

Case Management Part 2

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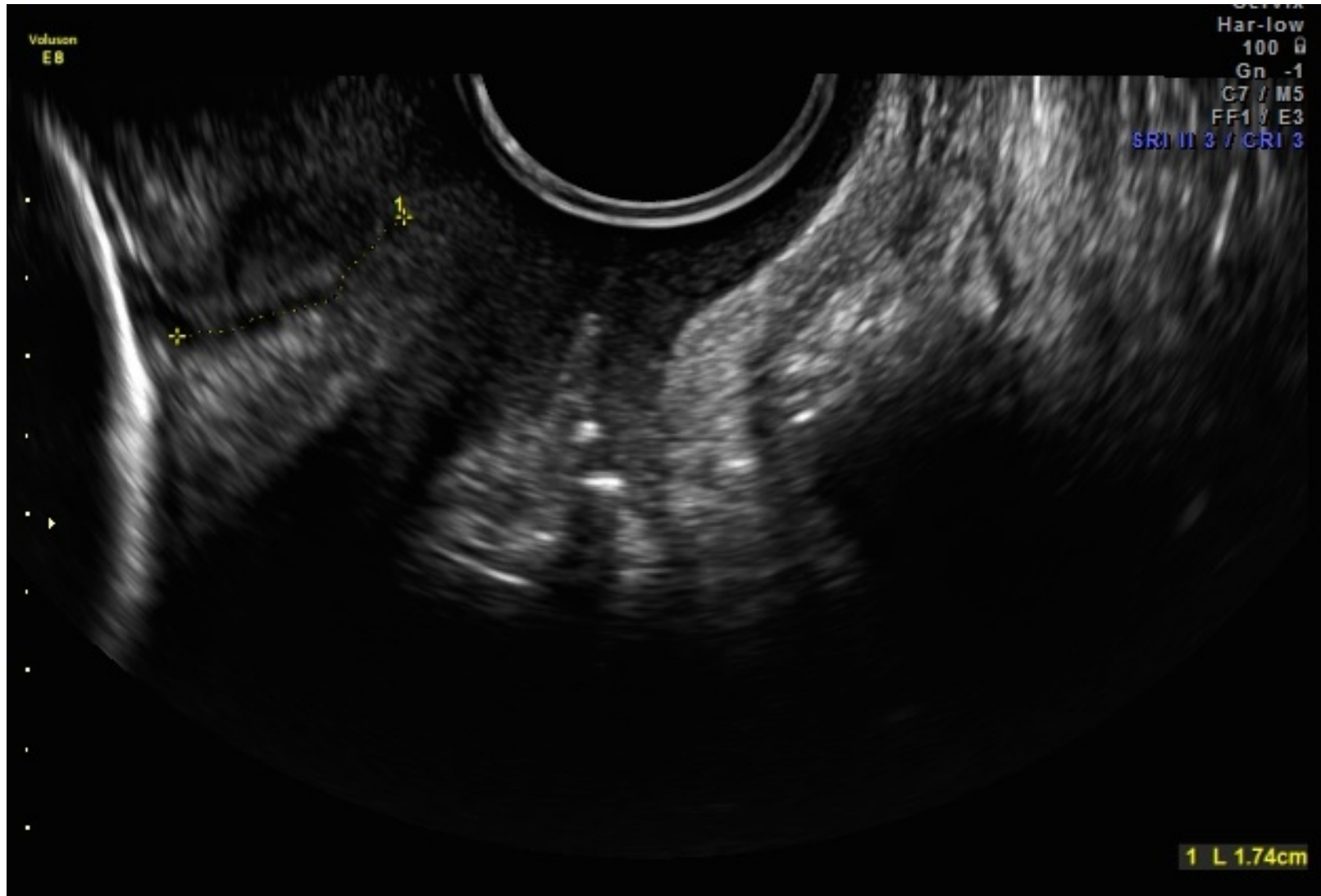
Summary &
Review of Literature

Case Management Part 2



After discussion with the patient of possible management options, the patient had an Arabin pessary placed and was started on once daily vaginal progesterone. Two weeks later her cervical length was measured to be 17 mm and one week later, at 26 weeks 3 days gestation, her cervical length was 25 mm without funneling. She was admitted to the hospital 6 weeks later, at 32 weeks 1 day gestation, for elevated blood pressures and was diagnosed with severe preeclampsia. She was delivered via a primary cesarean section at 33 weeks 0 days after receiving a course of betamethasone and magnesium sulfate. The pessary was removed after her cesarean section. Both babies had normal cord gases and were transferred to the Neonatal Intensive Care Unit (NICU). The mother was discharged home on postoperative day #4 after an uncomplicated postpartum course.

Image 4 - Transvaginal ultrasound 2 weeks later with pessary in place



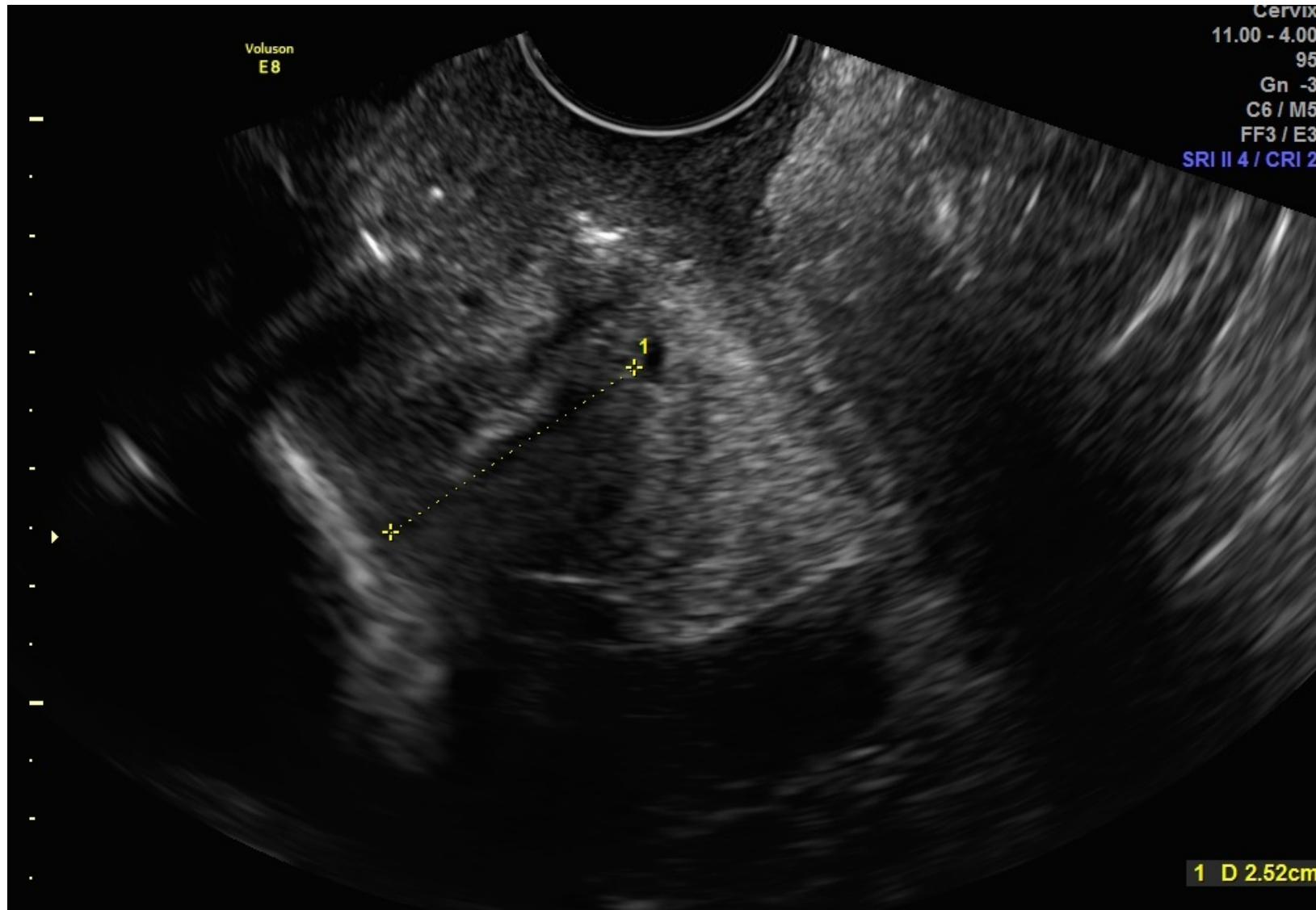
Ultrasound images
courtesy of:

Crystal Holt-Ayers,
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Image 5 - Transvaginal ultrasound 3 weeks later with pessary in place



Ultrasound images
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Review of Literature
& Summary

Review of Literature



Short Cervix and Twin Gestation: Definitions and Diagnosis:

The incidence of multifetal gestation in the United States has risen dramatically between 1980 to 2009, from 18.9 to 33.3 per 1000 live births predominantly driven by assisted reproductive technology and older maternal age at conception (American College of Obstetricians and Gynecologists, 2014). Twin pregnancies have a greater than 50% rate of preterm birth and 5 times higher risk of early neonatal death when compared to singletons.

Regarding screening of asymptomatic women, the ACOG Practice Bulletin on multifetal gestation (2014) states: “Several methods have been used in an attempt to further quantify the risk of spontaneous preterm birth when screening asymptomatic women with multifetal gestations, including transvaginal ultrasonographic cervical length, digital examination, fetal fibronectin screening, and home uterine monitoring. There are no interventions that have been shown to prevent spontaneous preterm delivery in asymptomatic women with multifetal gestations identified to be at risk based on these screening methods. The use of these screening methods in asymptomatic women with multifetal pregnancies is not recommended.”

Review of Literature - continued



Notwithstanding the ACOG recommendation, short cervix is a very powerful predictor of preterm birth in twin pregnancy. In a study of 1,163 women with twin pregnancy undergoing cervical length screening at 22-24 weeks, To, et al (2006) showed that progressively shorter cervical lengths, untreated, are strongly associated with progressively increased risks of spontaneous early preterm birth (birth <34 weeks), as summarized in the Table here:

Table II Rate of delivery and 95% CI before 30, 32, and 34 weeks according to cervical length at 22 to 24 weeks

Cervical length range (median)	Delivery before 30 wks		Delivery before 32 wks		Delivery before 34 wks	
	Rate (%)	% (95% CI)	Rate	% (95% CI)	Rate (%)	% (95% CI)
1-5 (3) mm	4/5	80.0 (44.9-100)	5/5	100	5/5	100
6-10 (8) mm	8/16	50.0 (25.5-74.5)	14/16	87.5 (71.2-100)	15/16	93.7 (81.9-100)
11-15 (14) mm	4/10	40.0 (9.6-70.3)	6/10	60.0 (29.6-90.3)	7/10	70 (41.5-98.4)
16-20 (19) mm	6/37	16.2 (4.3-28.1)	10/37	27.0 (12.7-41.3)	20/36	55.5 (39.3-71.8)
21-25 (23) mm	8/92	8.7 (14.4-2.9)	13/92	14.1 (7.0-21.2)	35/92	38.0 (28.1-47.9)
26-30 (29) mm	4/177	2.2 (0.07-4.4)	9/175	5.1 (1.9-8.4)	24/168	14.3 (9.0-19.6)
31-35 (33) mm	2/233	0.8 (0-2.0)	10/232	4.3 (1.7-6.9)	20/229	8.7 (5.1-12.4)
36-40 (38) mm	2/284	0.7 (0-1.7)	5/277	1.8 (0.2-3.4)	14/271	5.2 (2.5-7.8)
41-45 (43) mm	0/155	0	1/152	0.6 (0-1.9)	3/149	2.0 (0-4.3)
46-50 (48) mm	0/80	0	0/80	0	0/80	0
51-55 (53) mm	0/28	0	0/27	0	0/26	0
56-60 (59) mm	0/10	0	0/10	0	0/10	0

(Table from To, et al (2006) shows rates of spontaneous preterm birth (births due to preterm labor or prelabor rupture of membranes in 1,163 women with twin pregnancy)

Review of Literature - continued



A widely accepted definition of “short cervix” on transvaginal ultrasound is a cervical length 25 mm or less before 24 weeks gestation. Below this length, the rate of early preterm birth rises rapidly. Above this length, the rate is fairly low.

Proposed interventions to reduce preterm birth with a finding of short cervix include cervical cerclage, progesterone treatment, and pessary placement.

Review of Literature - continued



Cervical Cerclage:

A cerclage can be placed in a pregnancy if indicated by history (prophylactic), physical exam, or transvaginal ultrasound (short cervix). A Cochrane review published in by Rafael, Berghella and Alfirevic (2014) evaluated whether either of these cerclage indications improved obstetric and perinatal outcomes in multifetal gestations. They included five above average quality randomized controlled trials (RCT) with a final analysis of 128 women. When outcomes for cerclage were pooled together for all indications and compared with no cerclage, there was no statistically significant differences in perinatal deaths (19.2% vs. 9.5%; RR 1.74, 95% CI 0.92 - 3.28), serious neonatal morbidity (15.8% vs. 13.6%; RR 0.96, 95% CI 0.13 - 7.10), or composite perinatal death and neonatal morbidity (40.4% vs. 20.3%; RR 1.54, 95% CI 0.58 - 4.11). Ultrasound-indicated cerclage (n=98) was associated with an increased risk of low birth weight (RR 1.39, 95% CI 1.06 - 1.83), very low birth weight (RR 3.31, 95% CI 1.58 - 6.91), and respiratory distress syndrome (RR 5.07, 95% CI 1.75 - 14.70) (Rafael et al., 2014). This review did not evaluate any physical exam indicated cerclages. Miller, Rajan and Grobman (2014) retrospectively assessed outcomes in 104 twin gestations receiving a physical exam indicated cerclage and demonstrated similar outcomes, including gestational age at delivery, when compared to singletons.

Berghella, Odibo, To, Rust and Althuisius (2005) performed a meta-analysis on all randomized controlled trials involving the use of cerclage in women with a short cervical length. In singleton pregnancy, cerclage resulted in a 40% reduction in birth before 35 weeks among those with a history of prior preterm birth (RR 0.61, 95% CI 0.40 - 0.92) or prior second trimester loss (RR 0.57, 95% CI 0.33 - 0.99). However, in twin pregnancies, cerclage resulted in a 2-fold *increase* in birth before 35 weeks (RR 2.15; 95% CI 1.15 - 4.01, N=49). (Berghella et al., 2005). However, an updated individual patient-level meta-analysis of the same 49 twin pregnancies concluded that cerclage had no net effect on the rate of birth before 34 weeks after adjusting for confounders such as history of prior preterm birth and gestational age at randomization (adjusted OR 1.17, 95% CI 0.23-3.79) (Saccone et al 2015).

Review of Literature - continued



Progesterone Treatment :

In singleton pregnancy, women with history of prior spontaneous preterm birth should be offered prophylactic 17 alpha-hydroxyprogesterone caproate (17OHP) starting at 16-21 weeks (ACOG 2012). In unselected twin pregnancy, however, meta-analysis of 5 randomized trials concluded that prophylactic 17OHP does not reduce the rate of preterm birth or reduce perinatal morbidity (Schuit et al 2015). The same meta-analysis also evaluated 5 randomized trials of prophylactic vaginal micronized progesterone in unselected twin pregnancy and similarly found no significant effect on the rate of preterm birth or perinatal morbidity.

However, when looking specifically at the subgroup of twin pregnancy with short cervix, two meta-analyses concluded that vaginal micronized progesterone was associated with significant reduction in neonatal morbidity/mortality (RR 0.52 (95% CI: 0.29-0.93), Romero et al., 2012; and RR 0.57 95% CI 0.47-0.70, Schuit et al 2015), likely due to observed trends toward reduced rates of early preterm birth. In contrast, 17OHP does not appear to be effective in this subgroup (Schuit et al 2015).

Review of Literature - continued



Pessary placement:

Arabin, Halbesma, Vork, Hübener and van Eyck (2003) introduced the idea of using a cervical pessary as a treatment option for a short cervix in pregnancy. They evaluated 4 singleton and 7 twin pregnancies with a cervical length less than 15 mm before 24 weeks. Using matched controls, their results suggested great benefit; there were no spontaneous preterm birth (SPB) before 36 weeks in singletons and no SPB before 32 weeks in twin gestations with the pessary in place (Arabin et al., 2003). The theoretical mechanism of action of a pessary is a reduction in the inclination of the cervical canal, reducing the direct pressure on the internal cervical ostium and redistributing the uterine weight onto the vaginal floor.

An RCT of prophylactic use of the Arabin pessary in twin pregnancy was published by Liem et al., (2013). The ProTWIN trial was a multicenter, open-labeled RCT that included 813 women who prophylactically received a pessary regardless of CL. They concluded that a cervical pessary does not effectively prevent poor perinatal outcomes or preterm birth in unselected women with multifetal pregnancy. However, a planned subgroup analysis demonstrated a significant reduction in poor perinatal outcome and very preterm birth when women had a cervical length less than 38 mm (25th percentile) (Liem et al., 2013).

Review of Literature - continued



Pessary placement (continued):

A similar randomized trial by Nicolaides et al (2016) found that prophylactic Arabin pessary placement in 1,180 unselected twin pregnancies had no significant impact on rates of preterm birth or neonatal morbidity. In contrast to the study by Lim et al (2013), however, this trial found no reduction in preterm birth in the subgroup of 214 women with short cervix (cervical length less than 25 mm).

Another trial of Arabin pessary in twin pregnancy was reported by Goya et al (2016). In contrast to the above-cited trials in which the pessary was used prophylactically in unselected twin pregnancy, the Goya trial included only women with short cervix (25 mm or less, N = 134). Use of pessary resulted in a reduced rate of birth before 34 weeks (RR 0.43, 95% CI 0.24-0.78), but not a significant reduction in perinatal morbidity (RR 0.64, 95% CI 0.27-1.50).

A meta-analysis that included these three trials concluded that use of the Arabin Pessary in twin pregnancies with short cervical length before 24 weeks of gestation does not prevent spontaneous preterm birth or improve perinatal outcome (Saccone et al 2017).

Summary/Conclusion



In twin pregnancy, short cervix before 24 weeks of gestation is associated with increased risk of early preterm birth and the risk rises dramatically with progressively shorter cervical length.

Cervical cerclage has not been shown to reduce the risk of early preterm birth in twin pregnancy with short cervix. A previous meta-analysis that suggested that cerclage actually increases the risk of early preterm birth in twin pregnancy has been discounted by an updated meta-analysis that adjusted for confounders. The number of twin pregnancies evaluated in randomized trials is too small to support definitive conclusions. Observational studies have suggested that exam-indicated cerclage may be equally effective in twin pregnancy and singleton pregnancy.

Progestogens (vaginal micronized progesterone or injectable 17OHPC) are not effective as prophylaxis in unselected twin pregnancies. In twin pregnancy with short cervix, however, vaginal micronized progesterone may reduce early preterm birth and neonatal morbidity. 17OHPC appears to be ineffective in this subgroup.

Arabin pessary as treatment of short cervix in twin pregnancy has produced conflicting results in 3 moderately large trials, two studies suggesting efficacy and one finding no efficacy. As prophylaxis in unselected twin pregnancy, pessary does not appear to reduce the rate of early preterm birth. There is little or no data regarding combinations of interventions (e.g. progesterone plus cerclage, or progesterone plus pessary) for preterm birth prevention among twins with short cervix.

Several large randomized trials are ongoing worldwide comparing treatment options and combinations of treatments in this very high-risk population. The conclusions above may change as new data become available.