogram and initiate “progestogen” treatment for a cervix <25mm.

In addition, I think a short cervix is the indication for “progestogen” in singletons, so when in doubt, either offer treatment or follow cervical length and treat with “progestogen” if the cervix becomes short. Use 20 mm for all who have no history of concern. Without evidence, we use 25 mm as treatment threshold for “progestogen” treatment in women who have a confusing or uncertain history. See Laughon et al (Am J Obstet Gynecol 2014;210:131.e1–8) and Iams (AJOG 2014;210:97–8).